Journal of Feline Medicine and Surgery (2007) **9**, 404–410
doi:10.1016/j.jfms.2007.04.004

ELSEVIER

jfms

Bacteraemia in 66 cats and antimicrobial susceptibility of the isolates (1995–2004)

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Bacterial blood culture results of 292 privately owned cats presented to the Clinic for Small Animal Medicine, Ludwig Maximilian University Munich with signs of sepsis were evaluated retrospectively. Of the blood cultures, 23% were positive. In 88%, a single bacterial species was isolated. Of all bacterial isolates, 45% were Gram-positive, 43% were Gram-negative, and 12% were obligate anaerobes. The most frequently isolated bacteria were *Enterobacteriaceae*, obligate anaerobic species, *Staphylococcus* species and *Streptococcus* species. Of the cats with positive blood cultures, 32% were pretreated with antibiotics. Of all bacterial isolates, 77% were susceptible to enrofloxacin, 69% to chloramphenicol, 67% to gentamicin, and 64% to amoxycillin clavulanic acid. Only enrofloxacin reached an in vitro efficacy of more than 70% against Gram-positive and more than 74% against Gram-negative bacteria.

Date accepted: 25 April 2007

Bacteraemia is defined as the presence of live bacteria in the bloodstream (Goodwin and Schaer 1989, Brady and Otto 2001), whereas sepsis is the systemic inflammatory response to infection (eg, bacteria, fungi or parasites) (ACCM/SCCM Consensus Conference 1992). Bacteria frequently enter the bloodstream from heavily colonised mucosal surfaces or areas of localised infection in the body. However, sepsis generally only develops in patients with impaired host defenses or when the host defenses are overwhelmed by the number of bacteria entering the blood stream or bacteria that are inherently resistant (eg, some *Escherichia coli*) (Goodwin and Schaer 1989, Dow 1995). Sepsis in humans and animals is consistently associated with high mortality (Calvert et al 1985, Dow et al 1989, Davies and Hagen 1997, De Laforcade et al 2003); thus, early diagnosis and appropriate treatment are necessary (Weeren and Muir 1992, Opal and Horn 1999). There is limited available data on the prevalence and antimicrobial susceptibility of bacterial isolates in cats with suspected sepsis. It is, therefore, important that effective antibacterial treatment options are determined and published.

The aim of the study was to evaluate the types of bacteria isolated from blood cultures of cats with suspected sepsis and to determine their antibiotic susceptibility.

Materials and methods

Patient selection

In the years 1995–2004, 292 client-owned cats from private households with signs of sepsis that were presented to the Clinic for Small Animal Medicine, Ludwig Maximilian University Munich had at least one blood culture performed. Of these 292 cats, 66 (23%) had a positive blood culture, and their data were evaluated retrospectively. There was suspicion of sepsis if two or more 'systemic inflammatory response syndrome' (SIRS) criteria were fulfilled (Brady et al 2000) or a systemic infection was suspected. The study included only cats with suspected sepsis that demonstrated a positive bacterial blood culture. Cats with clinical signs of sepsis where bacterial blood culture was either negative or

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1098-612X/07/050404+07 $32.00/0

absent were excluded from the study. Age, sex and breed of the patients were obtained from medical records where available.

Sample technique

In all cases, blood samples for culture were obtained after the sample site was shaved. The skin was disinfected with alcohol and a poly (1-venyl-2-tyrrolidon)—iodine complex (Vet-Sept Spray; Albrecht, Aulendorf, Germany) before blood (5—10 ml, the exact amount was not recorded) was collected from a jugular vein aseptically. The blood was inoculated directly into commercially available blood culture bottles (Signal Blood Culture System, Oxoid, Hampshire, UK). To avoid contamination, a new needle was placed on the syringe and the stopper of the blood culture medium bottle was cleaned with alcohol before injection of the blood sample. The blood culture bottle is a vacuum-closed glass bottle filled with 84 ml of nutrient broth. This nutrient broth enables growth of both aerobic and anaerobic microorganisms. After inoculation of the blood, a sterile indicator device was attached to the glass bottle with a 50 mm needle. Bacterial growth within the bottle produces carbon dioxide and the resulting positive pressure leads to the ascent of nutrient broth through the needle into the indicator device. This visible signal indicates bacterial growth.

