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Skin microbiota: a source of disease or defence?

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Summary

Microbes found on the skin are usually regarded as pathogens, potential pathogens or innocuous symbiotic organisms. Advances in microbiology and immunology are revising our understanding of the molecular mechanisms of microbial virulence and the specific events involved in the host–microbe interaction. Current data contradict some historical classifications of cutaneous microbiota and suggest that these organisms may protect the host, defining them not as simple symbiotic microbes but rather as mutualistic. This review will summarize current information on bacterial skin flora including *Staphylococcus*, *Corynebacterium*, *Propionibacterium*, *Streptococcus* and *Pseudomonas*. Specifically, the review will discuss our current understanding of the cutaneous microbiota as well as shifting paradigms in the interpretation of the roles microbes play in skin health and disease.

Most scholarly reviews of skin microbiota concentrate on understanding the population structure of the flora inhabiting the skin, or how a subset of these microbes can become human pathogens. In the past decade, interdisciplinary collaborations at the interface of microbiology and immunology have greatly advanced our understanding of the host–symbiont and host–pathogen relationships.

There is surprisingly little literature that has systematically evaluated the influence of the resident cutaneous microflora in skin health. Primarily, studies have been conducted to analyse the types of microbes present on the skin and their pathogenic roles, with sparse attention given to other functions. The goal of the present review is to summarize current information on bacterial skin flora with special emphasis on new concepts that go beyond the narrow perception of these organisms as only potential agents of disease. Through an analysis of the limited current literature, we highlight a new hypothesis that suggests skin microbes directly benefit the host and only rarely exhibit pathogenicity. In this model, the delicate balance of the skin barrier and innate immunity combine to maintain healthy skin, and disturbance of this balance can predispose the host to a number of cutaneous infectious and inflammatory conditions.

Does the 'hygiene hypothesis' apply to the skin?

Several studies on noncutaneous epithelial surfaces have shown that the surface microflora can influence the host innate immune system (Fig. 1). Observations include how indigenous microbiota enable expansion and maintenance of the CD8 memory T cells in the lung,[1] how gut microflora influence inflammatory bowel disease,[2] and how lactobacilli in the intestine educate prenatal immune responses. These findings complement several studies that suggest disruption in microbial exposure early in development may lead to allergic disease.[3,4]

The 'hygiene hypothesis' stipulates that exposure of T regulatory cells to intestinal microbes generates a mature immune response that decreases reactions to self-antigens, as well as harmless antigens from nonpathogenic microbes.[5] Such a beneficial effect of microbiota in the gut has been used to support the use of probiotics. For example, *Lactobacillus acidophilus* secretes antibacterial substances that can prevent adhesion and invasion of enteroinvasive pathogens in experimental models such as cultured intestinal Caco-2 cells.[6–8] Furthermore, oral administration of various probiotics has been associated with reduced colorectal cancer and active ulcerative colitis in some clinical studies.[9,10] Although these approaches remain controversial, the benefits of resident gut microbiota are being actively explored through a variety of trial therapeutics and disease prevention measures.

Unlike the intestine, the role of microbes on the skin surface has not been well studied. An incomplete understanding of the fundamental biology of cutaneous microflora is the result of the limited research efforts to date. Existing clinical studies have provided invaluable information about the abundance and types of microbes on the skin, but fail to address their functions.[11–15] In light of symbiotic relationships of microbial mutualism and commensalism demonstrated as critical to human health in studies of gut microbiota, a need exists to expand this research in skin.

To begin this discussion it is helpful to outline the potential systems for symbiosis between skin flora and the host. These

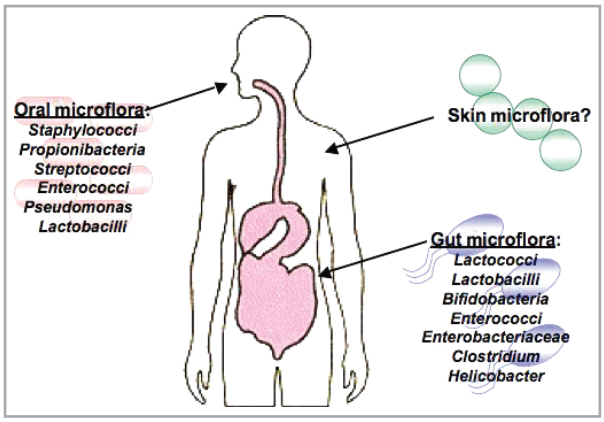

Fig 1. Resident microflora that are beneficial to the host. The gut and mouth contain many species of microflora. Microbiota in the intestines protect the host by educating the immune system and preventing pathogenic infections. These microflora benefit the systemic immune system of the host and positively affect other organs, such as the lung. In the mouth, over 500 species of bacteria protect the mucosa from infections by preventing colonization of dangerous yeasts and other bacteria. It is yet unclear if the microflora of the skin play a similar role in protecting the host. Image from http://www.giconsults.com with permission.

can fall into three categories: parasitism, commensalism or mutualism (Fig. 2). Commonly, a symbiotic relationship is understood to be one in which both organisms benefit each other. This perception is not correct. Symbiotic relationships can exist in which only one organism benefits while the other is harmed (parasitism, predation, ammensalism and competition), one organism benefits and no harm occurs to the other (commensalism) or both find benefit (mutualism and protocooperation). Microbes found on the surface of the skin that are only very infrequently associated with disease are typically referred to as commensal. This term implies that the microbe lives in peaceful coexistence with the host while benefiting

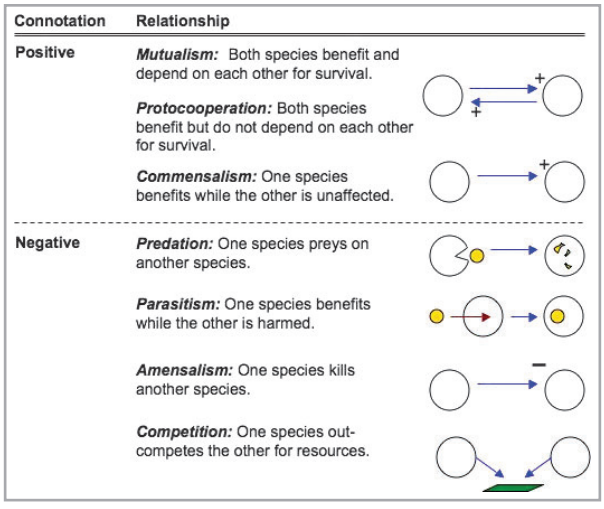

Fig 2. Types of symbiotic relationships.

from the sheltered ecological niche. An example of such a microbe is the Gram-positive bacterium *Staphylococcus epidermidis*. Emerging evidence to be discussed below indicates that this species and other so-called skin commensals may play an active role in host defence, such that they may represent, in fact, mutuals. One must recognize, however, that distinct categorizations such as parasitic, commensalistic or mutualistic may be oversimplified as the same microbe may take on different roles at different times. Understanding this premise, and the factors that dictate the type of microbe–host symbiosis, could lead to effective treatment and prevention strategies against skin infection.

