Skin Microflora and Bacterial Infections of the Skin

Katarina Chiller,* Bryan A. Selkin,† and George J. Murakawa†‡

*Department of Dermatology, University of California at San Francisco, San Francisco, California, U.S.A.; †Division of Dermatology, Albany Medical College, Albany, New York, U.S.A.; ‡Department of Dermatology, Wayne State University, Detroit, Michigan, U.S.A.

The skin is a milieu for controlled bacterial growth. Skin supports the growth of commensal bacteria, which protect the host from pathogenic bacteria. Environmental and local factors, host immunity, and organism adherence and virulence are intricately related to cutaneous infection. Resident gram-positive bacteria include *Staphylococcus*, *Micrococcus*, and *Corynebacterium sp*. *Staphylococcus aureus* and *Streptococcus pyogenes* are notoriously pathogenic in the skin. In order for bacteria to be pathogenic, they must be able to adhere to, grow on, and invade the host. Bacteria possess numerous virulence genes that allow for growth in these privileged niches. Epidermal infections caused by *S. aureus* and *S. pyogenes* include impetigo and ecthyma. Dermal infections consist of erysipelas, cellulitis, and necrotizing fasciitis. The pilosebaceous unit is involved in folliculitis, furunculosis, and carbunculosis. Moreover, *S. aureus* and *S. pyogenes* produce toxins that may elicit a superantigen response, causing massive release of cytokines. Staphylococcal scalded skin syndrome, toxic shock syndrome, and scarlet fever are all superantigen-mediated. Gram-negative organisms such as *Pseudomonas aeruginosa*, *Pasteurella multocida*, *Capnocytophaga canimorsus*, *Bartonella sp*., *Klebsiella rhinoscleromatis*, and *Vibrio vulnificus* are not typical resident skin microflora but may cause cutaneous infection. *Key words: commensals/epidermal, dermal, follicular, and subcutaneous infections/superantigens/virulence factors. Journal of Investigative Dermatology Symposium Proceedings 6:170–174, 2001*

THE SKIN AND HOST DEFENSE MECHANISMS

The skin is a barrier that limits invasion and growth of pathogenic bacteria. The cutaneous antimicrobial defense mechanisms include the mechanical rigidity of the stratum corneum and its low moisture content, stratum corneum lipids, production of lysozyme, acidity (pH 5), and defensins (Harder *et al*, 1997). Specifically, most areas of skin are dry, creating an unfavorable environment for bacterial replication. Dead keratinocytes slough and physically remove colonizing bacteria. Skin is cooler than normal body temperature and slightly acidic; most bacteria grow best at a neutral pH and at 37°C. If organisms can evade cutaneous host defenses, the next line of protection involves the inunune system, or skin-associated lymphoid tissue (SALT).

THE SKIN AS A MILIEU FOR BACTERIAL GROWTH

The skin is an intricate habitat for many bacteria. A sterile milieu prenatally, human skin soon becomes host to resident bacteria after birth. The type and density of bacteria are determined by anatomic location, local humidity, the amount of sebum and sweat production, and the host's hormonal status and age (Aly *et al*, 1991). Bacterial skin flora are commensal, symbiotic, or parasitic relative to the host; although alterations in host immune status are known to have a significant impact, the type of relationship established is often inherent to the bacteria. Persistent colonization is the result of the ability of bacteria to adhere to skin epithelium, grow in a relatively dry and acidic milieu, and rapidly re-adhere during the normal process of desquamation (Feingold, 1986).

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Reprint requests to: Dr. George J. Murakawa, Department of Dermatology, Wayne State University, 4201 St Antoine 5E UHC, Detroit, MI 48201. Email: Gmurakaw@med.wayne.edu

Abbreviations: SA, superantigen; SE, skin equivalent.

