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Hu M, Hui-Yu Li, Hu T, Zhou S ...+5 more authors

Institutions: Shanxi Medical University

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Topics: Bergeyella zoohelcum, Chocolate agar, Agar plate, Fastidious organism and Agar

The Detection of *Bergeyella zoohelcum* in Young Children after Cat Bite

Min Hu,[*]†[a] Hao Li,†[a] Tao Hu,[b] Shuang-Yan Zhou,[c] Ze-Hua Yang,[a] Cai-Lan Fan,[a] Rong Bao,[a] Jian-Guo Shi,[a] Ke-Bin Zhao[a]

[a]Department of Laboratory Medicine, The First Hospital of Shanxi Medical University, Taiyuan, Shanxi, China

[b]Department of General Surgery, The Sixth Hospital of Shanxi Medical University, Taiyuan, Shanxi, China

[c]Department of Center Laboratory, Shanxi Cardiovascular Hospital, Taiyuan, Shanxi, China

ABSTRACT *Bergeyella zoohelcum* is an uncommon zoonotic pathogen typically associated with cat or dog bites. Previously, only 14 cases of *B. zoohelcum* infection have been reported. We isolated the bacteria from the face of a 2-year-old girl who was bitten by a cat. The organism was identified by matrix-assisted laser desorption ionization-time of flight mass spectrometry (MALDI-TOF MS) and 16S rRNA gene sequence, and phylogenetic analysise supported that this isolate was belong to *B.*

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[*]Corresponding author. Mailing address: Department of Laboratory Medicine, The First Hospital of Shanxi Medical University, No. 85, South Jiefang Road, Taiyuan 030001, Shanxi, Tel./fax: +86-13934201449. E-mail: humin453056591@126.com
†Equal contributors

zoohelcum. Due to the contradicts of culture characteristics of *B. zoohelcum* which described in reported literatures, we used different media to culture the bacteria. After 24 h incubation, Colombia blood agar (CBA), Mueller-Hinton agar plate with 5% sheep blood and chocolate agar (CA) grew well, but blood agar (BA) grew well until 72 h. The strain did not grow on McConkey agar (MAC), Mueller-Hinton agar (MHA) and chocolate agar (containing vancomycin). The low detection rate of this strain was related to its harsh growth conditions and the limitations of traditional identification techniques. With the popularization of MALDI-TOF MS and 16S rRNA gene sequence and our further understanding of the fastidious bacteria, we will quickly and accurately identify the *B. zoohelcum*, meanwhile the detection rate of this bacterium will also be significantly improved. So that clinicians can achieve precise anti-infective treatment according to antimicrobial susceptibility testing.

KEYWORDS animal bites, *Bergeyella zoohelcum*, fastidious, detection rate, antimicrobial susceptibility

Visits to the emergency room (ER) on account of animal bites are not unusual. In fact, approximately 1% of all visits to the ER are related to bites by animals. Roughly 5 to 15% of the animal bites reported are feline inflicted (1). Cat bites are more likely to penetrate deeply, leaving only a small and deep punctures skin opening that provide access to the ideal subcutaneous breeding ground for any anaerobic opportunistic pathogen transferred from the cat′s mouth, and tend to carry a higher risk of infection and soft-tissue abscess (2). In general, the smaller the victim, the more likely a facial or scalp injury will occur; the frequency of 63% for victims less than 4 years of age are at a greatly increased risk of being bitten on the head, face, or neck (3).

Most infections caused by animal bites are polymicrobial, with mixed aerobic and anaerobic species (1). Common pathogens associated with animal bites include *Staphylococcus, Streptococcus, Pasteurella, Capnocytophaga, Moraxella, Corynebacterium, Neisseria*, and anaerobic bacteria. *Pasteurella multocida* subspecies *multocida* and *septica* were the most common isolates of cat bites (4). Up to now, a great deal of literature has commented on the pathogenic role of *Pasteurella multocida* in cat bite injuries. However, there have been few reports of *B. zoohelcum.* In our laboratory, both *Pasteurella multocida* and *B. zoohelcum* were simultaneously isolated from the secretion wound by a cat bite of a 2-year-old girl. In the literature review, only 14 cases of *B. zoohelcum* were reported, therefore, we further discussed the reasons for the low detection rate of *B. zoohelcum*.

