

The Normal Bacterial Flora of Humans (page 3)

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The Composition of the Normal Flora

The normal flora of humans are exceedingly complex and consist of more than 200 species of bacteria. The makeup of the normal flora may be influenced by various factors, including genetics, age, sex, stress, nutrition and diet of the individual.

Three developmental changes in humans, weaning, the eruption of the teeth, and the onset and cessation of ovarian functions, invariably affect the composition of the normal flora in the intestinal tract, the oral cavity, and the vagina, respectively. However, within the limits of these fluctuations, the bacterial flora of humans is sufficiently constant to give a general description of the situation.

A human first becomes colonized by a normal flora at the moment of birth and passage through the birth canal. In utero, the fetus is sterile, but when the mother's water breaks and the birth process begins, so does colonization of the body surfaces. Handling and feeding of the infant after birth leads to establishment of a stable normal flora on the skin, oral cavity and intestinal tract in about 48 hours.

It has been calculated that a human adult houses about 10^{12} bacteria on the skin, 10^{10} in the mouth, and 10^{14} in the gastrointestinal tract. The latter number is far in excess of the number of eucaryotic cells in all the tissues and organs which comprise a human. The predominant bacteria on the surfaces of the human body are listed in Table 3. Informal names identify the bacteria in this table. Formal taxonomic names of organisms are given in Table 1.

Table 3. Predominant bacteria at various anatomical locations in adults.

Anatomical Location	Predominant bacteria
Skin	staphylococci and corynebacteria
Conjunctiva	sparse, Gram-positive cocci and Gram-negative rods
Oral cavity	
teeth	streptococci, lactobacilli
mucous membranes	streptococci and lactic acid bacteria
Upper respiratory tract	
nares (nasal membranes)	staphylococci and corynebacteria
pharynx (throat)	streptococci, neisseria, Gram-negative rods and cocci
Lower respiratory tract	none
Gastrointestinal tract	
stomach	<i>Helicobacter pylori</i> (up to 50%)
small intestine	lactics, enterics, enterococci, bifidobacteria
colon	bacteroides, lactics, enterics, enterococci, clostridia, methanogens
Urogenital tract	
anterior urethra	sparse, staphylococci, corynebacteria, enterics

vagina

lactic acid bacteria during child-bearing years;
otherwise mixed

Normal Flora of the Skin The adult human is covered with approximately 2 square meters of skin. The density and composition of the normal flora of the skin varies with anatomical locale. The high moisture content of the axilla, groin, and areas between the toes supports the activity and growth of relatively high densities of bacterial cells, but the density of bacterial populations at most other sites is fairly low, generally in 100s or 1000s per square cm. Most bacteria on the skin are sequestered in sweat glands.

The skin microbes found in the most superficial layers of the epidermis and the upper parts of the hair follicles are Gram-positive cocci (*Staphylococcus epidermidis* and *Micrococcus* sp.) and corynebacteria such as *Propionibacterium* sp. These are generally nonpathogenic and considered to be commensal, although mutualistic and parasitic roles have been assigned to them. For example, staphylococci and propionibacteria produce fatty acids that inhibit the growth of fungi and yeast on the skin. But, if *Propionibacterium acnes*, a normal inhabitant of the skin, becomes trapped in hair follicle, it may grow rapidly and cause inflammation and acne.

Sometimes potentially pathogenic *Staphylococcus aureus* is found on the face and hands in individuals who are nasal carriers. This is because the face and hands are likely to become inoculated with the bacteria on the nasal membranes. Such individuals may autoinoculate themselves with the pathogen or spread it to other individuals or foods.

Normal Flora of the Conjunctiva A variety of bacteria may be cultivated from the normal conjunctiva, but the number of organisms is usually small. *Staphylococcus epidermidis* and certain coryneforms (*Propionibacterium acnes*) are dominant. *Staphylococcus aureus*, some streptococci, *Haemophilus* sp. and *Neisseria* sp. are occasionally found. The conjunctiva is kept moist and healthy by the continuous secretions from the lachrymal glands. Blinking wipes the conjunctiva every few seconds mechanically washing away foreign objects including bacteria. Lachrymal secretions (tears) also contain bactericidal substances including lysozyme. There is little or no opportunity for microorganisms to colonize the conjunctiva without special mechanisms to attach to the epithelial surfaces and some ability to withstand attack by lysozyme.

Pathogens which do infect the conjunctiva (e.g. *Neisseria gonorrhoeae* and *Chlamydia trachomatis*) are thought to be able to specifically attach to the conjunctival epithelium. Newborn infants may be especially prone to bacterial attachment. Since *Chlamydia* and *Neisseria* might be present on the cervical and vaginal epithelium of an infected mother, silver nitrate or an antibiotic may be put into the newborn's eyes to avoid infection after passage through the birth canal.

