International Journal of ChemTech Research
CODEN (USA): IJCRGG, ISSN: 0974-4290, ISSN(Online):2455-9555
Vol.10 No.4, pp 115-125, 2017

Role of Penems in Treatment of Animal Bite Infection

[1]Kavita Varma*, [2]Seema Kohli

[1]Faculty of Pharmacy, Pacific Academy of Higher Education and Research University, Udaipur., India
[2]Pharmacy Department, Government Kalaniketan Polytechnic College, Jabalpur, M.P, India

Abstract : The animal bite wound infections in humans is often polymicrobial in nature, covering a wide spectrum of aerobic and anaerobic microorganisms. Bacteria recovered from infected bite wounds are mostly derived from the oral flora of the biting animal. This article describes the microbiology of animal bite wound infections and the role of penems, specially faropenem sodium, in its management. Faropenem exhibited good activity against the full spectrum of human and animal bite pathogens and merits clinical evalution in skin and soft tissue infections due to bite wounds.

Introduction

The skin is the largest organ of the body and, with the underlying soft tissue, which includes the fat layers, fascia and muscle, represents the majority of the tissue in the body. It acts as a tough, flexible, structural barrier to invasion. Direct infection of the skin occurs by invasion of the epidermis, usually after damage to the skin, and infection may affect any anatomical layer.[1]

Animal bites are responsible for up to 1% of all emergency health care visits, with dog bites representing up to 90% of all animal bites. Cat and human bites represent the second and third most common mammalian bites respectively. Species of animals that cause at least 1 percent of bite injuries are rabbits, skunks, squirrels, horses, hogs, rats, and monkeys. The laboratory animal population is another source of bites; monkeys and rats are the most common offenders [2]

The incidence of dog, cat and human bites has been increasing steadily and represents an important cause of morbidity and mortality possible complications may include disfigurement, dismemberment and infection. Effective management requires rapid medical evaluation and may necessitate surgical intervention and prophylactic antibiotic therapy. As bite wounds are microbiologically diverse and most often polymicrobial in nature, selection of an appropriate antibiotic regimen requires knowledge of common pathogens.[3]

Bite victims who seek medical attention can be classified into two groups based upon the time of presentation. The first group presents within 8-12 hours of the incident, with fears of contracting rabies or other infections, and/or with concerns of permanent disfiguration of the injured body part.[4] These wounds are often contaminated with bacteria but do not show evidence of infection. The second group seeks help more than 12 hours after the incident, most often presenting with signs and symptoms of developing infections.[5, 6]

Infection tends to develop rapidly after such injuries, usually within 24±36 h. Localized pain, cellulitis, and a purulent and possibly malodorous discharge are the most common findings, with fever and adenopathy occurring infrequently.[7]

The severity of wounds may span from a simple scratch to more severe punctures, lacerations oravulsions. All can result in significant damage, regardless of the amount of bleeding present. A laceration is defined as a tear in the flesh that produces a wound with irregular borders, which may ultimately lead to scarring and permanent disfigurement.

An avulsion results from the forcible tearing of skin away from underlying tissue and bone. A puncture wound occurs when a sharp object pierces skin tissue, and requires careful treatment because the small entry hole may disguise serious underlying injury and possible abscess formation.[8]

Among the various wound types, puncture wounds have the highest incidence of infection, whereas injuries involving the hand or joint as a location carry the greatest risk of infection and disfigurement. Other potential complications that should be considered include osteomyelitis, septic arthritis, tenosynovitis, local abscesses and, rarely, endocarditis, meningitis, brain abscess and sepsis.[9, 10]

Injuries from animal bites reflect the anatomy of the teeth and the strength of the jaws of the biting animal. Dog bites tend to cause lacerations, with crush and avulsion injuries as a function of the large, broad, sharp teeth and powerful jaws. Bites by cats, mice, rats and snakes tend to cause puncture wounds because of the characteristic sharp, elongated, needle-like teeth.[3]

Microbiology

Most infections that develop from dog and cat bites are polymicrobial, with a mean of 2.8 to 3.6 bacterial species isolated per wound culture, including an average of one anaerobic species per wound.[11]*Staphylococcus*sp., *Streptococcus* sp., and *Corynebacterium* sp. are the most commonly isolated aerobic organisms from infected dog bites.[12] Anaerobic bacteria are present in 38% to 76% of dog and cat bites. The most frequently isolated anaerobes include *Bacteroides fragilis*, *Prevotella*, *Porphyromonas*, *Peptostreptococcus*, and *Fusobacterium* sp., as well as *Veillonella parvula*.[13]

