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RESEARCH ARTICLE

WOUND INFECTION IN DIABETES

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Abstract

Introduction:

Foot infections are the most common problems in persons with diabetes. These individuals are predisposed to foot infections because of a compromised vascular supply secondary to diabetes. Local trauma and/or pressure (often in association with lack of sensation because of neuropathy), in addition to microvascular disease.

The spectrum of foot infections in diabetes ranges from simple superficial cellulitis to chronic osteomyelitis. Infections in patients with diabetes are difficult to treat because these patients have impaired microvascular circulation, which limits the access of phagocytic cells to the infected area and results in a poor concentration of antibiotics in the infected tissues. For this reason, cellulitis is the most easily treatable and reversible form of foot infections in patients with diabetes. Deep skin and soft tissue infections are also usually curable, but they can be life threatening and result in substantial long-term morbidity.

In terms of the infecting microorganisms and the likelihood of successful treatment with antimicrobial therapy, acute osteomyelitis in people with diabetes is essentially the same as in those without diabetes. Chronic osteomyelitis in patients with diabetes mellitus is the most difficult infection to cure. Adequate surgical debridement, in addition to antimicrobial therapy, is necessary to cure chronic osteomyelitis.

Patients with diabetes also can have a combined infection involving bone and soft tissue called fetid foot. This extensive, chronic soft tissue and bone infection causes a foul exudate and usually requires extensive surgical debridement and/or amputation.

Individuals with diabetes may also have peripheral vascular disease that involves the large vessels, in addition to microvascular and capillary disease that results in peripheral vascular disease with gangrene. Dry gangrene is usually managed with expectant care, and gross infection is usually not present. Wet gangrene usually has an infectious component and requires surgical debridement and/or antimicrobial therapy to control the infection.

Except for chronic osteomyelitis, infections in patients with diabetes are caused by the same microorganisms that can infect the extremities of those without diabetes. Gas gangrene is conspicuous because of its low incidence in

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patients with diabetes, but deep skin and soft tissue infections, which are due to gas-producing organisms, frequently occur in patients with diabetes. In general, people with diabetes have infections that are more severe and take longer to cure than equivalent infections in other people.

Epidemiology:

-Here are recent estimates of the disease burden due to diabetes and projections for the future*****:

	2003		2025	
	Europe	Africa	Europe	Africa
Population -Total -Adult (20-79 years)	 872 million 621 million	 667 million 295 million	 863 million 646 million	 1107 million 541 million
Diabetes -No. of people (20-79 years) -Prevalence (20-79 years)	 48.4 million 7.8 %	 7.1 million 2.4 %	 65 million 7.8 %	 19million 4.3 %

*****Source:International Diabetes Federation and The International Working Group on Diabetes joint publication 2006

-People with foot ulcers*****:

- Developed countries: **15%** of people with diabetes get ulcers at least once in their lifetime.
- Developing countries: the prevalence is even higher at **20%**.

*****Source:International Diabetes Federation and The International Working Group on Diabetes joint publication 2005

-The diabetic foot affect individuals and society:

- Diabetic foot ulcers and their complications (explained later) are often painful. Patients often become dependent on others for mobility, suffer a loss of autonomy, reduced social function, and making depression common.
- The cost of diabetic foot management is **12-15%** of the total health care budget for diabetes in developed countries. This figure may as high as **40%** in developing countries*.

*IDF/IWG joint publication on diabetic foot.

Pathophysiology:

Diabetic foot ulcers may have multiple causes, the prominent ones being;

A. Peripheral neuropathy (nerve damage)
B. Peripheral vascular disease (poor pedal blood supply)
C. Trauma:
    1. Acute: any injury to the foot such as burns or cuts.
    2. Chronic: due to foot deformities(changes of foot shape that lead to ill-fitting shoes and, thereby, ulceration frequency)

International:

Diabetic foot infections range from cellulitis to chronic osteomyelitis, and, globally, they are the most common skeletal and soft tissue infections in patients with diabetes.

Mortality/Morbidity:

Mortality is not common, except in unusual circumstances. The mortality risk is highest in patients with chronic osteomyelitis and in those with acute necrotizing soft tissue infections.

Race:

The incidence of diabetic foot infections is similar to that of diabetes in various ethnic groups.

Sex:

No important sex differences exist.

Age:

Diabetic foot infections most frequently affect elderly patients.

Materials and Methods:

We have collected 10D.M. Foot samples from inpatientof King Fahad HospitalHofuf (KFHH)through swab touch and then had been planting in MacConkey's agar and Blood agar.Identified the bacteria was by VITEK 2 Systems (version:04.02), and then test the sensitivity of antibiotics was done.