PROTECTION BY COLONIZING BACTERIA

Skin supports the growth of commensal bacteria, which protect the host from pathogenic bacteria both directly and indirectly. Direct effects include bacteriocin production, production of toxic metabolites, induction of a low reduction oxidation potential, depletion of essential nutrients, prevention of adherence of competing bacteria, inhibition of translocation, and degradation of toxins. Commensal bacteria compete for nutrients, niches, and receptors. For example, *Staphylococcus epidermidis* bind keratinocyte receptors and inhibit adherence of virulent *S. aureus* (Bibel *et al*, 1983a). Commensals can release species-specific antibiotic substances known as bacteriocins. For example, *S. aureus* strain 502A release bacteriocins that inhibit other virulent staphylococcal organisms (Peterson *et al*, 1976). Indirectly, bacteria can induce the host to enhance antibody production, stimulate phagocytosis and clearance mechanisms, and augment interferon and cytokine production. For example, *Propionibacterium acnes* release fatty acids from lipid breakdown, acidifying the milieu and inhibiting growth of *Streptococcus pyogenes* (Hentges, 1993).

RESIDENT SKIN BACTERIAL FLORA (**TABLE I**)

Gram-positive bacteria *Staphylococcus sp*. are gram-positive cocci that aggregate in clusters. Commensal *Staphylococcus sp*. are distinguished by their inability to produce coagulase, an important virulence-associated enzyme. There are 32 species of coagulase-negative staphylococci, of which 15 are exclusive to humans, and 10 routinely isolated from normal glabrous skin. *Staphylococcus epidermidis* and *S. hominis* are the most prevalent coagulase-negative

Table I. Bacterial skin residents and their associated dermatoses

Bacteria	Location	Distinguishing features	Skin pathology
Gram (+)			
Staphylococcus			
S. epidermidis	upper trunk	produce slime	
S. hominis	glabrous skin		
S. haemolyticus	produce slime		
S. capitis	head		
S. midis			
S. warneri			
S. saprophyticus	perineum	cause UTI	
S. cohnii			
S. xylosus			
S. simulans			
S. saccharolyticus	forehead/antecubital	anaerobic	
Micrococcus			
M. luteus			
M. varians			
M. lylae	in children/cold temp		
M. kristinae	in children		
M. nishinomiyacnsis			
M. roseus			
M. sedentarius	pitted keratolysis		
M. agieis			
Corynebacterium			
C. minutissimum	intertriginous	lipophilic/porphyrin	erythrasma
C. tenuis	intertriginous	lipophilic	trichomycosis
C. xerosis	conjunctiva	lipophilic	conjunctivitis
C. jeikeium	intertriginous	lipophilic/antibiotic resistant	
Rhodococcus	lipophilic	granuloma in HIV	
Propionibacterium			
P. acnes	sebaceous gland	lipophilic/anaerobic	acne
P. granulosum	sebaceous gland	lipophilic/anaerobic	severe acne
P. avidum	axilla	lipophilic/anaerobic	
Brevibacterium	toe webs	nonlipophilic (large-colony)	foot odor, white piedra
Dermabacter	nonlipophilic (large-colony)	pitted keratolysis	
Gram (–)			
Acinetobacter	dry areas	gram-negative	burn wounds

commensals. Occasionally, these organisms cause nosocomial infections in patients with indwelling foreign bodies such as heart valves and intravenous catheters (Archer, 1995).

Micrococcus sp. are also gram-positive cocci, distinguished from staphylococci by the inability to produce acid anaerobically from glycerol. Moreover, *Micrococcus sp.* are not lysed by lysostaphin and nitrofuran. At least eight species have been isolated from human skin, the most common being *M. luteus*.