It is also important to recognize that the distinction between what we consider to be harmless flora or a pathogenic agent often lies in the skin's capacity to resist infection, and not the inherent properties of the microbe. Host cutaneous defence occurs through the combined action of a large variety of complementary systems. These include the physical barrier, a hostile surface pH, and the active synthesis of gene-encoded host defence molecules such as antimicrobial peptides, proteases, lysozymes and cytokines and chemokines that serve as activators of the cellular and adaptive immune responses. Virulence factors expressed by a microbe may enable it to avoid the host defence programme, but it is ultimately the sum effectiveness of this host response that determines if a microbe is a commensal (or mutual) organism or a dangerous pathogen for the host.

In the following review we focus on literature that describes the skin microbial flora. Although resident microflora on the skin include bacteria, viruses and many types of fungi, we will limit and focus the discussion by concentrating specifically on bacteria. The number of bacteria identified from human skin has expanded significantly, and will probably continue to increase as genotyping techniques advance.[11,12] Some of the best-studied long-term and transient bacterial residents isolated from the skin include those from the genera *Staphylococcus*, *Corynebacterium*, *Propionibacterium*, *Streptococcus* and *Pseudomonas* (Table 1). Unfortunately, little is known about many of the other bacterial species on skin due to their low abundance and apparent harmlessness.[11] Therefore, we will focus on those species best studied.

Staphylococcus epidermidis

Staphylococcus epidermidis, the most common clinical isolate of the cutaneous microbiota, is a Gram-positive coccus found in clusters. As a major inhabitant of the skin and mucosa it is thought that *S. epidermidis* comprises greater than 90% of the aerobic resident flora. Small white or beige colonies (1–2 mm in diameter), desferrioxamine sensitivity, lack of trehalose production from acid and coagulase-negative characteristics easily distinguish *S. epidermidis* from other bacteria in the same genus.

Despite its generally innocuous nature, over the past 20 years *S. epidermidis* has emerged as a frequent cause of nosocomial infections. Several extrinsic factors contribute to

Table 1 Frequency of microbial colonization through clinical and molecular detection methods[11,12]

Organism	Clinical isolate observations	Molecular detection
Staphylococcus epidermidis	Common, occasionally pathogenic	Frequent
Staphylococcus aureus	Infrequent, usually pathogenic	Frequent
Staphylococcus warneri	Infrequent, occasionally pathogenic	Occasional
Streptococcus pyogenes	Infrequent, usually pathogenic	Occasional
Streptococcus mitis	Frequent, occasionally pathogenic	Frequent
Propionibacterium acnes	Frequent, occasionally pathogenic	Frequent
Corynebacterium spp.	Frequent, occasionally pathogenic	Frequent
Acinetobacter johnsonii	Frequent, occasionally pathogenic	Frequent
Pseudomonas aeruginosa	Infrequent, occasionally pathogenic	Frequent

the conversion of *S. epidermidis* from a member of the resident microflora to an infectious agent. The bacteria primarily infect compromised patients including drug abusers, those on immunosuppressive therapy, patients with acquired immune deficiency syndrome (AIDS), premature neonates and patients with an indwelling device.[16] The major ports of entry for these infections are foreign bodies such as catheters and implants.[17] After entry, virulent strains of *S. epidermidis* form biofilms that partially shield the dividing bacteria from the host's immune system and exogenous antibiotics. Once systemic, *S. epidermidis* can cause sepsis, native valve endocarditis, or other subacute or chronic conditions in the patient risk groups outlined above.[18,19] A major complicating factor in the management of *S. epidermidis* blood infections is the inadequacy of many common antibiotic treatments. Biofilm formation reduces the access of antibiotics to the bacteria and often necessitates the removal of indwelling devices.[20]

In addition to catheter infections, patients with necrotic tumour masses from ulcerated advanced squamous cell carcinomas, head and neck carcinomas, breast carcinomas and sarcomas have a high propensity for infection by *S. epidermidis*. Also, myelosuppressive chemotherapy renders patients neutropenic, thereby increasing the risk of septicaemia. As abscesses infrequently form in neutropenic patients, *S. epidermidis* infections present as spreading cellulitis, associated with septicaemia.[21] These specific skin infections caused by *S. epidermidis* require a predisposed host and do not reflect the typical bacteria–host interaction. In fact, *S. epidermidis* resides benignly, if not as a mutual on the skin's surface, with infection arising only in conjunction with specific host predisposition.

Medical treatments for *S. epidermidis* infection range from systemic antibiotics to device modification and removal. Current research suggests that bacterial attachment to materials is dependent on the physicochemical properties of the bacterial and plastic surfaces.[22–24] In particular, *S. epidermidis* has been shown to adhere to highly hydrophobic surfaces, while detergent-like substances and electric currents reduce attachment to the surfaces of the prosthetics or catheters.[24,25] The autolysin protein AtlE, which possesses a vitronectin-binding domain, has been identified as a probable attachment factor. When the *atlE* gene is disrupted, the resulting *S. epidermidis* mutant exhibits reduced surface hydrophobicity and impaired attachment to a polystyrene surface.[26] Other adhesion factors belong to the MSCRAMM (microbial surface components recognizing adhesive matrix molecules) family of surface-anchored proteins, including fibrinogen-binding protein Fbe.[27,28] Other specific *S. epidermidis* proteins that may be involved in attachment to plastic-coated materials include Aas1, Aas2, SdrF and AAP (accumulation-associated protein).[29,30]