Results:

- All samples collected from D.M. foot.
- 4 samples were growing:

No.	Sex	Age	Collection Date	Organism	Bionumber
3	F	67	23/12/10	*Staphylococcus hominis*	040000004220231
3/2	F	67	23/12/10	*Pasteurellapneumotopica*	0401200210000210
4	F	42	25/12/10	*Unidentified* organism	0001200210300210
6	F		25/12/10	*Pseudomonas aeruginosa*	0043051243500252

- Sensitivity test: Resistant (R), Sensitive (S)

	Staphylococcus hominis	*Pasteurellapneumotopica*	*Unidentified* organism	*Pseudomonas aeruginosa*
VA 30	11 mm (S)	S	12 mm (S)	R
AMP 10	7 mm (S)	S	10 mm (S)	R
E 15	R	S	R	R
TE 30	5 mm (S)	S	R	5 mm (S)
AK 30	14 mm (S)	S	15 mm (S)	14 mm (S)
IPM 10	10 mm (S)	S	10 mm (S)	15 mm (S)
KF 30		S		R
SXT 25	R	6 mm (S)	R	R
BCDD	R	R	R	R
Fox 30	14 mm (S)	S	R	R
MET 5	10 mm (S)	S	R	R
CN 10	S	S	R	12 mm (S)
C 30	9 mm (S)	S	S	R
CAZ 30	10 mm (S)	S	S	14 mm (S)
AMC 30	S	S	S	R
P 10	10 mm (S)		10 mm (S)	R

Discussion and Conclusion:

In sample No. 3:

Staphylococcus hominis (Bionumber:040000004220231) is harmless in human.

In sample No. 3/2:

Pasteurellapneumotopica(Bionumber:0401200210000210) is an opportunistic organism prevalent in many commercial and research colonies of rodents. The incidence of clinical disease associated with this organism is low. In the presence of primary pathogens, this organism, like other opportunistic organism, potentiates the severity of disease.

P. pneumotropica belongs to the family of*Pasteurellaceae*, which also includes the genera *Haemophilus* and *Actinobacillus*. *P. pneumotropica* is a gram-negative short rod or coccobacillus. On primary culture the organism grows well on blood agar.

All efforts to detect *P.pneumotropica* must discriminate between *P. pneumotropica* infection and *P. pneumotropica* induced disease. Since rodents in many colonies are asymptomatically infected with this agent (in their respiratory tract, conjunctivae or other sites) without demonstrable disease, its diagnosis as a primary pathogenic agent must necessarily be one of exclusion, Important to characterize the bacteriologic, mycoplasma and viral status of animals in which this diagnosis is considered to rule out other possible causative agents and disease processes.

In sample No. 6:
Pseudomonas aeruginosa(Bionumber:0043051243500252) remains one of the most important pathogens in nosocomial infections, with high associated morbidity and mortality.

In intensive care units, *Pseudomonas aeruginosa* (PA) ranks among the top five organisms causing pulmonary, bloodstream, urinary tract, surgical site, and soft tissue infections. Current treatments, primarily antibiotics that kill or inhibit the growth of this bacterium, have been associated with unacceptably high rates of morbidity and mortality. The development of agents that antagonize virulence factors represents a novel and potentially fruitful approach to the treatment of severe infections caused by PA.

Any attempt to therapeutically target virulence determinants must build upon a thorough understanding of host-pathogen interactions in PA infections. Interactions between PA virulence factors and the host immune response dictate the severity and type of infection. Depending on the environmental conditions and the immune status of the host, PA can be a quiescent colonizer, a cause of chronic infection, or a highly virulent invader during acute infections. For example, in the respiratory tract PA may cause fulminant and acute ventilator-associated pneumonia (VAP), be a colonizer in chronic obstructive pulmonary disease, or cause a chronic infection in cystic fibrosis (CF) patients, causing slowly progressive deterioration of pulmonary function. Bacterial surface factors such as flagella, pili and lipopolysaccharide as well as active processes such as the secretion of toxins, biofilm formation, and quorum sensing are virulence determinants that impact the outcome of PA infections. Interaction with the host immune system via soluble and cell surface receptors (e.g. toll-like receptors) controls signalling molecules (e.g. cytokines), modulates the host response, which impacts disease severity both by influencing the rate of bacterial clearance and by causing collateral damage to host tissues.

Given the growing problem of antimicrobial resistance in PA, improving therapy has been designated a priority by the Antimicrobial Availability Task Force of the Infectious Diseases Society of America.

Because of its resistance attributes, PA is the most common antibiotic-resistant pathogen isolated from VAP, with a significant attributable mortality, even with early and optimal therapy. Unfortunately, the multi-faceted resistance mechanisms possessed by PA have made the development of new antipseudomonal antibiotics challenging. Thus, there is a need for novel approaches for controlling these infections in the future.

Recent technological advances in areas such as genomics, proteomics and microscopy have led to rapid progress in our understanding of PA pathogenicity. Scientists are now pushing these discoveries through the translational pipeline in the hope of developing new therapeutic agents useful in the treatment of PA infections. While many PA virulence determinants are being actively targeted (Table 1), here we will focus on four: type III secretion, quorum sensing, biofilm formation, and flagella. We will highlight recent advances in our understanding of basic mechanisms underlying each of these virulence determinants and cite examples of how each is being targeted for therapeutic intervention.

Table 1

Virulence determinants of PA that have been targeted for therapeutic intervention.