Coryneforms are gram-positive pleomorphic bacilli. Skin commensals include *Corynebacterium sp.*, *Propionibacterium sp.*, *Dermabacter sp.*, and *Brevibacterium sp.* Corynebacteria are classified as either lipophilic or nonlipophilic. Lipophilic organisms colonize areas rich in lipids or sebum such as the axilla and include *Arcanobacterium haemolyticum*, *C. xerosis*, *C. minutissimum*, and *C. striatus*. These organisms do not produce toxins and are nonmotile. *Propionibacterium acnes* is the dominant anaerobic coryneform on the skin. Unlike most commensals, its anaerobic requirements favor growth deep in adnexal structures as opposed to squamous epithelium. *Dermabacter* and *Brevibacterium sp.* prefer glabrous, humid skin such as the toewebs. The production of methane thiol by *Brevibacterium sp.* is the cause of "foot odor".

Gram-negative bacteria Gram-negative organisms do not normally reside in the dry environment of normal skin. Occasionally, moist intertriginous areas allow for the growth of *Acinetobacter sp.*

PATHOGENICITY AND VIRULENCE FACTORS

For an organism to become a pathogen, it must be able to circumvent normal host defense mechanisms. Perhaps the best-studied cutaneous pathogen is *S. aureus*, yet relatively little is known regarding the pathogenic mechanisms employed. *Staphylococcus aureus* readily adheres to all mammalian cell types, including keratinocytes (Bibel *et al*, 1983b; Ogawa *et al*, 1985; Cole and Silverberg, 1986; Murakawa, unpublished data). Teichoic acids mediate the binding of *S. aureus* to nasal epithelial cells as well as to fibronectin. *Staphylococcus aureus* binds most efficiently to well-differentiated keratinizing cells, and there is an increased affinity for keratinocytes derived from patients with atopic dermatitis (Cole and Silverberg, 1986).

Several *S. aureus* virulence genes have been identified, including numerous surface and extracellular proteins at the end of exponential growth (Foster and McDevitt, 1994). Expression of virulence genes is controlled by global regulatory elements, including *sar*, *agr*, *xpr* (Cheung *et al*, 1995). Adherence to extracellular matrix proteins is mediated by MSCRAMM (microbial surface components recognizing adhesive matrix molecules) (Patti *et al*, 1994). Other *S. aureus* virulence factors include catalase, hyaluronidase, and β-lactamase.

Our laboratory is investigating the interactions of *S. aureus* with keratinocytes and other components of the skin. *Staphylococcus aureus* is an ideal cutaneous pathogen to study because of its clinical relevance, well-delineated genome, and ability to grow on both liquid and solid media. Using plate assays, we have characterized the ability of *S. aureus* to adhere to, invade into, and grow on mammalian cells. Adherence assays are performed by incubating bacteria with mammalian cells, washing with PBS to remove nonadherent bacteria, and lysing the mammalian cells to free adherent or intracellular bacteria. Subsequently, the bacteria are diluted, plated, and counted to determine adherence. Intracellular

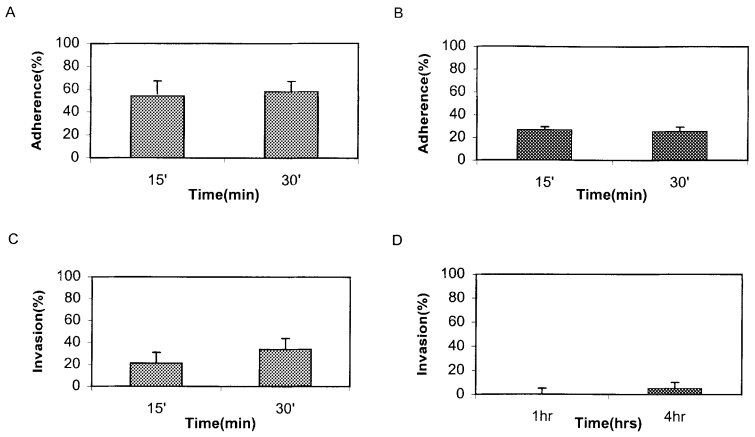

Figure 1. Invasion and adherence assays using *S. aureus* with mammalian cells. (*A*) Macrophage adherence; (*B*) macrophage invasion; (*C*) keratinocyte adherence; (*D*) keratinocyte invasion. As shown in (*A*) and (*B*), *S. aureus* adhere to macrophages and keratinocytes efficiently and immediately (20%–60%) within 15 min. As shown in (*C*) and (*D*), *S. aureus* invades macrophages efficiently and immediately (20–50%) within 30 min, but invade keratinocytes poorly (1%–4% in 4 h).