Increased virulence of *S. epidermidis* has also been attributed to a process known as intercellular adhesion (Fig. 3). Once the bacteria have gained entry, through a catheter for example, *S. epidermidis* produces factors responsible for growth, immune evasion and adhesion. In particular, polysaccharide intercellular adhesion (PIA) and poly-N-succinyl-glucosamine (PNSG), both encoded by the *ica* locus, mediate intercellular adhesion and have been implicated in virulence.[31,32] Although these studies are very interesting, only a fraction of the *S. epidermidis* strains contains these genes, with the majority of the positive strains isolated from catheter infections and not from healthy skin.[33] Other virulence factors are thought to be regulated by the *agr* (accessory gene regulator), *sar* and *sigB* loci. In a complex regulatory system, these three loci are involved in quorum-sensing and potentially biofilm (slime capsule) formation.[22,34] The studies on the *agr* system, although fascinating, fail to address how the individual components under regulation, themselves affect virulence. In addition, the *agr* locus does not solely regulate virulence factors, but other genes involved in the bacterium's physiology. The locus, also found in nonpathogenic staphylococci strains, has yet to be investigated under 'mutual' conditions on the skin's surface. The understanding and inhibition of biofilms is of great interest and may increase the effectiveness of antibiotics against *S. epidermidis* catheter infections or sepsis. In addition, anti-PIA antibodies are being investigated in biofilm formation prevention.[35] Interferon (IFN)-γ therapy, in addition to antibodies against specific *S. epidermidis* surface-binding proteins, has also proven effective in preventing catheter adhesion.[36]

Recent studies can be interpreted to suggest that *S. epidermidis* is a mutualistic organism, much like the bacteria of the gut. Many strains of *S. epidermidis* produce lantibiotics, which are lanthionine-containing antibacterial peptides, also known as bacteriocins (Fig. 3). Among the several identified

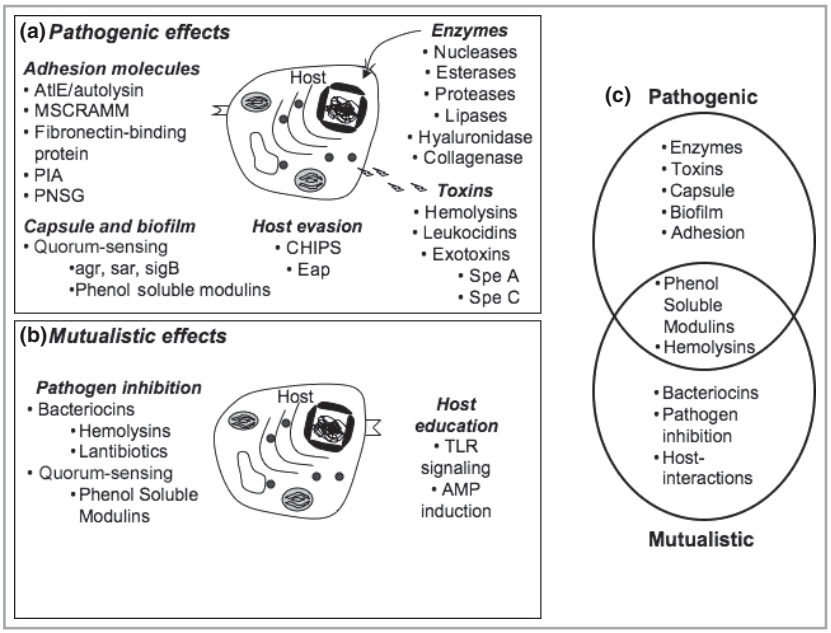

Fig 3. Staphylococci are pathogenic and mutualistic. (a) Virulence factors and molecules produced by staphylococci that aid in pathogenesis. (b) Staphylococci act mutually by inhibiting pathogens and priming the immune response. (c) Molecules from staphylococci that have dual functions.

bacteriocins are epidermin, epilancin K7, epilancin 15X, Pep5 and staphylococcin 1580.[37–39] Additional antimicrobial peptides on the surface of the skin have recently been identified as originating from *S. epidermidis*.[40] The identification of these peptides suggests the presence of intra- and interspecies competition, yet their direct regulatory, cytotoxic and mechanistic roles have yet to be addressed. Although *S. epidermidis* rarely damages the keratinocytes in the epidermis, the bacteria produce peptides toxic to other organisms, such as *S. aureus* and group A *Streptococcus* (GAS, *S. pyogenes*). The host epidermis permits *S. epidermidis* growth as the bacterium may provide an added level of protection against certain common pathogens, making the host–bacterium relationship one of mutualism. Protection afforded by *S. epidermidis* is further demonstrated in recent studies on pheromone cross-inhibition. The *agr* locus produces modified peptide pheromones, which subsequently affect the *agr* systems of various species by activating self and inhibiting nonself *agr* loci.[41,42] The activation of *agr* signals to the bacterium that an appropriate density is reached and leads to a downregulation of virulence factors.[43] Quorum-sensing decreases colonization-promoting factors and increases pheromones such as the phenol soluble modulin γ (δ-haemolysin, δ-toxin or δ-lysin).[41] These pheromones affect the *agr* signalling of competing bacteria (such as *S. aureus*) and ultimately lead to colonization inhibition.[42] Pheromones are being investigated for their therapeutic potential, such as δ-toxin, which reduces *S. aureus* attachment to polymer surfaces.[44] In contrast, δ-toxin has also been labelled a virulence factor. Thus far, no studies have examined the consequences of eliminating δ-toxin production by targeted mutagenesis to prove conclusively the beneficial or detrimental effects of the peptide.

Staphylococcus epidermidis may also promote the integrity of cutaneous defence through elicitation of host immune responses. Our own preliminary data suggest that *S. epidermidis* plays an additional protective role by influencing the innate immune response of keratinocytes through Toll-like receptor (TLR) signalling (Fig. 3). TLRs are pattern-recognition receptors that specifically recognize molecules produced from pathogens collectively known as pathogen-associated molecular patterns. This education of the skin's immune system may play an important role in defence against harmful pathogens. Through cellular 'priming', keratinocytes are able to respond more effectively and efficiently to pathogenic insults. New unpublished data suggest that *S. epidermidis* present on the skin amplifies the keratinocyte response to pathogens.

The removal of *S. epidermidis* (i.e. through overuse of topical antibiotics) may be detrimental to the host for two reasons. Firstly, removing *S. epidermidis* eliminates the bacterium's endogenous antimicrobial peptides, allowing potentially pathogenic organisms to colonize the skin more effectively. Secondly, without bacterial priming of the skin, the host may be less efficient in warding off infection. In this light, *S. epidermidis* may be thought of as a mutual, thus, adding to the human innate immune system. Understanding this interaction may advance our knowledge of cutaneous diseases and infectious disease susceptibility.