Case history. A healthy 2-year-old girl was bitten by a cat. Examination of the head and face showed multiple wounds, which damaged the muscle layer and was accompanied by obvious active bleeding. One hour after the girl was bitten, she was injected with rabies vaccine and tetanus immunoglobulin. In order to seek further treatment, the patient was admitted to the emergency department of hospital (The First Hospital of Shanxi Medical University, Taiyuan, shanxi, China), then, transferred to the department of plastic surgery. Laboratory evaluation revealed leukocyte count of 17,200 per cubic millimeter, with 81.5% neutrophils, 14.4% lymphocytes, and 3.7% monocytes. The girl was operated on within 2 h of admission. Basic medical management of bite wounds includes thorough cleansing and debridement. The wound was copiously irrigated with iodopor, hydrogen peroxide and normal saline. Debridement and suturing under general anesthesia was performed to remove wound edges and the tissue with poor activity. Wound specimens were taken for culture. Empirical antibiotic treatment with cefuroxime sodium 375 mg/8 h intravenously guttae was initiated. On the second day of hospitalization, all wounds healed well without further infection and swelling of her face had decreased substantially, therapy was swithed to apply mupiroxine ointment on the wounds. The patient was discharged from the hospital 8 days after admission.

MATERIALS AND METHODS

Bacterial strains. The strain was isolated from a 2-year-old girl after a cat bite wound.

Culture conditions. Growth was tested on the following media: BA (Autobio, Henan, China), CBA (Autobio, Henan, China), MH agar plate with 5% sheep blood (Autobio, Henan, China), CA (Autobio, Henan, China), CA containing vancomycin (Autobio, Henan, China), MAC (Autobio, Henan, China), and MHA (Autobio, Henan, China). The plate contents were incubated at 35°C with 5% CO_2. Growth was evaluated for the following cultured time range: 24 h, 48 h, 72 h.

Species identification. The isolated strain was identified by Vitek 2 system (bioMérieux SA, Marcy, France) and MALDI-TOF MS (bioMérieux SA, Marcy, France).

16S rRNA sequence and phylogenetic analysis. The isolate was characterized by amplifying, sequencing, and analyzing the 16S rRNA gene. A fragment of approximately 1400 bp was amplified by PCR from the extracted DNA using bacterial universal primer sets 27F (5′ AGA GTT TGA TCC TGG CTC AG 3′) and 1492R (5′ TAC GGC TAC CTT GTT ACG ACT T 3′). Sequences were determined using an automatic DNA sequencer (Applied Biosystems 3730XL DNA Analyzer, Foster, USA). The 16S rRNA gene sequences were compared with the records of the GenBank database (http://www.ncbi.nlm.nih.gov/blast) using BLAST searches. A subset of the DNAMAN alignment, including the isolate 16S-D3.13302251 sequence, related sequences (representatives of the *Chryseobacterium*, *Cloacibacterium* and *Elizabethkingia*), and the sequence of *Weeksella virosa* ATCC 43766 (used as an outgroup), was selected for more detailed phylogenetic analysis. Sequence alignments were carried out using Clustal X. Aligned sequences were analyzed using MEGA software (MEGA version 7.0). The phylogenetic distances were calculated by the maximum-likelihood methods and a phylogenetic tree was constructed using an neighbor-joining plot program. The robustness of this tree was assessed by bootstrap method (1000 replicates with resampling of all positions).

Antibiotic susceptibility testing (AST). The antimicrobial susceptibility of the *B. zoohelcum* strain was determined by the Kirby-Bauer disk diffusion method on MHA plate with 5% sheep blood with use of Oxoid disk.

Nucleotide sequence accession numbers. The GenBank accession numbers for the 16S rRNA sequence of the *B. zoohelcum* 16S-D3.13302251 strain is as follow:

MW534713.

RESULTS

Biochemical characteristics. The isolate grew well on the CBA, MHA plate with 5% sheep blood and CA after 24 h. While the strain did not grow on the blood agar plates after 24 h. Light growth of the strain was observed on the BA until cutrured for 48 h. The organism did not grow on CA (containing vancomycin), MAC and MHA after 24 h, 48 h and 72 h (Fig. 1). Colonies were circular, gray, wet, translucent, shiny, smooth, with entire edge and very sticky, making them difficult to remove from solid media. No hemolysis was seen on Colombia blood agar plates. The organism test positive for oxidase, catalase and indole. Urease is strongly positive immediately.