bacteria are identified similarly, except that prior to lysing, the samples are treated with lysostaphin, a cytotoxic agent that specifically targets all extracellular bacteria. Using these assays, we have shown that *S. aureus* adhere to all mammalian cells (including macrophages and keratinocytes) efficiently and immediately (20%–60% within 15 min). Additionally, *S. aureus* invade macrophages efficiently and immediately (20%–50% in 30 min), but invade keratinocytes poorly (1%–4% in 4 h) (**Fig 1**). Morphologic studies using light and electron microscopy have confirmed these results, and intracellular bacteria reside within vacuoles.

We have further characterized the interactions of *S. aureus* with skin by using skin equivalents (SE). Collagen and fibroblasts are combined to form a dermal matrix, and keratinocytes are subsequently added atop the matrix and allowed to differentiate, forming the SE. Bacteria readily adhere to and grow on the SE, but do not penetrate deeply into the epidermis or dermis (data not shown).

INFECTIONS CAUSED BY *S. AUREUS* AND *S. PYOGENES*

Staphylococcus aureus is the most common cause of cutaneous and systemic infections. It may transiently colonize the skin of newborn infants, the anterior nares in 20%–40% of healthy individuals, and the skin of atopic patients (Strange *et al*, 1996). *Staphylococcus aureus* is the most common cutaneous bacterial pathogen in HIV-infected patients, causing superficial and deep dermal pathology that can lead to life-threatening complications (Berger, 1993). In part, the susceptibility of HIV-infected patients to *S. aureus* may be a consequence of ongoing and increased nasal carriage of this organism. Recurrence after therapy is extremely common.

As with *S. aureus*, *Streptococcus sp.* are notoriously pathogenic in the skin. *Streptococcus* Groups A, B, C, D, and G (based on the Lancefield classification that segregates *Streptococcus sp.* according to M-protein serotype) are frequent human pathogens. M-protein is a virulence antigen that confers bacterial resistance to phagocytosis. *Streptococcus pyogenes* is not typically a cutaneous resident, but is asymptomatically carried in the throat of 15% of school-aged children (Bisno, 1995).

Table II lists the cutaneous infections caused by *S. aureus* and *S. pyogenes*.

Epidermal infections – impetigo and ecthyma Impetigo, the most common bacterial infection in children, is a highly communicable, superficial infection caused by either *S. aureus* or *S. pyogenes* (Wannamaker, 1970). Non-bullous impetigo typically occurs on the face or extremities following minor cutaneous trauma. Erythematous papules, pustules, or vesicles develop into erosions covered by characteristic honey-colored crust. Lesions are usually painless, and there may be associated lymphadenopathy and leukocytosis. Cellulitis, lymphadenitis, scarlet fever, and guttate psoriasis are rare sequelae. Bullous impetigo is characterized by flaccid bullae that rupture easily, leaving a thin collarette of scale. There is usually no associated lymphadenopathy. Bullous impetigo is mediated by exfoliative toxin, which also causes staphylococcal scalded-skin syndrome (SSSS).

Table II. *Staphylococcus aureus* and *S. pyogenes* skin infections

Infections	*S. aureus*	*S. pyogenes*
Epidermal		
Impetigo	+++	++
Ecthyma	+	+++
Dermal		
Erysipelas	+	+++
Cellulitis	+++	++
Necrotizing fasciitis	+	++
Follicular		
Folliculitis	+++	+
Furunculosis	+++	+
Carbunculosis	+++	+
Other		
Paronychia	+++	+
Blistering distal dactylitis	+	+++
Botryomycosis	+++	
Mastitis	+	

Ecthyma is a deeper form of impetigo in which ulcerations form beneath crusted plaques. The lower extremity is the most common site of involvement, and scarring is common. *Streptococcus pyogenes* or *S. aureus* are the usual culprits.