Staphylococcus aureus

Characterized by circular, golden-yellow colonies, and β-haemolysis of blood agar, the coagulase-positive *S. aureus* is a leading human pathogen. *Staphylococcus aureus* clinical disease ranges from minor and self-limited skin infections to invasive and life-threatening diseases. *Staphylococcus aureus* skin infections include impetigo, folliculitis, furuncles and subcutaneous abscesses, and through the production of exfoliative toxins, staphylococcal scalded skin syndrome.[45] The bacterium can

also cause serious invasive infections such as septic arthritis, osteomyelitis, pneumonia, meningitis, septicaemia and endocarditis.[45–47] Elaboration of superantigen toxins can trigger staphylococcal toxic shock syndrome.

Particular conditions predispose the skin to *S. aureus* infections, such as atopic dermatitis (AD). While viruses (e.g. herpes simplex type 1 virus and human papillomavirus) and fungi (e.g. *Trichophyton rubrum*) also opportunistically infect lesional and nonlesional AD skin, *S. aureus* is by far the most common superinfecting agent.[48] Like *S. epidermidis*, *S. aureus* is a frequent cause of infection in catheterized patients.[49]

At present, *S. aureus* infections are treated with antibiotics and with the removal of infected implants as necessary.[50] Unfortunately, there has been a dramatic rise in antibiotic-resistant strains, including methicillin-resistant *S. aureus* (MRSA) in both hospital and community settings, and even documented reports of vancomycin-intermediate and vancomycin-resistant *S. aureus* strains (VISA and VRSA).[46,51]

The emergence of methicillin resistance is due to the acquisition of a transferable DNA element called staphylococcal cassette chromosome *mec* (SCC*mec*), a cassette (types I–V) carrying the *mec*A gene, encoding penicillin-binding protein (PBP) 2a.[52–54] Through site-specific recombination, the DNA element integrates into the genome. Normally, β-lactam antibiotics bind to the PBPs in the cell wall, disrupt peptidoglycan layer synthesis and kill the bacterium. However, β-lactam antibiotics cannot bind to PBP2a, allowing a bacterium containing the *mec*A gene to survive β-lactam killing.[54] Plasmids have also been found to confer *Staphylococcus* resistance to kanamycin, tobramycin, bleomycin, tetracycline and vancomycin.[55,56]

Staphylococcus aureus expresses many virulence factors, both secreted and cell surface associated, that contribute to evasion (Fig. 3). *Staphylococcus aureus* secretes the chemotaxis inhibitory protein of staphylococci (CHIPS) which binds to the formyl peptide receptor and C5a receptor on neutrophils, thereby interfering with neutrophil chemotaxis.[57] Eap (also called major histocompatibility class II analogue protein Map) adheres to the intracellular adhesion molecule-1 on neutrophils, and prevents leucocyte adhesion and extravasation.[58] *Staphylococcus aureus* also secretes an arsenal of toxins that damage host cells. Such toxins include superantigens (enterotoxins A–E, toxic shock syndrome toxin-1, ETA, B and D) and cytoxins [α-, β-, δ-, γ-haemolysin, Panton–Valentine leucocidin (PVL), leucocidin E–D, *S. aureus* exotoxin].[45,46,59] Although PVL is epidemiologically associated with MRSA infections, its contribution to virulence is under dispute. Expression of PVL in a strain of *S. aureus*, previously not containing the toxin, increased virulence in a murine pneumonia model. Yet, the isogenic deletion of PVL in the MRSA clones USA300 and USA400 showed no reduction in virulence in other infection models. Extracellular enzymes secreted by *S. aureus* that may contribute to tissue damage include proteases, lipases, hyaluronidase and collagenase.[46,60] *Staphylococcus aureus* α-haemolysis secretion leads to pore formation in target cell membranes and subsequent activation of nuclear factor (NF)-κB inflammatory pathway.[61]

Staphylococcus aureus is relatively resistant to killing by cationic antimicrobial peptides produced by host epithelial cells and phagocytes. One key underlying mechanism for this resistance involves alterations in the charge of the bacterial cell surface. The Dlt protein causes D-alanine substitutions in the ribitol teichoic acids and lipoteichoic acids of the cell wall, slightly neutralizing the negatively charged cell surface to which cationic peptides usually bind.[62,63] The MprF enyme adds L-lysine to phosphatidyl glycerol, similarly neutralizing the negatively charged cell surface.[64] Mutants with defects in Dlt and MprF have been shown to be markedly more susceptible to human defensins.[62,65] The staphylokinase of *S. aureus* binds and protects against defensins, while aureolysin cleaves human cathelicidin LL-37, offering further protection.[66,67]

Staphylococcus aureus resists phagocyte killing at a number of different levels. Effective opsonization of the bacterium is inhibited by the polysaccharide capsule, the surface expressed clumping factor and protein A. The eponymous golden carotenoid pigment protects *S. aureus* against neutrophil killing *in vitro* by scavenging oxygen free radicals.[68]

Despite the usual classification of *S. aureus* as a transient pathogen, it may be better considered a normal component of the nasal microflora.[69,70] It is estimated that 86·9 million people (32·4% of the population) are colonized with *S. aureus*.[71] Other studies have suggested that among the population, 20% are persistently colonized, 60% of the population intermittently carry the bacteria and 20% are never colonized.[69] Colonization by *S. aureus* is certainly not synonymous with infection. Indeed, like *S. epidermidis*, healthy individuals rarely contract invasive infections caused by *S. aureus*.[54] *Staphylococcus aureus* found on healthy human skin and in nasal passages are in effect acting as a commensal, rather than a pathogen. Certain strains of *S. aureus* have been shown to produce bacteriocins such as staphylococcin 462, a peptide responsible for growth inhibition of other *S. aureus* strains.[72] Although the production of this bacteriocin probably aids in bacterial competition, further investigations, using mutagenesis and an *in vivo* model, would be helpful to illustrate the putative beneficial role of this organism. As *S. aureus* has generally been regarded as a pathogen, research has focused on its virulence factors, thereby minimizing studies about its role as an inhabitant of the normal flora.