Virulence Determinant	Type	References demonstrating role in pathogenicity*	Examples of therapeutic interventions	References demonstrating potential utility*	Furthest progress in translational efforts
type IV pili	Surface appendage	Tang et al (130) Chi et al (131)	active immunization	Kao et al (132) Ohama et al (133)	Preclinical
Flagella	Surface appendage	Feldman et al (134) Balloy et al (135)	active and passive Immunization	Doring et al (129) Doring et al (136)	phase III trial
Lipopolysaccharide	Outer membrane component	Danner et al (137) Moskowitz et al(138) Pier et al (139)	active and passive Immunization	Zuercher et al (140) Lang et al (141) Lai et al (142)	phase III trial
Alginate	cell surface exopolysaccharide	Simpson et al (143) Cabral et al (144)	active and passive Immunization	Kashef et al (145) Theilacker et al(146) Pier et al (147)	phase I trial
type III secretion	Secretion system	Shaver et al (20) Lee et al (148) Vance et al (149)	active and passive Immunization, small molecule inhibitors	Sawa et al (59) Neely et al (60)	Preclinical
Elastase	Protease	Park et al (150) Azghani et al (151)	active immunization	Matsumoto et al (152) Sokol et al (153)	Preclinical
Alkaline protease	Protease	Nicas et al (154) Guzzo et al (155)	active immunization	Matsumoto et al (152)	Preclinical
exotoxin A	Toxin	Nicas et al (154) Miyazaki et al (156)	active and passive immunization	Denis-Mize et al (157) Hertle et al (158) El-Zaim et al (159)	Preclinical
Quorum-sensing	cell-to-cell Communication	Pearson et al (160) Rumbaugh et al (161)	natural and synthetic Inhibitors	See Table 2	preclinicalz
Biofilms	Bacterial Aggregates	Jesaitis et al (162) Cochran et al (163)	antimicrobial coatings, small molecule inhibitors	see Table 3	phase III trial

Like people, PA bacteria behave differently depending on whether they are alone or in a crowd. They accomplish this by using an intercellular signalling process called quorum sensing (QS). In QS, small compounds called autoinducers are released by bacteria into the environment. Autoinducer concentrations are then sensed by neighboring bacteria to infer the density of the local bacterial population and to regulate gene expression accordingly. PA QS systems regulate about 350 genes (6% of the PA genome) and play a role in the regulation of a wide variety of processes including biofilm formation and production of numerous toxins. Given this regulatory breadth, it is not surprising that QS plays an essential role in virulence. Two primary QS systems were initially identified in PA, the *las* and the *rhl* systems. More recently a third QS system was identified in PA, referred to as the *Pseudomonas* Quinolone Signal (PQS). PQS is controlled by *las* system and itself regulates the *rhl* system, suggesting that it acts as link between the two systems.

Just as many environmental organisms synthesize antibiotics to gain an advantage over microbial competitors, some also produce enzymes that degrade the QS autoinducer signals of other species of bacteria. Recent evidence suggests that mammalian cells too have developed such capabilities. Paraoxonases (PONs) are mammalian enzymes that are capable of degrading PA autoinducer molecules and thereby have the potential to disrupt QS. Treatment of PA with PON-containing serum inhibited biofilm formation, which requires functional QS. Thus, these enzymes may play an important role in host defense against PA.

Numerous approaches have been successfully used to inhibit QS in culture and in vivo model systems (Table 2). For example, triclosan, an antimicrobial substance used in soaps, toothpaste, cleansers, and deodorants, has been shown to inhibit the synthesis of autoinducer. The anti-QS strategies of bacteria themselves have been exploited. Expression of bacterial enzymes that degrade autoinducers resulted in decreased production of QS-regulated toxins by PA. In another approach, natural and synthetic compounds have been screened for their utility in preventing the

interaction between the autoinducer and its receptor. Much effort has been directed towards furanones, compounds produced by marine macroalga with anti-fouling properties. Although naturally occurring furanones lacked substantial activity, modified furanone compounds inhibited QS and increased bacterial clearance in a mouse model of infection. Further investigations are necessary to determine whether these approaches will prove efficacious in inhibiting QS in human infections.

Table 2

Inhibitors of PA quorum sensing.

Class	Examples	Mechanism	References
autoinducer analogs	cyclopentanol, cyclopentylamide, and cyclohexanone compounds, tetrazole derivatives	block autoinducer receptor	(168–172, 104)
structurally unrelated autoinducer antagonists	4-nitro-pyridine-*N*-oxide, triphenyl compound	block autoinducer receptor	(173,174)
natural compounds	products from fungi (penicillic acid), marine macroalga (furanone derivatives), garlic, medicinal plants	decrease concentration of autoinducer receptor, unknown	(88–91, 101, 102 173, 175–178)
enzymes	AHL-lactonase, AHL-acylase	degrade autoinducers	(86,87)
antibiotics, metabolic compounds	azithromycin, triclosan, *S*-adenosylhomocysteine, *S*-adenosylcysteine, sinefungin	inhibit synthesis of autoinducer	(85, 179–180)

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