Determination of Vitek 2 system, MALDI-TOF MS and 16S rRNA gene sequence. A Vitek 2 system was used to identify the strain as *Sphingomonas parapaucimobilis*, with only 91% identity. Strain identified as *B. zoohelcum* by MALDI-TOF MS was subjected to 16S rRNA gene sequencing analysis to confirm identification by MALDI-TOF MS. Nucleotide alignment using investigated sequences from the GenBank database showed high similarity with *B. zoohelcum* strain. Thus, identification result obtained by MALDI-TOF MS were concordant with those obtained by 16S rRNA gene sequencing analysis.

phylogenetic analysis. Retrieving the 16S rRNA gene sequences of species showing relatively high similarities to the 16S-D3.13302251, a phylogenetic tree was constructed (Fig. 2). The type strain with the greatest pairwise similarity to strain

16S-D3.13302251 was *B. zoohelcum* ATCC 43767^T and *B. zoohelcum* D658^T, which demonstrated a sequence similarity of 99.71%. BLAST analysis placed the sequence of 16S-D3.13302251 within the group *B. zoohelcum*. In Fig. 2, the strain, 16S-D3.13302251, was clustered with *B. zoohelcum*, and their grouping was supported by bootstrap analysis. Consequently, the phylogenetic tree supported that the strain belonged to species of *B. zoohelcum.*

Antibiotic susceptibility testing. By now, although there are no accepted CLSI standards for AST or breakpoints for *B. zoohelcum*, the isolate exhibited large inhibition zone (millimeter) for all antimicrobials tested: aztreonam 26 mm, ceftriaxone 30 mm, ciprofloxacin 26 mm, clindamycin 30 mm, erythromycin 25 mm, linezolid 30 mm, teicoplanin 16 mm, trimethoprim-sulfamethoxazole 26 mm, ampicillin 26mm, ampicillin-sulbactam 26mm, vancomycin 17 mm, penicillin 23 mm, cefazolin 27 mm, meropenem26 mm, ertapenem 25 mm, gentamicin 18 mm, levofloxacin 23 mm, cefperazone-sulbactam 28 mm, piperacillin-tazobactam 30 mm, cefazolin 28 mm, cefuroxime 35 mm, which suggested the *B. zoohelcum* isolate was highly susceptible to β-lactams and fluoroquinolones.

DISCUSSION

B. zoohelcum is an uncommon zoonotic pathogen. Historically, this species was referred to as a Centers for Disease Control and Prevention group IIj organism. However, in 1986 Holmes et al. proposed the name *Weeksella zoohelcum* for the group IIj bacteria. *Weeksella virosa* is the only other species in this genus (5). Finally, in 1994 Vandamme et al. proposed a new genus, *Bergeyella*, and renamed *W. zoohelcum B. zoohelcum* based on the genetic differences with *W. virosa* (6). At present, *B. zoohelcum* is the only representative of the genus *Bergeyella*. *B. zoohelcum* is anonfermentative, gram-negative, rod-shaped, non-spore-forming, nonmotile aerobic bacterium. (7)

B. zoohelcum has become an increasingly recognized cause of cellulitis, leg abscess, tenosynovitis, septicemia, meningitis and infective endocarditis (8-20), which is closely related to animal bites or contact to dogs, cats or contaminated food (Table 1).

The reasons for the low detection rate of this strain are as follows: firstly, this strain is a caustic strain and has high requirements for growth environment. Previously reported that light growth of *B. zoohelcum* strain was observed only on the chocolate agar plates after 48 h of incubation (14,18). But it has been reported that after 18 to 24 h incubation the organism grew well on blood and chocolate agar (8,10,17). The strain investigated in our study did not grow on the chocolate plate containing vancomycin. Then, our AST data, indicate that the *B. zoohelcum* strain did not grow around to vancomyci on the Mueller-Hinton agar plates with 5% sheep blood. In addition, the bacteria grew well in the Colombia blood agar plate after cultured for 24 h. Whereas, the strain did not grow on blood plate until 48 hours later. In order to improve the detection rate of bacteria, we recommend using Colombian blood plate and vancomycin-free chocolate plate or delaying the culture time to 48 hours when cultivating bacteria infected by bite infection. Secondly, the *B. zoohelcum* has been misidentified as *Brevundimonas spp*. with the use of an automated identification system (Vitek 2 system) based on conventional phenotypic methodology, or has been considered as a contaminant on culture (8,15,17,19). Initially, our strain was identified by Vitek 2 system as *Sphingomonas parapaucimobilis*.