Corynebacterium diphtheriae

Coryneforms are Gram-positive, nonmotile, facultative anaerobic actinobacteria. These common members of the skin flora are divided into two species: *C. diphtheriae* and nondiphtheriae corynebacteria (diphtheroids). *Corynebacterium diphtheriae* is categorized by biotype: *gravis*, *mitis*, *belfanti* and *intermedius*, as defined by colony morphology and biochemical tests. *Corynebacterium diphtheriae* is further divided into toxigenic and nontoxigenic strains. Toxinogenic *C. diphtheriae* produce the highly lethal diphtheria toxin, which can induce fatal global toxaemia. Nontoxinogenic (nontoxin-producing) *C. diphtheriae* are capable of producing septicaemia, septic arthritis, endocarditis

and osteomyelitis.[73–75] Both nontoxigenic and toxigenic *C. diphtheriae* can be isolated from cutaneous ulcers of alcoholics, intravenous drug users and from hosts with poor hygiene standards, such as in endemic outbreaks in areas of low socioeconomic status.[76,77] Although immunization has successfully reduced the prevalence of diphtheria in most developed countries, the disease has surfaced in individuals impacted by socioeconomic deprivation, as well as nonimmunized and partially immunized individuals.[78]

Corynebacterium diphtheriae virulence is mainly attributed to diphtheria toxin, a 62-kDa exotoxin. The crystal structure shows a disulphide-linked dimer with a catalytic, transmembrane and receptor-binding domain.[79] Invasion of the exotoxin is a complex series of events that involves translocation into the cytosol and results in halted protein synthesis.

Corynebacterium jeikeium

The nondiphtheriae corynebacteria, diphtheroids, are a diverse group, containing 17 different species, of which not all are present on human skin. Several species commonly colonize cattle, while others, such as *C. jeikeium* (formerly known as CDC group JK), are normal inhabitants of our epithelium. Although many diphtheroids are found on human skin, *C. jeikeium* is the most frequently recovered and medically relevant member of the group. In the last few years, *Corynebacterium* diphtheroids have gained interest due to the increasing number of publications on nosocomial infections. *Corynebacterium jeikeium* causes infections in immune-compromised patients, in conjunction with underlying malignancies, on implanted medical devices and in skin-barrier defects.[80] In addition, *C. jeikeium* has been suggested as the cause of papular eruption with histological features of botryomycosis.[81] Once the bacterium has penetrated the skin's barrier, the bacterium can cause sepsis or endocarditis.[82]

Corynebacterium jeikeium treatment varies from other Gram-positive organisms because it is resistant to multiple antibiotics. However, it remains sensitive to glycopeptides including vancomycin or teicoplanin. *Corynebacterium jeikeium* antibiotic resistance stems from a variety of factors, ranging from the acquisition of antibiotic-resistant genes to the polyketide synthesis of FadD enzymes and subsequent corynomycolic acid in the cell envelope. Iron and manganese acquisition by *C. jeikeium* may contribute to virulence. Siderophores produced by the bacterium allow for efficient iron sequestration in the host. Manganese acquisition inhibits Mg-dependent superoxide dismutase, protecting the bacterium from superoxide production by the host or competing bacteria.[83] There is much evidence that oxygen radicals produced by the host are a mechanism for defence against pathogens. In contrast, it has rarely been investigated whether or not production or scavenging of reactive oxygen species reflects interspecies competition for an ecological niche on the skin epithelium.

The *C. jeikeium* genome sequence also reveals numerous putative proteins with homology to adhesion and invasion factors from other Gram-positive pathogens.[84] These include SurA and SurB (surface proteins similar to those of GAS and group B *Streptococcus*), Sap proteins (surface-anchored proteins that resemble *C. diphtheriae* factors used in pili formation), CbpA protein (belongs to the MSCRAMM family) and NanA protein (similar to neuraminidases from *Streptococcus pneumoniae*).[85–88]

Corynebacterium jeikeium is considered part of the normal skin flora, similar to *S. epidermidis*. This bacterium species resides on the skin of most humans and is commonly cultured from hospitalized patients.[80,89] In particular, colonization is seen in axillary, inguinal and perineal areas.[90] Almost all infections caused by *C. jeikeium* are nosocomial and occur in patients with pre-existing ailments. As with *S. epidermidis*, *C. jeikeium* is ubiquitous and largely innocuous, illustrating that the bacterium is commensal. In fact, *C. jeikeium* may offer epidermal protection, bolstering the argument that cutaneous microflora are mutualistic. Manganese acquisition effectively allows the bacteria to safeguard themselves from superoxide radicals. The enzyme superoxide dismutase may also function to prevent oxidative damage to epidermal tissue, a potential means by which bacteria protect the host. Moreover, iron and manganese are critical for organism survival, both pathogenic and nonpathogenic. The act of scavenging these elements may prevent colonization by other microbes. Finally, *C. jeikeium* produces bacteriocin-like compounds used to ward off potential pathogens and competitors. Lacticidin Q produced by *Lactococcus lactis* has a 66% homology to AucA, a hypothetical protein encoded in the *C. jeikeium* plasmid pA501.[91] AucA has yet to be investigated for its bacteriocin activity both *in vivo* and *in vitro*. Most likely, *C. jeikeium* produces other bacteriocins not yet identified. As the study of virulence factors dominates the fields of microbiology and infectious disease, little is known about the potential mutualism of *C. jeikeium*. Given the prevalence of skin colonization, the relative rarity of *C. jeikeium* pathogenesis and the yet unexplored benefits of the bacterium, *C. jeikeium* probably lives mutually on the skin.

Propionibacterium acnes

Commonly touted as the cause of acne vulgaris, *P. acnes* is an aerotolerant anaerobic, Gram-positive bacillus that produces propionic acid, as a metabolic byproduct. This bacterium resides in the sebaceous glands, derives energy from the fatty acids of the sebum, and is susceptible to ultraviolet radiation due to the presence of endogenous porphyrins.[92]

Propionibacterium acnes is implicated in a variety of manifestations such as folliculitis, sarcoidosis and systemic infections resulting in endocarditis.[93,94] Occasionally, *P. acnes* causes SAPHO syndrome (synovitis, acne, pustulosis, hyperostosis and osteitis), a chronic, inflammatory, systemic infection.[95] In the sebaceous gland, *P. acnes* produces free fatty acids as a result of triglyceride metabolism. These byproducts can irritate the follicular wall and induce inflammation through neutrophil chemotaxis to the site of residence.[96] Inflammation due to host tissue damage or production of immunogenic factors by *P. acnes* subsequently leads to cutaneous infections (Fig. 4).[97,98]

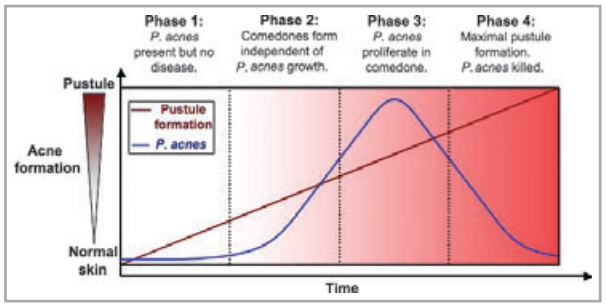

Fig 4. Hypothetical model for relationship between *Propionibacterium acnes* and pustule formation. The graph depicts pustule formation and P. *acnes* growth over time. In phase 1, P. *acnes* is present, but comedones are not. In phase 2, comedo formation begins, independently of P. *acnes* growth; P. *acnes* begins to proliferate only after comedo forms. In phase 3, P. *acnes* proliferates in trapped comedo. In phase 4, P. *acnes* is killed by an inflammatory response. Disease and pustule formation is maximal despite eradication of P. *acnes*. This model illustrates that acne formation is not triggered by the ubiquitous and resident P. *acnes* and at the maximal disease stage, P. *acnes* has already been eliminated.