Pasteurella multocida, the major pathogen isolated from cat bites, is also associated with bites from dogs and many other animals *P. multocida* is a small aerobic, facultatively anaerobic, gram-negative coccobacillus, which can be difficult to culture. It is a component of the normal oral flora in 70% to 90% of cats and 50% to 66% of dogs. *P. multocida* has been found in 50% to 80% of cat bite wound infection and in 25% of dog bite wounds. [14]

Common Microorganisms Isolated from Animal Bite Wounds

Bacteria isolated from dog bite wounds[15, 16, 17]

Aerobes and facultative		Anaerobes
Aeromonas hydrophilic	*Klebsiella sp.*	*Actinomyces* sp.
Acinetobacter sp.	*Micrococcus sp.*	*Bacteroides* sp.
Actinobacillus sp.	*Moraxella sp.*	*Eubacterium* sp.
Bacillis sp.	*Neisseria sp.*	*Fusobacterium* sp.
Brucella canis	*Pasteurella multocida*	*Leptotrichia bacillus*
Capnocytophaga canimorsus	*Pasteurella gas*	*Peptococcus* sp.
CDC alpha-numeric groups	*Proteus mirabilis*	*Peptostreptococcus* sp.
Chromobacterium sp.	*Pseudomonas sp.*	*Porphyromonas*
Coynebacterium sp.	*Staphylococcus aureus*	*Prevotella* sp.
Eikenella corrodens	*Staphylococcus epidermidis*	*Propionibacterium* sp.
Enterobacter cloacae	*Staphylococcus sp.*	*Veillonella* sp.
Enterococcus sp.	*Streptococcus*	
Escherichia coli		
Hemophilus aphrophillus		

Bacteria isolated from cat bite wounds[15, 16, 17]

Aerobic and Facultative	Anaerobic
Acinetobacter sp.	*Bacteroides* sp.
Capnocytophaga canimorsus	*Fusobacterium nucleatum*
Corynebacterium sp.	*Porphyromonas*
Enterobacter cloacae	*Prevotella*
Neisseria sp.	*Propionibacterium* sp.
Pasteurella multocida	
Staphylococcus aureus	
Staphylococcus epidermidis	
Streptococcus sp.	

Antimicrobial Therapy

Prophylactic treatment

The use of antibiotics in a documented bite wound infection is justified; however, consensus for the prophylaxis of infection after a bite is less defined and remains controversial. Some authors have suggested that antibiotics should be considered therapeutic rather than prophylactic, arguing that no bite can be considered `clean', owing to the accompanying inoculation of bacteria.[18] Additionally, patients who present more than 24 h following injury without signs or symptoms of infection may not require antibiotics, as the majority of wounds become infected within this time period. If true prophylaxis is the goal, it has been suggested that antibiotic serum concentrations should be therapeutic within 3 hours after the injury.[18, 19] It is likely that many injuries are not evaluated this quickly, and if oral antibiotics are administered, the inherent absorption time would increase this delay. Although parenteral antibiotic administration to achieve early therapeutic serum concentrations before emergency department discharge may appear useful, literature recommendations do not support this level of aggressiveness for uncomplicated wounds.[18] In summary, data demonstrating the benefits of prophylactic antibiotic therapy are limited, with the majority of studies failing to show statistical significance owing to low infection rates and small numbers of patients. Dog-bite wounds have demonstrated the lowest frequency of infection, whereas cat bites appear to develop infection at a significantly higher rate. Differences in these studies, such as the non-standardization of wound care, utilization of different antibiotic regimens, and the inclusion of wounds of varying severity make them difficult to compare. Larger, better designed studies are needed to answer these questions definitively; however, it appears that antibiotic prophylaxis may not be necessary in low risk bite wounds, but may be of benefit in higher risk patients and patients suffering from cat bites. Time of presentation and interventions such as meticulous wound care may prove to be more important in preventing infection than prophylactic antibiotic therapy.[3]

Emperic therapy of infected wounds

An appropriate emperic antibiotic regimen must be directed at the pathogens most likely to cause infection, including both aerobic and anaerobic bacteria. Therapy should target organisms from both the oral cavity of the animal causing the bite, as well as potential pathogens from the skin flora of the victim. For dog and cat bites, therapy should include coverage of *S. aureus*, *P. multocida*, *streptococcus* spp. and anaerobes. Cultures of infected wounds should be obtained, and antibiotic therapy tailored towards identified pathogens and sensitivities where available. As most infected wounds are polymicrobial in nature, pathogens such as anaerobes may be difficult to isolate and should still be included in the antibiotic regimen. *Capnocytophaga canimorsus* is another difficult organism to isolate and may take as long as 2 weeks to grow in culture.[20] A gram stain of the wound may be of limited benefit, as it has been shown to be a specific but insensitive test when evaluated in a small number of patients.[21] The most commonly utilized agent to treat mammalian bite wounds is amoxicillin/clavulanate, owing to the additional anaerobic coverage offered by the β-lactamase inhibitor, allowing for monotherapy. Alternative regimens include clindamycin plus ciprofloxacin, dicloxacillin plus penicillin, tetracyclines, trimethoprim/sulfamethoxazole, and second- or third-generation cephalosporins such as cefuroxime. Monotherapy with dicloxacillin, first-generation cephalosporins, clindamycin and erythromycin should be avoided in dog and cat bites due to poor in vitro *P. multocida* activity.[22] A number of significant clinical failures have been reported with the use of erythromycin monotherapy.[23]

Role of Penems.