Bacterial cultures

The culture bottles were incubated for 5—7 days at 37—39°C. As soon as a positive signal occurred, approximately 1 ml of broth was taken from the chamber to inoculate subcultures on a set of routine primary media plates. Nutrient agar with and without 6% sheep blood, Gassner-agar, Rambach-agar (all Merck, Darmstadt, Germany), and Columbia colistin nalidixic acid blood-agar

Table 1. Species of bacteria isolated from the blood of 66 feline patients

Bacterial isolates	Gram	Number of isolates	(%)
Enterobacteriaceae family	−	23	31.0
Escherichia coli	−	12	16.0
Enterobacter species	−	6	8.0
Salmonella species	−	3	4.0
Klebsiella pneumoniae	−	1	1.3
Yersinia pseudotuberculosis	−	1	1.3
Pseudomonas aeruginosa	−	3	4.0
Pasteurella multocida	−	2	2.7
Acinetobacter species	−	2	2.7
Other Gram-negative bacteria (unclassified)	−	1	1.3
Staphylococcus species	+	9	12.0
coagulase-negative *Staphylococci*	+	8	10.7
Staphylococcus intermedius	+	1	1.3
Streptococcus species	+	9	12.0
β-Haemolytic Streptococci species	+	3	4.0
α-Haemolytic Streptococci species	+	3	4.0
Non-haemolytic Streptococci species	+	3	4.0
Corynebacterium species	+	4	5.3
Micrococcaceae	+	4	5.3
Actinomyces species	+	2	2.7
Enterococcus species	+	2	2.7
Other Gram-positive bacteria (unclassified)	+	3	4.0
Obligate anaerobic bacteria	+ or −	9	12.0
Other bacteria (unclassified)		2	2.7
Total			
Gram-positive aerobes	+	33	45.2
Gram-negative aerobes	−	31	42.5
Obligate anaerobic bacteria	+ or −	9	12.3
All bacteria	+ or −	73	100

Table 2. Percentage of susceptible aerobic and facultatively anaerobic isolates (n = number of samples)

Antibiotics	Overall efficacy (%)	Gram-positive (%)	Gram-negative (%)
Doxycycline	45.1 ($n = 51$)	68.2 ($n = 22$)	25.9 ($n = 27$)
Trimethoprim + sulphonamide	47.1 ($n = 51$)	41.7 ($n = 24$)	48.1 ($n = 27$)
Ampicillin/amoxycillin	31.9 ($n = 47$)	40.9 ($n = 22$)	20.0 ($n = 25$)
Amoxycillin + clavulanic acid	63.6 ($n = 44$)	86.4 ($n = 22$)	40.9 ($n = 22$)
Gentamicin	66.7 ($n = 51$)	70.8 ($n = 24$)	59.3 ($n = 27$)
Chloramphenicol	69.4 ($n = 49$)	82.6 ($n = 23$)	50.0 ($n = 26$)
Enrofloxacin	76.5 ($n = 51$)	70.8 ($n = 24$)	74.1 ($n = 27$)
Cephalexin	63.2 ($n = 38$)	65.2 ($n = 23$)	60.0 ($n = 15$)
Lincomycin	38.2 ($n = 34$)	61.9 ($n = 21$)	0.0 ($n = 13$)

(Becton Dickinson, Heidelberg, Germany) were incubated at 37–39°C under aerobic conditions and examined daily for at least 2 days. For anaerobic cultures, blood agar plates were incubated with enhanced carbon dioxide using the Anaerocult P systems (Merck, Darmstadt, Germany). For biochemical differentiation of isolates, ID-32-Staph, API-20-NE, ID-32-E rapid (all Bio Mérieux, Lyon, France), and BBL Enterotube (Becton Dickinson, Heidelberg, Germany) were used. Obligate anaerobic species were defined as those growing only in anaerobic conditions and further classification of individual species was not performed. In blood culture bottles without an indication of bacterial growth, subcultures were performed as described after 5–7 days of incubation. Bacterial isolates were grouped together by species for evaluation (Table 1).