In the recent years, MALDI-TOF MS is an effective tool for rapid identification of rarely isolated, difficult-to-identify microorganisms, derived from not only human clinical samples but also animal samples. Our strain was identified as *B. zoohelcum* by using MALDI-TOF MS. For a more precise identification, we performed a molecular identification analysis for the stain based on the 16S rRNA gene sequences. Molecular biological characterization has been well-accepted as a powerful tool for identification of bacterial species and strains because of its accuracy. 16S rRNA gene sequencing analysis has shown advantages for identification and differentiation of bacteria from various origins (21). Additionally, the results of phylogenetic analysis also confirmed that the strain belonged to the *B. zoohelcum.* We suggest that when dealing with samples cultured from wound secretions after animal bites, the colony morphology should be carefully observed. If the colony is viscous and difficult to remove from the solid medium, and the oxidase and indole test are positive, we should highly suspect that it is *B. zoohelcum.* It can be seen from table 1 that automated identifification system are not recommended for the identification method of the bacteria. We can identify the organism use the API 20NE systems. It is recommended to use MALDI-TOF MS and sequencing techniques to identify the bacteria.

Whether antibiotics prevent infection after bites remains controversial. Currently, antibiotics are not given routinely, but they are almost always recommended for high-risk wounds, such as deep punctures (particularly if inflicted by cats), those that require surgical repair (22). There is no specific antibiotic treatment recommended for infections caused by *B. zoohelcum*. Nevertheless, it is essential to perform antibiotic susceptibility studies for all clinical isolates until more epidemiological information regarding *B. zoohelcum* is available (10). Optimal selection of empirical antibiotic agents should be based on the most common pathogens. Our patient who was isolated *B. zoolhelcum* from wound, but there was no progressive infection. The reason is attributed to immediate irrigated and debridement of wounds and minimize the risk of the child developing serious or even fatal infections. After being bitten by an animal, adherence to standard principles of wound management provides the best defense against bacterial infections. Copious irrigation at high pressure markedly decreases the concentration of bacteria in contaminated wounds. Debridement of devitalized tissue further decreases the likelihood of infection, with repair only when the possibility of infection has been eliminated (23). Furthermore, we know that local blood supply is excellent in the head, neck, scalp and face, so wounds are at lower risk for infection than other sites (24). Moreover, choose appropriate antibiotics for empirical coverage when indicated for prophylaxis or for treatment of infection. An adequate antibiotic regimen should provide coverage for the potential pathogenic aerobic and anaerobic flora from the mouth of the animal inflicting the bite. However, patients can be treated with agents that have been demonstrated to be effective against strains isolated from animals. Cefotaxime, amoxicillin-clavulanic acid cefuroxime, ampicillin-sulbactam, ciprofloxacin, ceftriaxone, levofloxacin and meropenem have been used to treat patients successfully. Use of amoxicillin-clavulanic acid and ampicillin-sulbactam is appropriate for the treatment of bite-related infection and is a reasonable choice for possible coinfection with other pathogens including *Pasteurella multocida* and anaerobess (Table 2). The little girl was treated with cefuroxime sodium with a good outcome.

With our understanding of the fastidous bacteria and the widespread use of MALDI-TOF MS , 16S rRNA gene sequence and next-generation sequences (NGS). We should be able to isolate more *B. zoohelcum* from animal bite wounds and identify the pathogen accurately and quickly.

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We declare no conflict of interests.