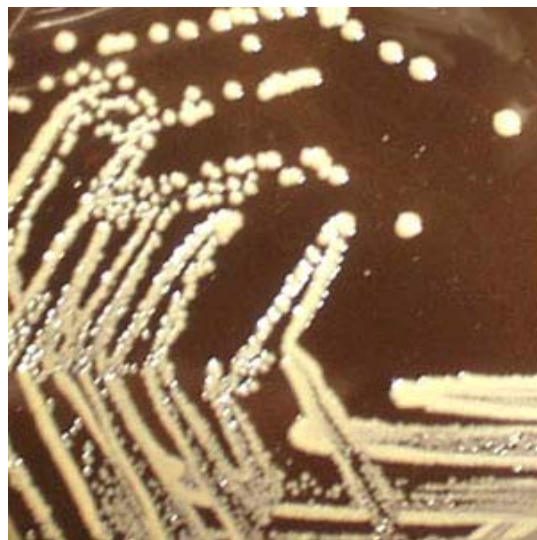


Figure 4. Colonies of *Propionibacterium acnes*, found on skin and the conjunctiva.

Normal Flora of the Respiratory Tract A large number of bacterial species colonize the upper respiratory tract (nasopharynx). The nares (nostrils) are always heavily colonized, predominantly with *Staphylococcus epidermidis* and corynebacteria, and often (in about 20% of the general population) with *Staphylococcus aureus*, this being the main carrier site of this important pathogen. The healthy sinuses, in contrast are sterile. The pharynx (throat) is normally colonized by streptococci and various Gram-negative cocci. Sometimes pathogens such as *Streptococcus pneumoniae*, *Streptococcus pyogenes*, *Haemophilus influenzae* and *Neisseria meningitidis* colonize the pharynx.

The lower respiratory tract (trachea, bronchi, and pulmonary tissues) is virtually free of microorganisms, mainly because of the efficient cleansing action of the ciliated epithelium which lines the tract. Any bacteria reaching the lower respiratory tract are swept upward by the action of the mucociliary blanket that lines the bronchi, to be removed subsequently by coughing, sneezing, swallowing, etc. If the respiratory tract epithelium becomes damaged, as in bronchitis or viral pneumonia, the individual may become susceptible to infection by pathogens such as *H. influenzae* or *S. pneumoniae* descending from the nasopharynx.

Normal Flora of the Urogenital Tract Urine is normally sterile, and since the urinary tract is flushed with urine every few hours, microorganisms have problems gaining access and becoming established. The flora of the anterior urethra, as indicated principally by urine cultures, suggests that the area may be inhabited by a relatively consistent normal flora consisting of *Staphylococcus epidermidis*, *Enterococcus faecalis* and some alpha-hemolytic streptococci. Their numbers are not plentiful, however. In addition, some enteric bacteria (e.g. *E. coli*, *Proteus*) and corynebacteria, which are probably contaminants from the skin, vulva or rectum, may occasionally be found at the anterior urethra.

The vagina becomes colonized soon after birth with corynebacteria, staphylococci, streptococci, *E. coli*, and a lactic acid bacterium historically named "Doderlein's bacillus" (*Lactobacillus acidophilus*). During reproductive life, from puberty to menopause, the vaginal epithelium contains glycogen due to the actions of circulating estrogens. Doderlein's bacillus predominates, being able to metabolize the glycogen to lactic acid. The lactic acid and other products of metabolism inhibit colonization by all except this lactobacillus and a select number of lactic acid bacteria. The resulting low pH of the vaginal epithelium prevents establishment by most other bacteria as well as the potentially-pathogenic yeast, *Candida albicans*. This is a striking example of the protective

effect of the normal bacterial flora for their human host.

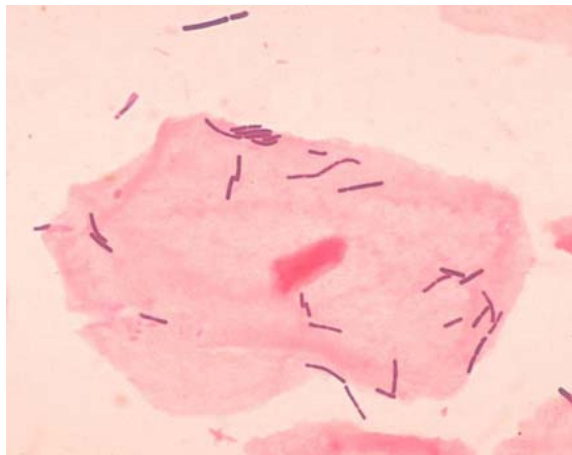


Figure 5. A *Lactobacillus* species, possibly Doderlein's bacillus, in association with a vaginal epithelial cell.