β-lactam antimicrobials are widely recognized for their efficacy and low toxicity and form the cornerstone of therapy for the treatment of infections caused by gram-positive and gram-negative bacteria. However, extensive use of β-lactams during the past 50 years has resulted in the development of microbial resistance to these agents among clinically important bacteria.[24] This resistance commonly takes the form of β-lactamase production or alterations in penicillin binding proteins (PBPs).[24, 25] Such mechanisms have reduced the clinical utility of frequently prescribed β-lactams such as amoxicillin, amoxicillin plus clavulanate (a β-lactamase inhibitor), and cephalosporins. The issue of resistance continues to drive the search for new compounds with increased stability and efficacy against resistant pathogens.

The options for derivatizing naturally occurring β-lactams have been explored to near exhaustion, with attention focused on synthetic β-lactams, the penems, in the search for novel compounds.[26] Designed and synthesized in 1977, these molecules are derived from the core structures of penicillin and cephalosporin molecules.[27] They offer good β-lactamase stability and in vitro activity against a broad range of pathogenic bacteria.

Faropenem (previously known as SUN5555, SY5555, WY49605, RU67655, ALP201, BLA 857, YM 044, farom, fropenem, and furopenem) is the most well-studied member of the penem class. Three forms of faropenem have been described: free acid, sodium salt, and daloxate prodrug derivative (Figure 1).

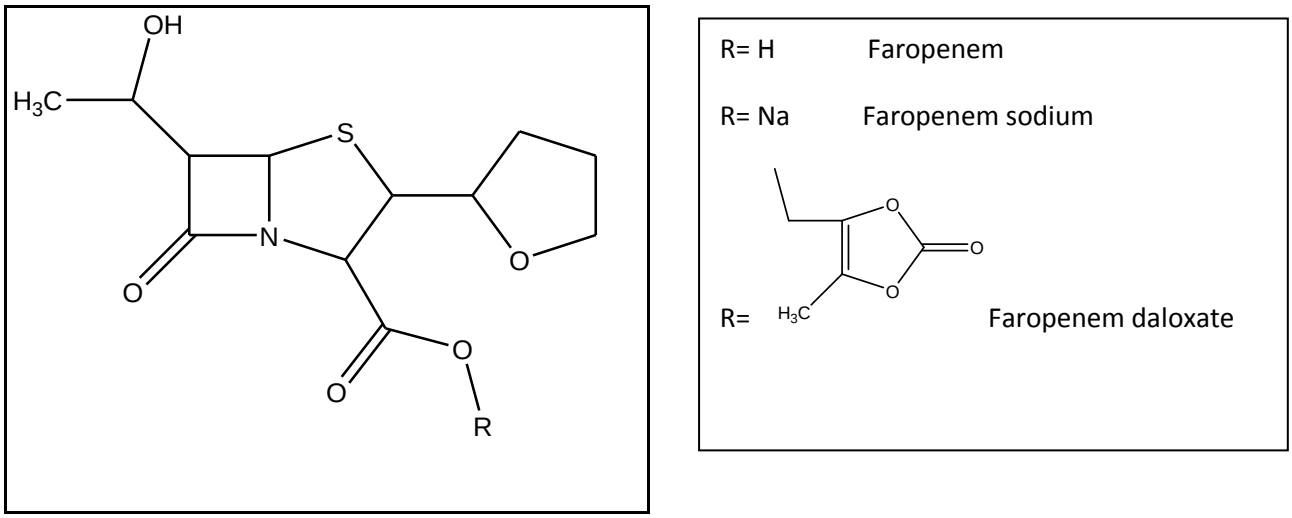

Figure 1 Structures of the three forms of faropenem.

Faropenem originally was synthesized as the sodium salt, but the oral bioavailability of this compound was only 20-30%. In contrast, the daloxate ester has an oral bioavailability of 70-80%.[28] This ester is hydrolyzed rapidly in vivo to release the active free acid.