Dermal infections – erysipelas, cellulitis, necrotizing fasciitis Erysipelas is an acute infection caused by *S. pyogenes* involving the dermis and dermal lymphatics (Jorup-Ronstrom, 1986). Sharply demarcated, tender, erythematous plaques with an elevated advancing border occur on the lower extremities or face following an inflammatory dermatosis or traumatic insult. Vesicles and bullae may develop, resulting in local gangrene. Lesional cultures are usually negative. Constitutional symptoms and leukocytosis are common. A devastating complication of erysipelas is cavernous sinus thrombosis (Wortman, 1993).

Cellulitis, unlike erysipelas, involves the subcutaneous tissue, and is caused by *S. pyogenes* or *S. aureus* (Hook *et al*, 1986). There is usually a background of chronic edema and stasis dermatitis, and tinea pedis is most common portal of entry associated with leg cellulitis. The edematous, warm plaques of cellulitis are poorly demarcated, and lymphangitis occurs less frequently than with erysipelas. Constitutional symptoms are mild, and the causative organism is difficult to isolate. Local abscesses, necrotizing fasciitis, and septicemia may occur.

Table III. *Streptococcus pyogenes* and *S. aureus* toxins[a]

Disease	Organism	Toxin
SSSS	*S. aureus*	Exfolative toxin A Exfoliative toxin B
Bullous impetigo	*S. aureus*	Exfoliative toxin A Exfoliative toxin B
TSS	*S. aureus*	TSST-1
TSS	*S. pyogenes*	SPE-A SPE-B SPE-C Streptococcal superantigen Mitogenic factor
Scarlet fever	*S. pyogenes*	SPE-B SPE-C

[a]For further details, see Manders (1998).

Two forms of cellulitis occurring in children deserve special mention. Perianal cellulitis caused by *S. pyogenes* presents in young children as perianal erythema, which may be associated with painful defecation and blood-tinged stool (Barzilai and Choen, 1998). Perianal cellulitis may be a trigger for guttate psoriasis. *Haemophilus influenzae*, a gram-negative rod, causes a facial cellulitis in children 3 mo to 4 y of age characterized by violaceous, indurated plaques. Meningitis is a feared complication. The advent of the *H. influenzae* vaccine has dramatically reduced the incidence of this form of cellulitis.

Necrotizing fasciitis is a potentially life-threatening infection of the subcutaneous fascia (Tharakaram and Keczkes, 1988). Within 48 h, erythema, pain, and edema progress to violaceous, dusky plaques that quickly necrose. Anesthesia of the involved skin is characteristic. The most common cause is *S. pyogenes*, but *S. aureus*, coliforms, enterococci, *Pseudomonas sp*., and *Bacteroides sp*. have also been culprits.

Follicular infections – folliculitis, furunculosis, carbunculosis Infections of the hair follicle or pilosebaceous unit are classified as either superficial or deep (Wortman, 1993). Folliculitis, caused by *S. aureus*, is characterized by discrete, follicular-based pustules. Carriage of *S. aureus* in the nares may lead to sycosis barbae in young men, presenting as inflammatory plaques in the beard area.

Deeper infections of hair follicle can lead to furuncles or carbuncles. A furuncle, or boil, is a nodule in a hair-bearing area that discharges purulent, necrotic debris. Carbuncles are multiple furuncles that coalesce to form large, deep, interconnected abscesses. *Staphylococcus aureus* is the cause in nearly all cases.