Susceptibility testing

Susceptibility was tested against nine different antibiotics (Table 2). Testing was performed with the agar disc diffusion method. Bacterial samples were applied on Müller Hinton agar (Merck, Darmstadt, Germany), and antibiotic discs (Oxoid, Hampshire, UK) were placed on the surface. The concentrations of each antibiotic in the discs were ampicillin 10 µg, amoxycillin clavulanic acid 20 and 10 µg, cephalexin 30 µg, trimethoprim sulphonamide 1.25 and 23.75 µg, gentamicin 10 µg, chloramphenicol 30 µg, lincomycin 15 µg, doxycycline 30 µg, and enrofloxacin 5 µg. After overnight incubation at 37–39°C, the size of inhibitory zones was measured. Depending on the standardised diameter (DIN 58940) of the inhibitory zones, bacterial isolates were

Table 3. Antibiotic efficacy against most important isolated aerobic bacterial species (in %; n = number of samples)

Antibiotics	*Staph* species	*Strept* species	*E. coli*	*Enterobacteriaceae* species (other than *E. coli*)	*Pasteu* species	*Pseud* species
Doxycycline	50.0 ($n = 8$)	100 ($n = 6$)	27.3 ($n = 11$)	0.0 ($n = 8$)	100 ($n = 2$)	0.0 ($n = 3$)
Trimethoprim + sulphonamide	25.0 ($n = 8$)	66.7 ($n = 6$)	54.5 ($n = 11$)	37.5 ($n = 8$)	100 ($n = 2$)	0.0 ($n = 3$)
Ampicillin/ amoxycillin	28.6 ($n = 7$)	60.0 ($n = 5$)	11.1 ($n = 9$)	25.0 ($n = 8$)	100 ($n = 2$)	0.0 ($n = 3$)
Amoxycillin + clavulanic acid	87.5 ($n = 8$)	100 ($n = 5$)	40.0 ($n = 10$)	40.0 ($n = 5$)	100 ($n = 2$)	0.0 ($n = 3$)
Gentamicin	87.5 ($n = 8$)	100 ($n = 6$)	63.6 ($n = 11$)	62.5 ($n = 8$)	50.0 ($n = 2$)	33.3 ($n = 3$)
Chloramphenicol	87.5 ($n = 8$)	100 ($n = 5$)	50.0 ($n = 10$)	62.5 ($n = 8$)	100 ($n = 2$)	0.0 ($n = 3$)
Enrofloxacin	87.5 ($n = 8$)	66.7 ($n = 6$)	81.8 ($n = 11$)	75.0 ($n = 8$)	100 ($n = 2$)	33.3 ($n = 3$)
Cephalexin	75.0 ($n = 8$)	83.3 ($n = 6$)	71.4 ($n = 7$)	66.7 ($n = 6$)	– ($n = 0$)	0.0 ($n = 2$)
Lincomycin	71.4 ($n = 7$)	60.0 ($n = 5$)	0.0 ($n = 5$)	0.0 ($n = 6$)	– ($n = 0$)	0.0 ($n = 2$)

considered 'susceptible' or 'resistant' to a certain antibiotic. An intermediate growth was considered as 'resistant'. The efficacy (in percentage) of different antibiotics against the most important isolated bacteria was documented (Table 3).

Results

Signalment

Median age of the patient population was 6 years and mean age was 6.9 years. Of the cats, 40% (25/63) were female and 60% (38/63) were male. In three cats, sex was not recorded. Breed distribution showed 80% (48/60) European Shorthair cats, 13% (8/60) Persian or Persian-mix, 2% (1/60) each Siamese-mix, Angora-mix, Maine Coon, and Devon Rex. In six cats, breed was not available.

Bacterial cultures

Of 292 cats with suspected sepsis that had blood cultures performed, 66 (23%) showed a positive bacterial blood culture. In most cases (89%, 59/66 of the positive samples) only one sample for culture was taken. Two blood cultures were taken in six cats, and three in one cat, but in three of these seven cases, a bacterial species was found in only one of the samples. In the remaining four cats, the same bacterium was isolated in all subsequent blood cultures taken from the cat.