As with other penems, faropenem induces bactericidal effects by binding to PBPs and inhibiting bacterial cell wall synthesis. These bactericidal effects were found to be affected by the nature of the tetrahydrofuran side chain, with an unsaturated derivative showing reduced activity compared with that of the saturated derivative (faropenem).[29] Faropenem is also less susceptible to the actions of DHP-1 than are the carbapenems imipenem and meropenem[30]; it has been proposed that the absence of a protonable group in the 2-side chain of faropenem, in contrast to the presence of such groups in the equivalent side chains of the carbapenems, is responsible for this phenomenon.[30] Finally, faropenem is resistant to the effects of many bacterial β-lactamases. This property is thought to be due to the 1-(R)-hydroxyethyl group at C6 of the bicyclic molecule.

In vitro studies of faropenem have focused primarily on typical respiratory pathogens and staphylococci.[31] The present review evaluates the activity of faropenem against the specific range of bacteria commonly found in human and animal bite wound infections, which are unique in that the pathogen source is the oral flora of the biting animal, such as *Pasteurella* spp., *Eikenella corrodens*, *Prevotella heparinolytica* and

some skin pathogens. Goldstein *et al* determinedthe activity of faropenem against 407 aerobic and anaerobic strains isolated from such infections in humans.[32]The specific sources were: dog bites, 99; cat bites, 108; human bites, 191; and other animal bites, seven. All isolates were identified by standard criteria, the numbers and species tested are given in Table 1.[32]

Organism	**Agent**	**MIC (mg/L)**	
		50%	**90%**
Pasteurella multocida subsp. *multocida* (12)	faropenem	0.25	0.25
	penicillin	0.125	0.125
	ampicillin-sulbactam	0.25	0.25
	co-amoxiclav	0.25	0.25
	imipenem	0.125	0.5
	meropenem	≤0.015	≤0.015
	ertapenem	≤0.015	≤0.015
	ciprofloxacin	≤0.06	≤0.06
	moxifloxacin	≤0.06	≤0.06
	levofloxacin	≤0.06	≤0.06
	doxycycline	0.25	0.25
	erythromycin	1	2
Pasteurella multocida subsp. *septica* (11)	faropenem	0.25	0.25
	penicillin	0.125	0.125
	ampicillin-sulbactam	0.25	0.25
	co-amoxiclav	0.25	0.25
	imipenem	0.125	0.25
	meropenem	≤0.015	0.03
	ertapenem	≤0.015	≤0.015
	ciprofloxacin	≤0.06	≤0.06
	moxifloxacin	≤0.06	≤0.06
	levofloxacin	≤0.06	≤0.06
	doxycycline	0.125	0.25
	erythromycin	1	2
Pasteurella canis/dagmatis/stomatis (16)	faropenem	0.25	0.25
	penicillin	0.06	0.125
	ampicillin-sulbactam	0.125	0.25
	co-amoxiclav	0.125	0.25
	imipenem	0.125	0.25
	meropenem	≤0.015	0.03
	ertapenem	≤0.015	≤0.015
	ciprofloxacin	≤0.06	≤0.06
	moxifloxacin	≤0.06	≤0.06
	levofloxacin	≤0.06	≤0.06
	doxycycline	0.125	0.25
	erythromycin	0.5	1
Bergeyella zoohelcum (12)	faropenem	0.25	0.5
	penicillin	0.125	0.25
	ampicillin-sulbactam	0.125	0.125
	co-amoxiclav	0.125	0.125
	imipenem	0.06	0.06
	meropenem	0.06	0.06
	ertapenem	0.25	0.5
	ciprofloxacin	≤0.06	≤0.06
	moxifloxacin	≤0.06	≤0.06
	levofloxacin	≤0.06	≤0.06
	doxycycline	1	2