Miscellaneous infections Acute paronychia, caused by *S. aureus*, presents as purulent tender swellings of the nailfold (Brook, 1981). Blistering distal dactylitis, caused by *S. pyogenes* and occasionally *S. aureus*, is characterized by tense blisters on an erythematous base over the volar fat pad of the phalanx of a finger (McCray and Esterly, 1981). Botryomycosis is a granulomatous and suppurative infection caused by *S. aureus*, presenting on the lower extremity as crusted granulomatous plaques, ulcers, and sinus tracts draining purulent material.

TOXIN-MEDIATED *S. AUREUS* AND *S. PYOGENES* SYNDROMES (**TABLE III**)

Staphylococcus aureus and *S. pyogenes* produce several toxins that can cause localized destruction or systemic symptoms (Hackett and Stevens, 1993). Systemic symptoms are mediated by superantigens (SA). Conventional antigens are expressed on the cell surface of antigen-presenting cells in association with the major histocompatibility type II complex (MHC II). Interaction with the T cell receptor occurs in a very specific, antigen-restricted fashion. Superantigens circumvent this process, interacting directly with a portion of the MHC II complex and with only the V-β section of the T cell receptor, without antigen (Rosen, 1997). Large-scale T cell activation leads to the massive release of tumor necrosis factor-α (TNF-α), interleukin-1 (IL-1), and interleukin-6 (IL-6) (Jupin *et al*, 1988). These cytokines lead to the clinical findings of fever, emesis, erythematous rash, hypotension, tissue injury, and shock. Physical signs common in toxin-induced staphylococcal and streptococcal syndromes include strawberry tongue, acral erythema with subsequent desquamation, and perineal erythema.

SSSS, most commonly seen in infants, presents with a prodrome of fever, skin tenderness, and erythema localized primarily to flexural areas (Resnick, 1992). There is sparing of the palms, soles, and mucous membranes. Generalized exfoliation quickly ensues, and the Nikolsky's sign is positive. Group 2 *S. aureus*, most commonly phage type 71, can be isolated from mucous membranes (skin erythema and desquamation are due to remote effects of the toxin). Exfoliative toxins A and B (ETA and ETB) have been implicated in the pathogenesis of SSSS, along with δ-hemolysin (Manders, 1998).

Toxic shock syndrome (TSS) is a multisystern illness caused by *S. aureus* or *S. pyogenes*. Clinically, diffuse macular erythema is followed by desquamation, especially of palms and soles. Staphylococcal TSS is typically associated with tampon use (Shands *et al*, 1980). Cases associated with *S. pyogenes* usually involve a soft-tissue infection. Most cases of staphylococcal TSS are mediated by TSST-1, although *S. aureus* strains expressing enterotoxins B and C (SEB, SEC) have been isolated. Streptococcal TSS is primarily associated with SPE-A, although SPE-B, SPE-C, streptococcal superantigen, and mitogenic factor have been occasional culprits (Manders, 1998).

Scarlet fever, caused by *S. pyogenes*, occurs shortly after an episode of pharyngitis and is characterized by a papular erythematous "sandpaper" rash on the trunk and extremities accompanied by perioral pallor (Stevens, 1992). A linear petechial eruption (Pastia's lines) occurs in flexural areas. A white coating on the tongue with hypertrophied projecting papilla leads to the so-called "white strawberry tongue". Currently, SPE-B and SPE-C are the toxins most frequently isolated. Staphylococcal scarletina mimics classic scarlet fever, but the strawberry tongue is not seen.

OTHER GRAM-POSITIVE BACTERIAL SKIN INFECTIONS

Corynebacteria are normally found in intertriginous areas, where growth is enhanced by hyperhidrosis. Erythrasma, caused by *C. minutissimum*, is characterized by sharply defined, brown, slightly scaling plaques in intertriginous areas (Sindhuphak *et al*, 1985). Characteristic coral-red fluorescence is due the production of porphyrin. Pitted keratolysis presents as discrete coalescing crater-like pits on the plantar surface of the feet. In trichomycosis axillaris, concretions on axillary or pubic hair shafts occur.