Of all cats with positive blood cultures, 32% had been treated with an antibiotic for a median period of 5 days (mean 6.4 days). In 58 of 66 cats, a single species was detected. The other eight cats showed polymicrobial bacteraemia. Of these eight cats, all had infection with two bacterial species.

Of all bacterial isolates, 45% were Gram-positive, 43% were Gram-negative, and 12% were obligate anaerobes. The most frequently isolated bacteria were *Enterobacteriaceae* (31% of the positive samples), obligate anaerobic species (12%), *Staphylococcus* species (12%), and *Streptococcus* species (12%) (Table 1). *Enterobacteriaceae* are a family of bacteria into which the genera *Escherichia coli* (12 isolates), *Enterobacter* species (six), *Salmonella* species (three), *Klebsiella pneumoniae pneumoniae* (one), and *Yersinia pseudotuberculosis* (one) belong. Amongst the nine *Staphylococcus* species, eight were coagulase-negative *Staphylococci*, the remaining isolate being *Staphylococcus intermedius*. *Streptococcus* species consisted of *β-haemolytic Streptococci*, *α-haemolytic*, and *non-haemolytic Streptococci* species.

Susceptibility testing

Enrofloxacin had the highest efficacy against Gram-positive (71%) and Gram-negative (74%) aerobic and facultatively anaerobic bacteria (Table 2). The combination of enrofloxacin with amoxycillin clavulanic acid revealed the best overall efficacy with 85% of the above isolates susceptible to this combination. Most isolates of *Escherichia coli* were sensitive to enrofloxacin, cephalexin, and gentamicin, but resistant to lincomycin, doxycycline, ampicillin, and amoxycillin. Most isolates of *Staphylococcus* species were susceptible to enrofloxacin, gentamicin, chloramphenicol, and amoxycillin clavulanic acid (Table 3), but resistant to ampicillin, amoxycillin, and trimethoprim sulphonamide. *Streptococcus* species were sensitive to amoxycillin clavulanic acid, doxycycline, gentamicin, and chloramphenicol. Against *Enterobacteriaceae* species isolates other than *Escherichia coli*, the most effective antimicrobial was enrofloxacin. The susceptibility testing of the obligate anaerobes was excluded from the results as no validated method exists for susceptibility testing.

Discussion

The aim of this study was to evaluate the types of bacteria isolated from blood cultures of cats with suspected sepsis, to determine their antibiotic susceptibility, and to provide information about possible antibacterial treatment options in cats with sepsis. Like all retrospective studies, this study has some limitations. A complete record was not available in all cases of this study. Furthermore, in most of the cases, only one blood culture was submitted and any growth in a single blood culture could potentially be a contaminant regardless of the agent grown. Even with these limitations, however, this study provides important information to clinicians and facilitates the choice of initial treatment in cats with suspected sepsis.

Only 23% of cats with suspected sepsis had a positive blood culture in the present study; similar results were found in the studies by Calvert and Greene (1986) and Greiner et al (2007) in dogs with suspected sepsis. Dow et al (1989), however, found that 71% of the bacterial blood cultures of cats were positive. This could be due to the different study design used. To be included in the study of Dow et al (1989), cats with bacteraemia had to have at least two bacteriological cultures yielding the same pathological microbe (defined as 'positive blood cultures') or to have a bacterium not considered to be part of the animal's normal skin flora. The low number of

positive samples in the present study could be explained by the fact that intermittent bacteraemia is very common. Shedding of bacteria into the bloodstream is usually intermittent even during most serious septicaemias (Dow and Jones 1989). Furthermore, the number of organisms per millilitre of blood is usually low (Tilton 1982). In human studies it has been demonstrated that the volume of blood taken for blood culture is the most important factor in determining the sensitivity of blood culture (Li et al 1994). This might be another explanation for the low number of positive samples in our study, as the blood volume that can be taken from cats is limited.

Dow et al (1989) demonstrated that prior antibiotic therapy did not reduce the percentage of positive cultures. Although 32% of cats in the present study were pretreated with antibiotics, they still had a positive blood culture. Thus, if sepsis is suspected, blood cultures should be performed even after prior antibiotic therapy, especially in those animals that become septic during antibiotic therapy, as they are likely to have become infected with an antibiotic-resistant pathogen.