	erythromycin	0.5	0.5
EF-4 a and b (13)[c]	faropenem	0.125	0.25
	penicillin	0.25	2
	ampicillin-sulbactam	0.25	0.5
	co-amoxiclav	0.25	0.5
	imipenem	0.125	0.25
	meropenem	≤0.015	0.03
	ertapenem	≤0.015	≤0.015
	ciprofloxacin	≤0.06	≤0.06
	moxifloxacin	≤0.06	≤0.06
	levofloxacin	≤0.06	≤0.06
	doxycycline	0.25	0.5
	erythromycin	0.5	1
Eikenella corrodens (19)	faropenem	0.25	0.25
	penicillin	1	4
	ampicillin-sulbactam	0.5	1
	co-amoxiclav	0.5	0.5
	imipenem	0.125	0.25
	meropenem	0.03	0.03
	ertapenem	0.03	0.03
	ciprofloxacin	≤0.06	≤0.06
	moxifloxacin	≤0.06	≤0.06
	levofloxacin	≤0.06	≤0.06
	doxycycline	2	4
	erythromycin	4	16
Moraxella spp. (10)*d*	faropenem	0.03	0.125
	penicillin	0.06	0.25
	ampicillin-sulbactam	0.03	0.25
	co-amoxiclav	0.06	0.5
	imipenem	0.06	0.125
	meropenem	≤0.015	≤0.015
	ertapenem	≤0.015	≤0.015
	ciprofloxacin	≤0.06	≤0.06
	moxifloxacin	≤0.06	≤0.06
	levofloxacin	≤0.06	≤0.06
	doxycycline	0.25	0.5
	erythromycin	0.25	0.5
Neisseria weaverii (M-5) (11)	faropenem	0.06	0.125
	penicillin	0.125	0.125
	ampicillin-sulbactam	0.125	0.25
	co-amoxiclav	0.125	0.25
	imipenem	0.06	0.125
	meropenem	≤0.015	≤0.015
	ertapenem	≤0.015	≤0.015
	ciprofloxacin	≤0.06	≤0.06
	moxifloxacin	≤0.06	≤0.06
	levofloxacin	≤0.06	≤0.06
	doxycycline	0.25	0.25
	erythromycin	0.5	1
Corynebacterium and other Gram-positive bacilli (21)*g*	faropenem	0.25	4
	penicillin	0.125	4
	ampicillin-sulbactam	0.25	4
	co-amoxiclav	0.25	4
	imipenem	0.03	1

	meropenem	0.125	1
	ertapenem	0.125	2
	ciprofloxacin	0.25	2
	moxifloxacin	0.125	0.25
	levofloxacin	0.25	2
	doxycycline	0.25	0.5
	erythromycin	0.125	2
Enterococcus spp. (10)*h*	faropenem	0.5	1
	penicillin	0.06	2
	ampicillin-sulbactam	0.125	1
	co-amoxiclav	0.125	0.5
	imipenem	0.06	1
	meropenem	0.125	4
	ertapenem	1	8
	ciprofloxacin	0.5	1
	moxifloxacin	0.125	0.25
	levofloxacin	0.5	1
	doxycycline	0.125	8
	erythromycin	≤0.125	>32
Staphylococcus aureus (19)	faropenem	0.125	0.25
	penicillin	2	>8
	ampicillin-sulbactam	1	8
	co-amoxiclav	0.5	2
	imipenem	≤0.015	0.03
	meropenem	0.06	0.20
	ertapenem	0.125	0.5
	ciprofloxacin	0.125	0.5
	moxifloxacin	≤0.06	≤0.06
	levofloxacin	0.125	0.25
	doxycycline	0.125	0.125
	erythromycin	0.25	>32
Staphylococcus epidermis(12)	faropenem	0.06	0.5
	penicillin	0.125	2
	ampicillin-sulbactam	0.25	2
	co-amoxiclav	0.125	0.5
	imipenem	≤0.015	0.125
	meropenem	0.06	0.5
	ertapenem	0.125	1
	ciprofloxacin	0.125	0.125
	moxifloxacin	≤0.06	≤0.06
	levofloxacin	0.125	0.25
	doxycycline	0.125	2
	erythromycin	≤0.125	>32
Streptococcus spp. (37)*j*	faropenem	0.06	0.06
	penicillin	0.06	0.125
	ampicillin-sulbactam	0.125	0.25
	co-amoxiclav	0.06	0.25
	imipenem	≤0.015	0.03
	meropenem	0.03	0.06
	ertapenem	0.06	0.25
	ciprofloxacin	1	4
	moxifloxacin	0.25	0.25
	levofloxacin	1	1
	doxycycline	0.25	16

	erythromycin	≤0.125	16
Anaerobes *Bacteroides tectum* (13)	faropenem	0.25	0.25
	penicillin	0.03	8
	ampicillin-sulbactam	0.06	1
	co-amoxiclav	0.06	0.25
	imipenem	0.125	0.25
	meropenem	0.03	0.125
	ertapenem	0.03	0.125
	ciprofloxacin	0.5	2
	moxifloxacin	0.125	0.25
	levofloxacin	0.25	1
	doxycycline	0.25	4
	erythromycin	0.25	0.5
Fusobacterium spp. (20)*m*	faropenem	≤0.015	0.06
	penicillin	≤0.015	0.125
	ampicillin-sulbactam	≤0.015	0.25
	co-amoxiclav	≤0.015	0.25
	imipenem	≤0.05	0.25
	meropenem	≤0.015	≤0.015
	ertapenem	≤0.015	0.03
	ciprofloxacin	2	>8
	moxifloxacin	0.25	8
	levofloxacin	1	>8
	doxycycline	≤0.06	0.25
	erythromycin	2	4
Porphyromonas spp. (18)*n*	faropenem	≤0.015	0.06
	penicillin	≤0.015	0.5
	ampicillin-sulbactam	0.03	0.06
	co-amoxiclav	≤0.015	0.06
	imipenem	≤0.015	0.125
	meropenem	≤0.015	0.03
	ertapenem	≤0.015	0.03
	ciprofloxacin	1	2
	moxifloxacin	≤0.06	0.5
	levofloxacin	0.25	1
	doxycycline	0.125	0.25
	erythromycin	≤0.125	0.25
Prevotella heparinolytica (14)	faropenem	0.125	0.25
	penicillin	0.25	0.25
	ampicillin-sulbactam	0.25	0.25
	co-amoxiclav	0.25	0.25
	imipenem	0.125	0.25
	meropenem	0.125	0.25
	ertapenem	0.125	0.25
	ciprofloxacin	2	2
	moxifloxacin	0.25	0.5
	levofloxacin	0.5	1
	doxycycline	≤0.06	2
	erythromycin	≤0.125	≤0.125
Eubacterium spp. (19)*q*	faropenem	0.06	0.5
	penicillin	0.03	0.06
	ampicillin-sulbactam	0.03	0.125
	co-amoxiclav	≤0.015	0.125
	imipenem	0.03	0.125