Erysipelothrix rhusiopathiae is a gram-positive aerobic bacillus that causes erysipeloid, a localized cellulitis typically on the hands (Barnett, 1983). Clinical findings include bright-red or violaceous, well-demarcated, polygonal plaques, often with central clearing. *Erysipelothrix rhusiopathiae* is present on dead matter of animal origin. Infection following trauma is seen in fish, meat, and poultry handlers, as well as farmers.

Bacillus anthracis is a nonmotile, gram positive aerobic rod that is capable of forming spores, and can produce both a localized cutaneous and a systemic infection (Dixon, 1999). Cutaneous anthrax accounts for 95% of all anthrax infections in the USA, and typically develops in patients with a history of occupational contact with animals or animal products.

GRAM-NEGATIVE BACTERIAL SKIN INFECTIONS

An atypical form of cellulitis occurring in HIV-infected patients is caused by *Helicobacter cinaedi* (Sullivan *et al*, 1997). Red-brown or

copper plaques with minimal warmth are characteristic. The cellulitis may be multifocal and recurrent.

Pseudomonas aeruginosa is an aerobic gram-negative rod found in moist environments. Ecthyma gangrenosum occurs primarily in immunosuppressed patients in the setting of *Pseudomonas* sepsis (Baze *et al*, 1985). Hemorrhagic bullae progress to deep ulcerations with eschar. ''Hot tub'' folliculitis presents as pruritic, discrete erythematous papules and pustules on the trunk and buttocks 8–48 h after water immersion. It is a self-limited disease resolving within 7–10 d; however, immunocompromised patients may develop ecthyma gangrenosum. Other diseases caused by *P. aeruginosa* include gram-negative toe web infections and green nail syndrome. *Pseudomonas aeruginosa* is also an important cause of morbidity and mortality in burn victims.

Pasteurella multocida is a gram-negative coccobacillus that is part of the commensal flora in dogs and cats (Griego *et al*, 1995). Following an animal bite, a rapidly progressive cellulitis with gray-colored serous drainage develops. Local complications including septic arthritis are common.

Bartonella sp. are aerobic, fastidious gram-negative bacteria. *Bartonella henselae* causes cat scratch disease (CSD) and bacillary angiomatosis (BA), *B. quintana* causes trench fever and BA, and *B. bacilliformis* causes verruga peruana and Oroya fever. CSD develops at the site of trauma, usually in the head and neck area, and is associated with unilateral lymphadenopathy. BA and verruga peruana are characterized by vascular skin lesions resembling pyogenic granulomas. Patients with trench fever and Oroya fever present with systemic symptoms but no cutaneous lesions (Murakawa and Berger, 1999).

Capnocytophaga canimorsus, formerly referred to as DF-2, is a gram-negative rod that is commensal flora of dog and cats. Human infection is characterized by necrotizing eschar at the site of the bite. Alcoholics and patients who have undergone splenectomy are particularly predisposed to severe septicemia following the bite (Herbst *et al*, 1989).

Rhinoscleroma is a granulomatous infection of the nasal mucosa and surrounding tissues caused by *Klebsiella rhinoscleromatis* (Andraca *et al*, 1993). Patients present with infiltrative and destructive granulomatous plaques that may lead to life-threatening complications. Transmission is by nasal secretions.

Consumption of raw seafood or seawater exposure may lead to infection with *Vibrio vulnificus* (Hlady *et al*, 1993). Erythematous, indurated plaques studded with hemorrhagic bullae, pustules, petechiae, and areas of gangrene are found on the lower extremities.

In summary, the skin is a poor media for bacteria given the large number of inherent defense mechanisms; however, when altered or breached or under moist occlusive conditions, the skin can support the growth of both commensal and pathogenic bacteria. Although the bacteria–host interactions have been studied in depth, much remains unknown regarding the pathogenic mechanisms that bacteria employ and the host defense mechanisms to counteract infections.

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