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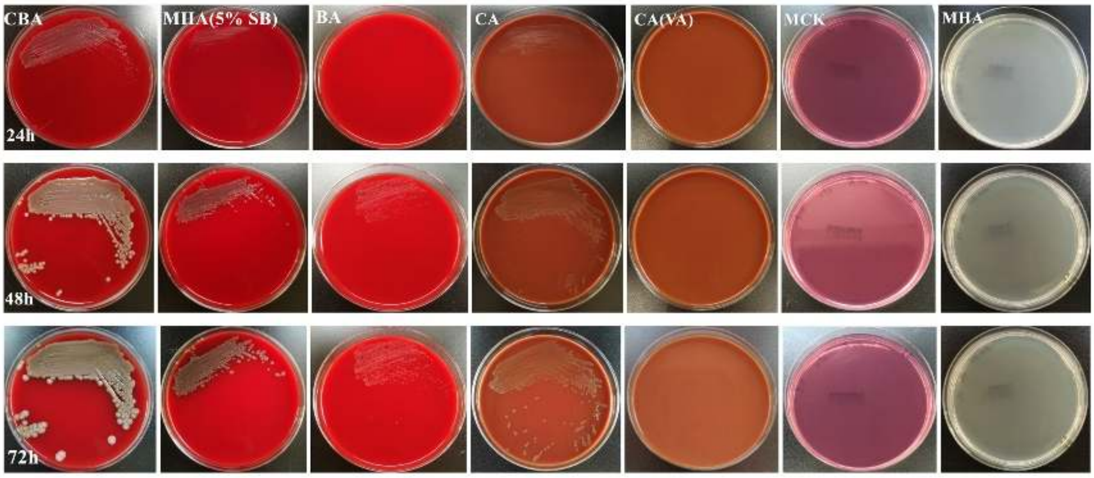

FIG 1. The growth of *B .zoohelcum* cultured on different media for different time

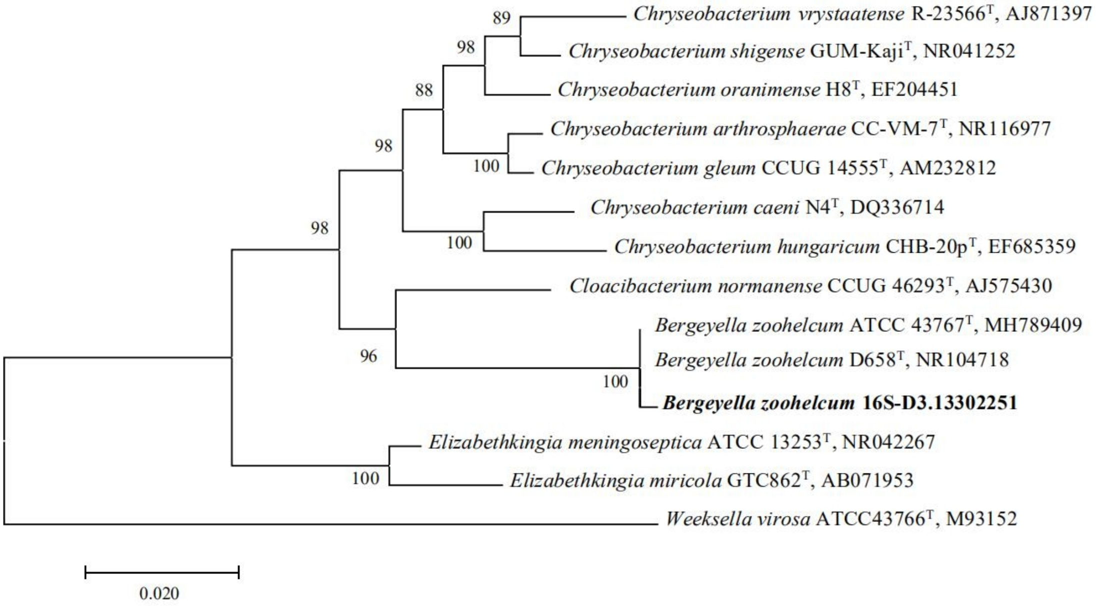

FIG 2. .The evolutionary history was inferred using the Neighbor-Joining method. The percentage of replicate trees in which the associated taxa clustered together in the bootstrap test (1000 replicates) are shown next to the branches. The tree is drawn to scale, with branch lengths in the same units as those of the evolutionary distances used to infer the phylogenetic tree. The evolutionary distances were computed using the Maximum Composite Likelihood method and are

in the units of the number of base substitutions per site. The analysis involved 14 nucleotide sequences. All positions containing gaps and missing data were eliminated. There were a total of 1271 positions in the final dataset. Evolutionary analyses were conducted in MEGA7.