	meropenem	≤0.015	0.125
	ertapenem	0.06	0.5
	ciprofloxacin	0.5	2
	moxifloxacin	0.25	1
	levofloxacin	0.5	4
	doxycycline	0.125	1
	erythromycin	≤0.125	0.25
Peptostreptococcus spp. (16)*r*	faropenem	0.125	1
	penicillin	0.125	0.5
	ampicillin-sulbactam	0.25	1
	co-amoxiclav	0.25	2
	imipenem	0.06	0.25
	meropenem	0.06	0.25
	ertapenem	0.25	1
	ciprofloxacin	0.5	2
	moxifloxacin	0.25	0.5
	levofloxacin	0.5	4
	doxycycline	≤0.06	16
	erythromycin	≤0.125	>32
Veillonella spp. (11)	faropenem	0.25	4
	penicillin	0.25	8
	ampicillin-sulbactam	0.125	1
	co-amoxiclav	0.125	2
	imipenem	0.06	0.25
	meropenem	0.03	0.25
	ertapenem	0.06	2
	ciprofloxacin	0.125	0.125
	moxifloxacin	0.125	0.125
	levofloxacin	0.25	0.5
	doxycycline	1	2
	erythromycin	4	8

Discussion

Selection of an inappropriate antimicrobial agent for the therapy of infected bite wounds can lead to therapeutic failure and long-term sequelae.[33, 34] While beta-lactams have been the traditional drugs of choice; many patients report a history of penicillin allergy or side effects and require the selection of an alternative agent. This choice has been somewhat problematic in the past, since erythromycin MICs against bite pathogens have been inconsistent[35] and clinical failures erythromycin therapy have been reported [33, 34, 36]

Other agents, such as the fluoroquinolones, were also attractive, but some relatively common bite isolate species, such as the fusobacteria, were often resistant[37] prior clinical experience had suggested that tetracyclines were attractive alternative agents, but tetracycline resistance evolved, both because of efflux-based and ribosomal protection mechanisms, and some bite isolates were resistant[38]

Faropenem inhibited 395/405 (98%) of the aerobic and anaerobic isolates at ≤1 mg/L. The 10 isolates that required ≥2 mg/L for inhibition were *Acinetobacter lwoffi* (one strain, 4 mg/L), *Corynebacterium* '*aquaticum*' (two strains, 8 mg/L), *Corynebacteriumminutissimum* (one strain, 4 mg/L), *Bacteroidesovatus* (one strain, 2 mg/L), *Lactobacillus delbrueckii* (one strain, 4 mg/L), *Peptostreptococcus tetradius* (one strain, 4 mg/L) and *Veillonella* spp. (three strains, 4–8 mg/L). Von Eiff *et al.*[39] found faropenem to be 'active against a considerable number of methicillin-resistant strains of *Staphylococcus aureus* (MRSA) and coagulase-negative staphylococci'. They reported that 18 of 31 MRSA strains were inhibited by ≤2 mg/L of faropenem but had an MIC90 of >128 mg/L. All *Staphylococcus epidermidis* isolates, both methicillin-susceptible and resistant, were inhibited by 0.25 mg/L of faropenem. All our *S. aureus* isolates, none of which was methicillin resistant, were