In 88% of the positive blood cultures in this study a single bacterial species was found. In contrast, Dow et al (1989) reported about polymicrobial bacteraemia in cats occurring in 30% of positive blood cultures and however, the number of cats was very low (10 cats). In their study, blood cultures were taken only from severely ill cats. As the immune system's ability to provide adequate protection might be more impaired in very ill patients, polymicrobial bacteraemia may occur more commonly in these patients. Furthermore, their inclusion criteria were two positive blood cultures with the same bacteria cultured and they excluded suspected normal flora. Thus comparison to the present study might be difficult due to different study designs.

Bacteria most frequently isolated from blood in this study were *Enterobacteriaceae* (mainly *Escherichia coli*), obligate anaerobes, *Staphylococcus* species, and *Streptococcus* species. These bacteria also have been reported to be the most common isolates from humans and dogs with bacteraemia (Cohen and Lynn 1998, Greiner et al (2007)). The reason for the occurrence of these bacteria might be that they are likely to be common colonisers of the gastrointestinal tract and skin that have invaded due to compromised host defenses (eg, catheter, skin wound, severe periodontal disease) and when entered have overwhelmed host defenses by their number or inherent serum resistance or pre-existing weakened host immunity. There are not many studies in cats so far. All the studies published only contained a very low number of cats. In a study of 10 positive feline blood cultures, Dow et al (1989) isolated *Enterobacteriaceae* and anaerobic bacteria most frequently and did not find Gram-positive *cocci*. Brady et al (2000) found *Escherichia coli* in 58% and *β-haemolytic Streptococcus* species in 4 of 12 positive bacterial cultures from cats. The inclusion criteria of Dow et al (1989) were already described earlier. In the study of Brady et al (2000) cats were included, if there was histopathological evidence of bacterial infection with multi-organ necrosis and/or inflammation with intralesional bacteria. In the present study, all positive blood cultures were included, although in most cases (89% of the positive samples) only one bacterial culture of the blood was taken. Nevertheless, the results of the present study confirm the types of bacterial species suggested in the older studies with small cat numbers.

Of all bacterial isolates, 45% were Gram-positive, 43% were Gram-negative, and 12% were obligate anaerobe bacteria. In a study of 229 dogs with bacteraemia by Greiner et al (2007), Gram-positive bacteria were more common (68%). Certain Gram-positive bacteria may signify contamination, if they are only isolated once (Dow and Jones 1989) and positive blood culture results do not necessarily indicate true bacteraemia (Dow 1995). Resident organisms on feline skin surface and hair include a number of different bacteria, eg, *Staphylococci*, *α-haemolytic Streptococci*, *Micrococcus*, *Corynebacterium* species, and *Acinetobacter* (Krogh and Kristensen 1976, Biberstein et al 1984, Cox et al 1985, Dow 1995, Lilenbaum et al 1998, Sorum and Sunde 2001). On the other hand, any bacterial organism possessing virulence factors can cause bacteraemia or sepsis, especially in immunosuppressed patients (Garvey and Aucoin 1984, Bodmann and Vogel 2001), independent of its origin. However, some bacteria, like *Micrococcus* species, do not possess virulence factors. In general, the clinical status of the patient and the source of bacteraemia should be considered when a positive blood culture occurs (Dow and Jones 1989).

In the second part of the study, results of antimicrobial susceptibility testing were evaluated. The efficacy of nine different antibiotics against aerobe and facultative anaerobe bacteria was determined. The overall best in vitro antibacterial efficacy in this study was demonstrated for enrofloxacin, which showed an overall efficacy of 77% against all bacteria. This fluoroquinolone showed very good efficacy against Gram-positive as well as Gram-negative bacteria, which is similar to the