TABLE 1 Literature review of *Bergeyella zoohelcum* infections in humans

NO.	Reference	Age (yr)/sex	Type of Infection	Exposure	Location of wound	Underlying disease	Treatment	Outcome	Identification method
1	Bracis et al,1979	5/F	Meningitis	Dog bite	Head and neck	None	Day1-2:nafcillin,penicillin, chloramphenicol Day3-13:penicillin	Recovered	Not mentioned
2	Noell et al,1989	80/F	Septicaemia,bedsore	Cat contact	None	Diabetic	Cefotaxime	Recovered	Conventional biochemical tests
3	Reina et al,1992	10/M	Leg abscess	Dog bite	Right leg	None	Day1-5:cefotaxime, nitrofurazone	Recovered	API 20E and API 20NE systems

4	Isotalo et al,2000	35/M	Tenosynovitis	Siberian tiger bite	Left palm	None	Day1-3:cefazolin, gentamicin Day4-13:amoxicillin-clavulanic acid	Recovered	On the basis of biochemical reactions and cellular fatty acid composition data
5	Montejo et al,2001	33/M	Bacteremia	Dog bite	Left forearm	None	Amoxicillin-clavulanic acid	Recovered	95-carbon substrate oxidation and API 20NE

6	Kivinen et al, 2003	77/F	Skin infection	Cat contact	None	Diabetes type II,pernicious anaemia,hypertension with heart failure, polymyalgia rheumatica,mild Morbus Alzheimer	Day1-4:cefuroxime Day5-29: cephalexin	Recovered	Not mentioned
7	Sanjay et al,2004	60/F	Cellulitis	Cat bite	Left hand	None	Day1:amoxicillin-clavulanic acid Day2-7: ampicillin-sulbactam	Recovered	16S rDNA sequence analysis
8	Beltran et al,2006	44/F	Diarrhea.bacteremia	Goat’s blood	None	None	Day2-8:ciprofloxacin	Recovered	Not mentioned

				ingestion					
9	Lin et al,2007	73/M	Cellulitis	Dog contact	None	Liver cirrhosis, transitional cell carcinoma of urinary bladder	Day1-14:cefazolin,gentamicin	Recovered	Not mentioned
10	Kyung et al,2015	26/M	Infective endocarditis	None	None	None	Day4-5:ampicillin-sulbactam Day6-48:ceftriaxone	Recovered	16S rRNA sequence analysis
11	Kyung et al,2015	47/M	Infective endocarditis	None	None	Paroxysmal supraventricular tachycardia	Day1-3:ceftriaxone, ampicillin, and gentamicin Day4-32: piperacillin-	Recovered	16S rRNA sequence analysis

							tazobactam , amikacin Day33–36:ampicillin-sulbactam		
12	Yi et al,2016	22-month-old/M	Abscess and cellulitis	Dog bite	Right-sided facial	None	Day1-2:ceftriaxone, clindamycin Day3-10:amoxicillin-clavulanate	Recovered	MALDI-TOF MS and 16S rRNA gene sequencing
13	Chen et al,2017	27/F	Infective endocarditis	None	None	None	Day1-42:cefuroxime	Recovered	16S rRNA sequence analysis
14	Sharma et al,2019	43/transgender M to F	Bacteremia	Dog contact	None	AIDS on antiretroviral	Levofloxacin , meropenem	Recovered	Not mentioned

						therapy, ESRD on hemodialysis, severe systolic heart failure with AICD and supraventricular tachycardia			
15	This case	2/F	None	Cat bite	Head and face	None	Day1:cefuroxime sodium Day2-6:mupiroxine ointment	Recovered	MALDI-TOF MS and 16S rRNA gene sequencing

AIDS: Acquired immunodeficiency syndrome; ESRD: End-stage renal disease; AICD: Automated implantable cardioverter defibrillator

TABLE 2 Empirical Antibiotics for Animal Wounds

Penicillin sensitivity			Penicillin allergy	
Type of bite	Oral	Parenteral	Oral	Parenteral
Dog, cat	Amoxicillin clavulanate	Ampicillin-sulbactam	Extended-spectrum cephalosporin or trimethoprim-sulfamethoxazole plus clindamycin	Extended-spectrum cephalosporin or trimethoprim-sulfamethoxazole plus clindamycin or carbapenem