The most well-known ailment associated with P. *acnes* is the skin condition known as acne vulgaris, affecting up to 80% of adolescents in the U.S.A.[99] Several factors are thought to contribute to an individual's susceptibility. Androgens, medications (including steroids and oral contraceptives), the keratinization pattern of the hair follicle, stress and genetic factors all contribute to acne predisposition.[100,101] Clinically, patients present with distended, inflamed or scarred pilosebaceous units. Noninflammatory acne lesions form either open or closed comedones, while inflammatory acne lesions develop into papules, pustules, nodules or cysts.

Like *S. epidermidis*, P. *acnes* causes many postoperative infections. Prosthetic joints, catheters and heart valves transport the cutaneous microflora into the body.[102] Sepsis and endocarditis result from systemic infections.[103] Another common port of entry for P. *acnes* is through ocular injury or operation. *Propionibacterium acnes* causes endophthalmitis (inflammation of the interior of the eye causing blindness) weeks or months after trauma or eye surgery. The infection delay probably results from the low-virulence phenotype of P. *acnes*.[104]

Treatment for P. *acnes* infections varies depending on the presentation of disease. For acne, various medications and prevention strategies are currently employed. Benzoyl peroxide and topical antibiotics are bactericidal and bacteriostatic, respectively, against P. *acnes* infections. Topical retinoids such as tretinoin and adapalene reduce inflammation of follicular keratinocytes and may interfere with TLR2 and P. *acnes* interactions.[105] A regimen of oral antibiotics is given to individuals with moderate acne. In addition to reducing the number of P. *acnes* on the skin, antibiotics provide an anti-inflammatory effect.[106] Oral isotretinoin, a compound related to retinol (vitamin A), is currently the only treatment that leads to permanent remission.[107] The cutaneous effects of isotretinoin and other vitamin A derivatives are currently being researched. Rare systemic infections, including endocarditis, which can develop postoperatively or in immune-compromised patients, have been treated effectively with penicillin or vancomycin.[108–110]

Proposed P. *acnes* virulence factors include enzymes that aid in adherence and colonization of the follicle. In particular, hyaluronate lyase degrades hyaluronan in the extracellular matrix, potentially contributing to adherence and invasion.[111] The genome of P. *acnes* also encodes sialidases and endoglycoceramidases putatively involved in host tissue degradation.[99] *Propionibacterium acnes* also produces biofilms, limiting antibiotic access to the site of infection.[96]

Studies have shown that TLRs play an important role in inflammation associated with P. *acnes* infection. *Propionibacterium acnes* induces expression of TLR2 and TLR4 in keratinocytes,[112] and the bacterium can induce interleukin (IL)-6 release from $TLR1^{-/-}$, $TLR6^{-/-}$ and wild-type murine macrophages but not from $TLR2^{-/-}$ murine macrophages.[113] These combined data show that P. *acnes* interacts with TLR2 to induce cell activation. *Propionibacterium acnes* infection also stimulates production of pro-inflammatory cytokines such as IL-8 (involved in neutrophil chemotaxis), tumour necrosis factor-α, IL-1β and IL-12.[114,115]

The major factors contributing to acne are the hypercornification of the outer root sheath and the pilosebaceous duct, increased sebum production and, potentially, the overgrowth of P. *acnes*. Some have suggested that P. *acnes* involvement in inflammation is relatively minor and the abnormal bacterial growth in the sebaceous ducts may be a side-effect of inflammation rather than a root cause (Fig. 4). Although the bacterium is commonly associated with acne pathogenesis, healthy and acne-prone patients alike are colonized.[11] Studies have also shown that antibiotics primarily reduce inflammation and only secondarily inhibit P. *acnes* growth.[106] These data suggest that P. *acnes* has a low pathogenic potential with a minor role in the development of acne. The prevalence of P. *acnes* on healthy skin suggests a relationship of commensalism or mutualism rather than parasitism.

Together, the avirulence of P. *acnes* and the studies showing a beneficial effect on the host suggest that the bacterium is a mutual. In one study, mice, immunized with heat-killed P. *acnes* and subsequently challenged with lipopolysaccharides, showed increased TLR4 sensitivity and MD-2 upregulation.[116] The authors suggested that the hyperelevated cytokine levels indicated a detrimental effect by P. *acnes in vivo*. The data, although interesting, do not identify the P. *acnes* molecule associated with the effect. Alternatively, the data may suggest that P. *acnes* enables host cells to respond effectively to a pathogenic insult, in which case P. *acnes* would serve a protective role. It is probable that a similar response could be seen with injections of other types of bacteria but these results serve to highlight a potential mechanism for mutualism. Propionibacteria have also been shown to produce bacteriocins or bacteriocin-like compounds. These include propionicin PLG-1, jenseniin G, propionicin SM1, SM2, T1[117,118] and acnecin,[119] with activity against several strains of propionibacteria, several lactic acid bacteria, some Gram-negative bacteria, yeasts and moulds.

Little is known about the production or role of bacteriocins in P. *acnes* oral or cutaneous survival. These bacteriocins may potentially secure the pilosebaceous niche and protect the duct from other pathogenic inhabitants. By depleting P. *acnes* through antibiotic use, the host could theoretically increase susceptibility to infection by pathogens. The supply of nutrient-rich sebum in exchange for protection against other microbes may be one mechanism by which P. *acnes* acts mutualistically.

Group A *Streptococcus* (*S. pyogenes*)

Known for causing superficial infections as well as invasive diseases, GAS forms chains of Gram-positive cocci. The bacterium is β-haemolytic on blood agar and catalase-negative. GAS strains are further subclassified by their M-protein and T-antigen serotype.