inhibited by ≤0.5 mg/L of faropenem. All our *S. epidermidis* isolates and other coagulase-negative *Staphylococcus* species isolates, none of which was methicillin resistant, were inhibited by ≤1 mg/L. However, Hikida *et al.*[40] and Miyazaki *et al.*[41]found faropenemto have an MIC90 of 0.2 mg/L against methicillin-susceptible*S. aureus* but to be inactive against MRSA with MIC50s of>100mg/L and>128 mg/L, respectively. Their reports suggest abimodal distribution of activity against *S. epidermidis* withHikida *et al.*6 reporting an MIC50 of 0.1 mg/L and an MIC90>100 mg/L, and Miyazaki *et al.*7 reporting an MIC50 of 2 mg/Land an MIC90 of >128 mg/L for methicillin-resistant strains. Faropenem had similar MIC ranges and MIC90s to coamoxiclav,which was active against most aerobic and anaerobicisolates. The carbapenems tested (imipenem, meropenem and ertapenem) had excellent activity against almost all isolates, except for the enterococci. The fluoroquinolones tested(ciprofloxacin, moxifloxacin and levofloxacin) had goodactivity against most aerobes but were less active than faropenemagainst most anaerobes. Erythromycin was the leastactive agent tested.

Faropenem exhibited good activity against the full spectrumof human and animal bite pathogens and merits clinical evaluationin skin and soft tissue infections due to bite wounds. Theactivity of faropenem, coupled with its β-lactamase stabilityand the ability to be taken orally, makes it suitable for treating the outpatient bite wound population.

References

1. Mims C, Playfair J, Roitt I et al. Medical Microbiology. Mosby Int Ltd, London. ISBN 0 7234 2781 X
2. Sacks JJ, Kresnow M, Houston B. Dog Bites: how big a problem? *Inj. Prev.* 1996; **2**: 52–4.
3. Smith P.F, Meadowcroft A.M, Maya D.B Treating mammalian bite wounds Journal of Clinical Pharmacy and Therapeutics (2000) 25, 85±99
4. Sacks JJ, Lockwood R, Hornreich J, Sattin RW. (1996) Fatal dog attacks, 1989±1994. Pediatrics, 6, 891±895.
5. Goldstein EJC, Citron DM, Finegold SM. (1980) Dog bite wounds and infection: a prospective clinical study. Annals of Emergency Medicine, 9, 508±512.
6. Goldstein EJC (1995) In: Mandell GL, Bennett JE, Dolin R, eds. Principles and Practice of Infectious Diseases, 4th edn. New York: Churchill Livingstone, 2765±2769.
7. Rest Goldstein EJC. (1985) Management of human and animal bite wounds. Emergency Medicine Clinics of North America, 3(1), 117±126.
8. Feder HM, Shanley JD, Barbera JA. (1987) Review of 59 patients hospitalized with animal bites. Pediatric Infectious Disease Journal, 6, 24±28.
9. Anon. (1990) The Bantam Medical Dictionary. Bantam Books, New York.
10. Brook I. (1989) Human and animal bite infections. Journal of Family Practice, 28(6), 713±718.
11. Weber DJ, Hansen AR. Infections resulting from animal bites. Infect Dis Clin North Am 1991;5:663-80.
12. Goldstein EJC, Citron DM, Finegold SM. Dog bite wounds and infection: a prospective clinical study. Ann Emerg Med 1980;9:508-12.
13. Brook I. Microbiology of human and animal bite wounds in children. Pediatr Infect Dis J 1987;6:29-32.
14. Weber DJ, Wolfson JS. Swartz MN. Pasteurella multocida infections: reports of 34 cases and review of the literature. Medicine 1984;63:133-54.
15. Goldstein EJC (1995) In: Mandell GL, Bennett JE, Dolin R, eds. Principles and Practice of Infectious Diseases, 4th edn. New York: Churchill Livingstone, 2765±2769.
16. Weber DJ, Hansen AR. (1991) Infections resulting from animal bites. Infectious Disease Clinics of North America, 5(3), 663±680.
17. Agahbabian RV, Conte JE. (1980) Mammalian bites wounds. Annals of Emergency Medicine, 9(2), 79±82.
18. Levy JA. (1989) Human immunodeficiency viruses and the pathogenesis of AIDS. Journal of the American Medical Association, 261(20), 2997±3006.
19. Brook I. (1987) Microbiology of human and animal bite wounds in children. Pediatric Infectious Disease Journal, 6, 29±32.
20. Sacks JJ, Lockwood R, Hornreich J, Sattin RW. (1996) Fatal dog attacks, 1989±1994. Pediatrics, 6, 891±895.