Normal Flora of the Oral Cavity The presence of nutrients, epithelial debris, and secretions makes the mouth a favorable habitat for a great variety of bacteria. Oral bacteria include streptococci, lactobacilli, staphylococci and corynebacteria, with a great number of anaerobes, especially bacteroides.

The mouth presents a succession of different ecological situations with age, and this corresponds with changes in the composition of the normal flora. At birth, the oral cavity is composed solely of the soft tissues of the lips, cheeks, tongue and palate, which are kept moist by the secretions of the salivary glands. At birth the oral cavity is sterile but rapidly becomes colonized from the environment, particularly from the mother in the first feeding. *Streptococcus salivarius* is dominant and may make up 98% of the total oral flora until the appearance of the teeth (6 - 9 months in humans). The eruption of the teeth during the first year leads to colonization by *S. mutans* and *S. sanguis*. These bacteria require a non-desquamating (non-epithelial) surface in order to colonize. They will persist as long as teeth remain. Other strains of streptococci adhere strongly to the gums and cheeks but not to the teeth. The creation of the gingival crevice area (supporting structures of the teeth) increases the habitat for the variety of anaerobic species found. The complexity of the oral flora continues to increase with time, and bacteroides and spirochetes colonize around puberty.

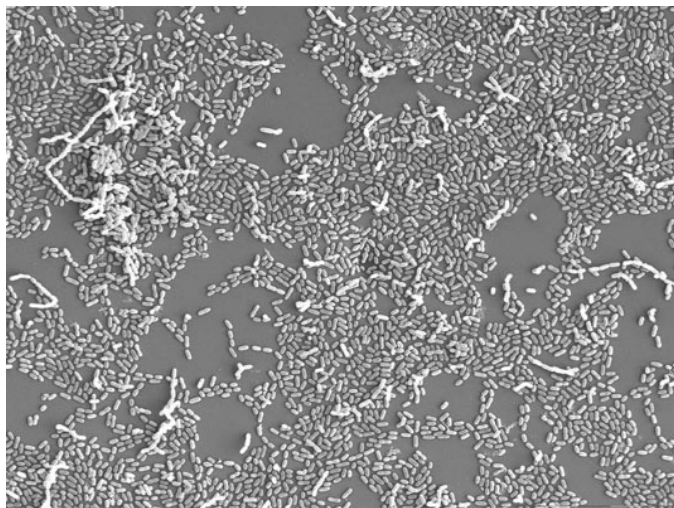


Figure 6. Various streptococci in a biofilm in the oral cavity.

The normal bacterial flora of the oral cavity clearly benefit from their host who provides nutrients and habitat. There may be benefits, as well, to the host. The

normal flora occupy available colonization sites which makes it more difficult for other microorganisms (nonindigenous species) to become established. Also, the oral flora contribute to host nutrition through the synthesis of vitamins, and they contribute to immunity by inducing low levels of circulating and secretory antibodies that may cross react with pathogens. Finally, the oral bacteria exert microbial antagonism against nonindigenous species by production of inhibitory substances such as fatty acids, peroxides and bacteriocins.

On the other hand, the oral flora are the usual cause of various oral diseases in humans, including abscesses, dental caries, gingivitis, and periodontal disease. If oral bacteria can gain entrance into deeper tissues, they may cause abscesses of alveolar bone, lung, brain, or the extremities. Such infections usually contain mixtures of bacteria with *Bacteroides melaninogenicus* often playing a dominant role. If oral streptococci are introduced into wounds created by dental manipulation or treatment, they may adhere to heart valves and initiate subacute bacterial endocarditis.



Figure 7. Colonies of *E. coli* growing on EMB agar.

Normal Flora of the Gastrointestinal Tract The bacterial flora of the gastrointestinal (GI) tract of animals has been studied more extensively than that of any other site. The composition differs between various animal species, and within an animal species. In humans, there are differences in the composition of the flora which are influenced by age, diet, cultural conditions, and the use of antibiotics. The latter greatly perturbs the composition of the intestinal flora.

In the upper GI tract of adult humans, the esophagus contains only the bacteria swallowed with saliva and food. Because of the high acidity of the gastric juice, very few bacteria (mainly acid-tolerant lactobacilli) can be cultured from the normal stomach. However, at least half the population in the United States is colonized by a pathogenic bacterium, *Helicobacter pylori*. Since the 1980s, this bacterium has been known to be the cause of gastric ulcers, and it is probably a cause of gastric and duodenal cancer as well. The Australian microbiologist, Barry Marshall, received the Nobel Prize in Physiology and Medicine in 2005, for demonstrating the relationship between *Helicobacter* and gastric ulcers.