The types of M protein and T antigen expressed indicate the strain's potential to cause superficial or invasive disease. GAS infections are diverse in their presentation, with 'strep throat', a mucosal infection and impetigo of the skin being most common. Superficial GAS infections differ with age and cutaneous morphology. Nonbullous impetigo (pyoderma) prevails in infants and children. The postinfectious nonpyogenic syndrome rheumatic fever can follow throat infection and poststreptococcal glomerulonephritis can follow either skin or throat infection.[120] GAS is also associated with deeper-seated skin infections such as cellulitis and erysipelas, infections of connective tissue and underlying adipose tissue, respectively. These types of disease occur frequently in the elderly and in individuals residing in densely populated areas.[121] Bacterial infections generally occur in association with diabetes, alcoholism, immune deficiency, skin ulcers and trauma. The invasive necrotizing fasciitis, or 'flesh-eating' disease, carries a high degree of morbidity and mortality and is frequently complicated by streptococcal toxic shock syndrome. GAS can also cause infections in many other organs including lung, bone and joint, muscle and heart valve, essentially mimicking the disease spectrum of *S. aureus*.

GAS disease treatment depends on location, severity and type of infection. Superficial infections such as impetigo are easily eradicated with topical antibacterial ointments such as mupirocin (Bactroban®) or fusidic acid (Fucidin®). More extensive skin infections are treated with oral antibiotics such as penicillin, erythromycin or clindamycin.[122] Invasive infections require systemic antibiotics and intensive support; surgical debridement of devitalized tissue is critical to management of necrotizing fasciitis.[123]

For the most part, GAS is sensitive to β-lactams (penicillin), but in severe infections the antibiotic fails due to the large inoculum of bacteria and the ability of GAS to downregulate PBPs during stationary growth phase.[124] In severe systemic infections, adjunctive therapy with intravenous gammaglobulin may provide neutralizing antibodies against streptococcal superantigens to prevent development of streptococcal toxic shock syndrome.[125]

GAS is capable of subverting the host immune response in a variety of ways. Inhibiting phagocyte recruitment, GAS expresses the proteases ScpC or SpyCEP, that cleave and inactivate the neutrophil chemokine IL-8.[126,127] GAS also produces a C5a peptidase that cleaves and inactivates this chemoattractant byproduct of the host complement cascade.[128,129] Invasive strains of GAS produce DNases (also known as streptodornases) that degrade the chromatin-based neutrophil extracellular traps (NETs) employed by the host innate immune system to ensnare circulating bacteria.[130,131] Targeted mutagenesis revealed that DNase Sda I promotes GAS NET degradation and neutrophil-killing resistance both *in vivo* and *in vitro*. Hyaluronidase, secreted by GAS, allows for bacterial migration through the host extracellular matrix.[132] The surface-expressed streptokinase sequesters and activates host plasminogen on the bacterial surface, effectively coating the bacteria with plasmin that promotes tissue spread. The pore-forming toxins streptolysin O (SLO) and streptolysin S are broadly cytolytic against host cells including phagocytes, as shown through targeted mutagenesis. A variety of streptococcal superantigens, e.g. SpeA, SpeC and SmeZ, can promote rapid clonal T-cell expansion and trigger toxic shock-like syndrome.[133] GAS causes disease in compromised and healthy individuals alike, illustrative of a parasitic symbiosis between GAS and the host.

Potential host benefits of GAS may be deciphered in certain interactions of GAS with host epithelium. For example, several studies have shown that SLO promotes wound healing *in vitro* through stimulating keratinocyte migration.[134] Sublytic concentrations of SLO may induce CD44 expression, potentially modulating collagen, hyaluronate and other extracellular matrix components in mouse skin. Both the tight skin mouse (Tsk) model of scleroderma and the bleomycin-induced mouse skin fibrosis model showed decreased levels of hydroxyproline after treatment with SLO.[135]

Plasminogen activation in the epidermis leads to keratinocyte chemotaxis, suppression of cell proliferation, and potential re-epithelialization of wounds.[136] Also, streptokinase is now being used clinically for therapeutic fibrinolysis.[137,138] Thus, in a tissue-specific context, limited expression of certain GAS virulence factors may aid rather than harm the host.

Pseudomonas aeruginosa

This Gram-negative, rod shaped, aerobic bacterium is well known for its ability to produce fluorescent molecules, including pyocyanin (blue-green), pyoverdin or fluorescein (yellow-green) and pyorubin (red-brown). Fluorescence and the grape-like sweet odour allow for easy identification of P. *aeruginosa* from other Gram-negative bacteria.

Pseudomonas aeruginosa is commonly found in nonsterile areas on healthy individuals and, much like *S. epidermidis*, is considered a normal constituent of a human's natural microflora. The bacteria normally live innocuously on human skin and in the mouth, but are able to infect practically any tissue with which they come into contact. Flexible, nonstringent metabolic requirements allow P. *aeruginosa* to occupy a variety of

niches, making it the epitome of an opportunistic pathogen. Due to the general harmlessness of the bacteria, infections occur primarily in compromised patients and in conjunction with hospital stays. Explicitly, immune-compromised individuals with AIDS, cystic fibrosis, bronchiectasis, neutropenia, and haematological and malignant diseases develop systemic or localized *P. aeruginosa* infections. Transmission often occurs through contamination of inanimate objects and can result in ventilator-associated pneumonia and other device-related infections.

The main port of entry is through compromised skin, with burn victims commonly suffering from *P. aeruginosa* infections. Entry into the blood results in bone, joint, gastrointestinal, respiratory and systemic infections. On the skin, *P. aeruginosa* occasionally causes dermatitis or deeper soft-tissue infections. Dermatitis occurs when skin comes into contact with infected water, often in hot tubs. The infection is very mild and is treated easily with topical antibiotics. Severe infections are treated with injectable antibiotics, such as aminoglycosides (gentamicin), quinolones, cephalosporins, ureidopenicillins, carbapenems, polymyxins and monobactams, although multidrug resistance is increasingly common in hospital settings and in chronically infected individuals (e.g. patients with cystic fibrosis).