21. Goldstein EJC, Citron DM, Finegold SM. (1980) Dog bite wounds and infection: a prospective clinical study. Annals of Emergency Medicine, 9, 508±512.
22. Goldstein EJC, Citron DM, Vagvolgyi AE, Finegold SM. (1986) Susceptibility of bite wound bacteria to seven oral antimicrobial agents, including RU-985, a new erythromycin: considerations in choosing emperic therapy. Antimicrobial Agents and Chemotherapy, 29, 556±559.
23. Levin JM, Talan DA. (1990) Erythromycin failure with subsequent Pastrurella multocida meningitis and septic arthritis in a cat-bite victim. Annals of Emergency Medicine, 19, 1458±1461.
24. Gold HS, Moellering RC. Antimicrobial drug resistance. N Engl J Med 1996;335:1445-53.
25. Livermore DM. β-lactamases in laboratory and clinical resistance. Clin Microbiol Rev 1995;8:557-84.
26. Bryskier A. Penems: new oral β-lactam drugs. Exp Opin Invest Drugs 1995;4:705-24.
27. 27.Woodward RB. Recent advances in the chemistry of β-lactam antibiotics. In: Elks J, ed. Recent advances in the chemistry of β-lactam antibiotics. Special publication, vol 23. London: The Chemical Society, 1977:167-80.
28. Bayer Corporation. Data on file. West Haven, CT; 2003.
29. Ishiguro M, Iwata H, Nakatsuka T, et al. Synthesis and in vitro activity of novel 2-chiral substituted penems. J Antibiot 1988;41:1685-93.
30. Amyes SGB, Thomson CJ. Faropenem, the first furanem. [abstr]. Presented at the 1st international meeting on penems, carbapenems and related compounds, 'nems 2001. Venice, Italy, December 13-15, 2001.
31. Miyazaki, S., Hosoyama, T., Furuya, N., Ishii, Y., Matsumoto,T., Ohno, A. et al. (2001). In vitro and in vivo antibacterial activities of L-084, a novel oral carbapenem, against causative organisms of respiratory tract infections. Antimicrobial Agents and Chemotherapy 45, 203–7.
32. Ellie J. C. Goldstein, Diane M. Citron, C. Vreni Merriam, Yumi A. Warren, Kerin L. Tyrrell and Helen T. Fernandez, Comparative *in vitro* activity of faropenem and 11 other antimicrobial agents against 405 aerobic and anaerobic pathogens isolated from skin and soft tissue infections from animal and human bites *Journal of Antimicrobial Chemotherapy* (2002) 50, 411–420
33. Kumar, A., H. R. Devlin, and H. Velland. 1990. *Pasteurella multocida* meningitis in an adult: case report and review. Rev. Infect. Dis. **12:**440–448.
34. Levin, J. M., and D. A. Talan. 1990. Erythromycin failure with subsequent *Pasteurella multocida* meningitis and septic arthritis in a cat bite victim. Ann. Emerg. Med. **19:**1458–1461.
35. Goldstein, E. J. C., D. M. Citron, and G. A. Richwald. 1988. Lack of in vitro efficacy of oral forms of certain cephalosporins, erythromycin, and oxacillin against *Pasteurella multocida*. Antimicrob. Agents Chemother. 32:213–215.
36. Orton, D. W. 1984. *Pasteurella multocida*: bilateral septic knee joint prosthesis from a distant cat bite. Ann. Emerg. Med. 13:1065–1067.
37. Goldstein, E. J. C., D. M. Citron, M. Hudspeth, S. H. Gerardo, and C. V. Merriam. 1997. In vitro activity of Bay 12-8039, a new 8-methoxy quinolone, compared to 11 other oral antimicrobial agents against 390 aerobic and anaerobic bacteria isolated from human and animal bite wound skin and soft tissue infections in humans. Antimicrob. Agents Chemother. 41:1552–1557.
38. Petersen, P. J., N. V. Jacobus, W. J. Weiss, P. E. Sum, and R. T. Testa. 1999. In vitro and in vivo antibacterial activities of a novel glycylcycline, the 9-*t*-butylglycylamino derivative of minocycline (GAR-936). Antimicrob. Agents Chemother. 43:738–744.
39. Von Eiff, C., Scheepers, S. & Peters, G. (2001). Comparative invitro activity of faropenem against staphylococci. In Proceedings of the Forty-first Interscience Conference on Antimicrobial Agents and Chemotherapy, Chicago, IL, 2001. Abstract 798, p. 184. American Society for Microbiology, Washington, DC, USA.
40. Hikida, M., Itahashi, K., Igarashi, A., Shiba, T. & Kitamura, M. (1999). In vitro antibacterial activity of LJC 11,036, an active metabolite of L-084, a new oral carbapenem antibiotic with potent antipneumococcal activity. Antimicrobial Agents and Chemotherapy 43, 2010–6.
41. Miyazaki, S., Hosoyama, T., Furuya, N., Ishii, Y., Matsumoto, T., Ohno, A. et al. (2001). In vitro and in vivo antibacterial activities of L-084, a novel oral carbapenem, against causative organisms of respiratory tract infections. Antimicrobial Agents and Chemotherapy 45, 203–7.

*****