Figure 8. *Helicobacter pylori*. ASM

The proximal small intestine has a relatively sparse Gram-positive flora, consisting mainly of lactobacilli and *Enterococcus faecalis*. This region has

about 10^5 - 10^7 bacteria per ml of fluid. The distal part of the small intestine contains greater numbers of bacteria (10^8 /ml) and additional species, including coliforms (*E. coli* and relatives) and *Bacteroides*, in addition to lactobacilli and enterococci.

The flora of the large intestine (colon) is qualitatively similar to that found in feces. Populations of bacteria in the colon reach levels of 10^{11} /ml feces. Coliforms become more prominent, and enterococci, clostridia and lactobacilli can be regularly found, but the predominant species are anaerobic *Bacteroides* and anaerobic lactic acid bacteria in the genus *Bifidobacterium* (*Bifidobacterium bifidum*). These organisms may outnumber *E. coli* by 1,000:1 to 10,000:1. Sometimes, significant numbers of anaerobic methanogens (up to 10^{10} /gm) may reside in the colon of humans. This is our only direct association with archaea as normal flora. The range of incidence of certain bacteria in the large intestine of humans is shown in Table 4 below.

Table 4. Bacteria found in the large intestine of humans.

BACTERIUM	RANGE OF INCIDENCE
<i>Bacteroides fragilis</i>	100
<i>Bacteroides melaninogenicus</i>	100
<i>Bacteroides oralis</i>	100
<i>Lactobacillus</i>	20-60
<i>Clostridium perfringens</i>	25-35
<i>Clostridium septicum</i>	5-25
<i>Clostridium tetani</i>	1-35
<i>Bifidobacterium bifidum</i>	30-70
<i>Staphylococcus aureus</i>	30-50
<i>Enterococcus faecalis</i>	100
<i>Escherichia coli</i>	100
<i>Salmonella enteritidis</i>	3-7
<i>Klebsiella sp.</i>	40-80
<i>Enterobacter sp.</i>	40-80
<i>Proteus mirabilis</i>	5-55
<i>Pseudomonas aeruginosa</i>	3-11
<i>Peptostreptococcus sp.</i>	?common
<i>Peptococcus sp.</i>	?common

At birth the entire intestinal tract is sterile, but bacteria enter with the first feed. The initial colonizing bacteria vary with the food source of the infant. In breast-fed infants, bifidobacteria account for more than 90% of the total intestinal bacteria. *Enterobacteriaceae* and enterococci are regularly present, but in low proportions, while bacteroides, staphylococci, lactobacilli and clostridia are practically absent. In bottle-fed infants, bifidobacteria are not predominant. When breast-fed infants are switched to a diet of cow's milk or solid food, bifidobacteria are progressively joined by enterics, bacteroides, enterococci lactobacilli and clostridia. Apparently, human milk contains a growth factor that enriches for growth of bifidobacteria, and these bacteria play an important role in preventing colonization of the infant intestinal tract by non indigenous or pathogenic species.



Figure 9. *Clostridium difficile*. Gram stain. The growth of "C. diff" in the intestinal tract is normally held in check by other members of the normal flora. When antibiotics given for other infections cause collateral damage to the normal intestinal flora, the clostridium may be able to "grow out" and produce a serious diarrheal syndrome called pseudomembranous colitis. This is an example of an "antibiotic induced diarrheal disease".

The composition of the flora of the gastrointestinal tract varies along the tract (at longitudinal levels) and across the tract (at horizontal levels) where certain bacteria attach to the gastrointestinal epithelium and others occur in the lumen. There is frequently a very close association between specific bacteria in the intestinal ecosystem and specific gut tissues or cells (evidence of tissue tropism and specific adherence). Gram-positive bacteria, such as the streptococci and lactobacilli, are thought to adhere to the gastrointestinal epithelium using polysaccharide capsules or cell wall teichoic acids to attach to specific receptors on the epithelial cells. Gram-negative bacteria such as the enterics may attach by means of specific fimbriae which bind to glycoproteins on the epithelial cell surface.

It is in the intestinal tract that we see the greatest effect of the bacterial flora on their host. This is due to their large mass and numbers. Bacteria in the human GI tract have been shown to produce vitamins and may otherwise contribute to nutrition and digestion. But their most important effects are in their ability to protect their host from establishment and infection by alien microbes and their ability to stimulate the development and the activity of the immunological tissues.

On the other hand, some of the bacteria in the colon (e.g. *Bacteroides*) have been shown to produce metabolites that are carcinogenic, and there may be an increased incidence of colon cancer associated with these bacteria. Alterations in the GI flora brought on by poor nutrition or perturbation with antibiotics can cause shifts in populations and colonization by nonresidents that leads to gastrointestinal disease.

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