During infection, the type IV pilus and nonpilus adhesins anchor the bacteria to the tissue. *Pseudomonas aeruginosa* secretes alginate (extracellular fibrous polysaccharide matrix), protecting the bacterium from phagocytic killing and potentially from antibiotic access.[139] Postmortem lung material from *P. aeruginosa*-infected cystic fibrosis patients showed the bacterial cells in distinct fibre-enclosed microcolonies. *Pseudomonas aeruginosa* also produces a variety of toxins and enzymes including lipopolysaccharide, elastase, alkaline protease, phospholipase C, rhamnolipids and exotoxin A, to which the host produces antibodies.[140] The regulation of these virulence factors is very complex and is modulated by the host's response. The role of many of these antigens in host immunity is incompletely understood. Also, the contribution of many of the toxins to bacterial virulence remains controversial, with toxin-lacking strains still exhibiting virulence in murine models of infection.[140] It was found that *P. aeruginosa* is able to sense the immune response and upregulate the virulence factor type I lectin (*lec*A).[141] IFN-γ binds to the major outer-membrane protein OprF and the OprF–IFN-γ interaction induces the bacteria to express lectin and quorum-sensing related (bacterial communication system) virulence factors.[141,142] Many genes that encode porins and other virulence factors are also being studied in relation to quorum sensing and *P. aeruginosa* metabolism.

The medical significance of *P. aeruginosa* infections is heightened due to antibiotic resistance. *Pseudomonas aeruginosa* expresses genes that encode enzymes which hydrolyse specific antibiotics. Specifically, the bacteria produce AmpC cephalosporinase, β-lactamases (PSE, OXA, TEM, SHV and other class-A type) and metallo-carbapenemases.[143] Antibiotic resistance also results from mutations in the porin OMP, which normally encodes the D2 porin, OprD.[144] Subsequent inactivation of OprD leads to imipenem resistance. Aminoglycoside resistance due to a variety of mechanisms occurs through acquisition of gene-resistance cassettes occasionally present in integrons simultaneously encoding metallo-β-lactamases.[145] Other antibiotic-resistant mechanisms are attributed to upregulation of efflux pumps, such as the MexAB–OprM system, and to mutations in topoisomerases II and IV.[146,147]

Despite intermittent disease caused by *P. aeruginosa*, the bacteria have been shown to protect the human host from a variety of infections. The byproducts of *Pseudomonas* are so potent that several have been turned into commercial medications. One of the most well-known products of a *Pseudomonas* (particularly *P. fluorescens*) is pseudomonic acid A, also called mupirocin or Bactroban®.[148] Mupirocin is one of the only topical antibiotics used in treatment of topical infections caused by staphylococcal and streptococcal pathogens. *Staphylococcus aureus* with resistance to multiple antibiotics often shows sensitivity to mupirocin. *Pseudomonas aeruginosa* also produces compounds with similar antimicrobial activity. A peptide called PsVP-10, produced by *P. aeruginosa*, was shown to have antibacterial activity against *Streptococcus mutans* and *S. sobrinus*.[149] In addition, *P. aeruginosa* suppresses fungal growth (Fig. 5). Fungal species that the bacteria fully or partially inhibit include *Candida krusei, C. keyfr, C. guilliermondii, C. tropicalis, C. lusitaniae, C. parapsilosis, C. pseudotropicalis, C. albicans, Torulopsis glabrata, Saccharomyces cerevisiae* and *Aspergillus fumigatus*.[150] Studies have shown that *P. aeruginosa* and *C. albicans* coexist in the host and the attenuation of *P. aeruginosa* results in *C. albicans* growth. The mechanism by which *P. aeruginosa* inhibits *C. albicans* may be due to the quorum-sensing molecule 3-oxo-C12 homoserine lactone (3OC12HSL).[151] This and other molecules, such as 1-hydroxyphenazine or pyocyanin, are shown to suppress the filamentous, or virulent, phase of *C. albicans* growth (Fig. 5). Although *in vitro* data show inhibition by both molecules, future targeted mutagenesis will be required to show conclusively the relevance of these compounds in cross-inhibition.[152] The presence of *P. aeruginosa*

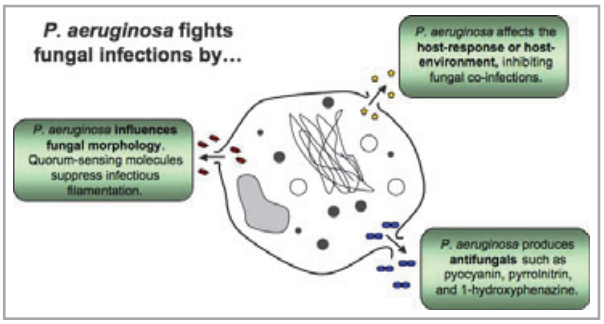

Fig 5. *Pseudomonas aeruginosa* fights fungal infections. It produces compounds such as pyocyanin, pyrrolnitrin and 1-hydroxyphenazine which kill and inhibit fungal growth. *Pseudomonas aeruginosa* also prevents the morphological transition of fungi from yeast-form cells to virulent filamentous cells. Filamentation of *Candida albicans* is associated with pathogenesis, adhesion, invasion and virulence-related products. *Pseudomonas aeruginosa* interacts with the host creating an environment inhospitable to fungi.

probably attenuates *C. albicans* and possibly other yeasts, thereby preventing infection. The repression of microbial growth by *P. aeruginosa* is not restricted to yeasts, and inhibition is also seen with *Helicobacter pylori*.[153]

The obvious benefit of *P. aeruginosa* leads toward the classification of this microbe as a mutual. The rarity of *P. aeruginosa*-related disease and the impedance of pathogenic organisms suggest that this bacterium maintains homeostasis between host and microbe, preventing disease. The antifungal activity of phenazines may explain the rarity of yeast infections in cystic fibrosis patients. In the same vein, removing *P. aeruginosa* from the skin, through use of oral or topical antibiotics, may inversely allow for aberrant yeast colonization and infection. Thus, the bacterium's ubiquitous presence could contribute against colonization by more pathogenic organisms, effectively making *P. aeruginosa* a participant in the host's cutaneous innate immune system.

Conclusions

Current research related to infectious diseases of the skin targets microbial virulence factors and aims to eliminate harmful organisms. Some of these same microbes potentially also play an opposite role by protecting the host. The complex host–microbe and microbe–microbe interactions that exist on the surface of human skin illustrate that the microbiota have a beneficial role, much like that of the gut microflora. Microbes participate in inflammatory diseases yet may not cause infections. For the clinician, understanding these principles should guide appropriate use of currently available systemic and topical antibiotics. An overuse of antibiotics may disrupt the delicate balance of the cutaneous microflora leaving the skin susceptible to pathogens previously kept at bay by the existing resident and mutual microbiota. Further advances in our understanding of microbial pathogens as well as an increase in the appreciation of the complex relationship that humans have with the resident microbes promise to lead to novel diagnostic and therapeutic approaches to dermatological disease.

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