findings of Petzinger (1991), Aucoin (2000), and Walker (2000). Use of enrofloxacin, however, is limited in cats due to its potential adverse side effects. If used, dosages should always be within the recommended therapeutic range to prevent progressive retinal degeneration (Gelatt et al 2001). The β-lactam antibiotics ampicillin or amoxycillin had a very low efficacy against *Escherichia coli* (11%) and against *Staphylococcus* species (29%). Although there are no comparable data in cats available, these results are similar to a study of bacteraemia in dogs in which 25% of *Escherichia coli* and 27% of *Staphylococcus* species were sensitive to ampicillin (Calvert and Greene 1986). Normand et al (2000) describe a statistically significant increase over time in the resistance of *Escherichia coli* to amoxycillin and amoxycillin clavulanic acid. Several Gram-negative bacteria, including *Escherichia* species, *Klebsiella* species, *Salmonella* species, and *Pseudomonas* species, as well as Gram-positive bacteria, including *Staphylococcus* species, are able to produce β-lactamase. β-Lactamase is a bacterial enzyme that disrupts the β-lactam ring so that acidic derivatives are produced with no antibacterial activity. To overcome this mechanism of bacterial resistance, β-lactam antibiotics are often combined with β-lactamase inhibitors (Wishart 1984, Mealey 2001). Addition of the β-lactamase inhibitor clavulanic acid improved the overall efficacy from 32% to 64% and the efficacy against *Staphylococcus* species from 29% to 88%. As seen in this study, *Pseudomonas* species are intrinsically resistant to amoxycillin clavulanic acid (Wishart 1984), thus, no difference was seen in susceptibility between amoxycillin and amoxycillin clavulanic acid.

The aminoglycoside gentamicin was effective against 88% of *Staphylococcus* species isolates and 63% of *Enterobacteriaceae*. A similar spectrum of activity of the aminoglycosides was described by Benitz (1984), Calvert and Greene (1986), and Calvert and Wall (2006). Striking is the 100% efficacy against *Streptococcus* species in the present study, as Benitz (1984), Calvert and Greene (1986), and Calvert and Wall (2006) described a poor efficacy against these bacteria. In addition, in a study of bacteraemia in dogs by Greiner et al (2007), efficacy against *Streptococcus* species was only 63%. Different bacterial susceptibility in Germany and the United States, the use of different culture media or the small number of *Streptococcus* species isolates in the present study could be possible explanations.

For anaerobic bacteria, the use of the agar disc diffusion method is not standardised. Thus, the results of resistance testing in anaerobic bacteria have not been evaluated in this study. According to the literature (Dow and Jones 1987, Boothe 1990, Whittem and Gaon 1998, Aucoin 2000, Calvert and Wall 2006), β-lactam antibiotics (eg, penicillins, including amoxycillin/clavulanic acid, and cephalosporins), chloramphenicol, clindamycin, and metronidazole are recommended if an anaerobic bacterium is isolated or suspected. However, those infections caused by *Bacteroides* species are becoming increasingly resistant to both penicillins and first-generation cephalosporins. Doxycycline is effective against many obligate anaerobes. However, its activity is variable. Lincomycin, aminoglycosides, and fluoroquinolones are ineffective against anaerobic organisms. Trimethoprim sulphadonamides are a poor choice for anaerobic infections as despite their in vitro efficacy their in vivo efficacy is poor, because exudates and debris in anaerobic infections contain material that inactivates the action of sulphonamide antimicrobials. As sepsis often involves cats with impaired host defenses, using a bactericidal drug as first choice against anaerobic infections is recommended.

If sepsis is suspected, antibiotics often have to be given before bacteriological culture and susceptibility test results are available, as it takes at least 24–72 h for bacteria to grow in vitro (Jones 2006). It can be helpful to consider the original site of infection for antibiotic selection. If the gastrointestinal tract or the reproductive tract is suspected as the site of primary infection, Gram-negative rods are most common. When gastrointestinal perforation has led to peritonitis, Gram-negative rods and anaerobic bacteria must be suspected (Purvis and Kirby 1994). Unfortunately, in many cases the site of primary infection is unknown or uncertain. Calvert and Greene (1986), Aucoin (2000) and Calvert and Wall (2006) proposed certain antibiotic combinations in patients with life-threatening bacteraemia based upon their data. A combination of an aminoglycoside with ampicillin or a first-generation cephalosporin as well as a fluoroquinolone with amoxycillin/clavulanic acid was recommended. Effective antimicrobial therapy with bactericidal drugs such as cephalosporins and fluoroquinolones was thought to increase the release of endotoxin and, therefore, their usage was not recommended. However, in humans with Gram-negative bacteraemia, bactericidal antibiotics did not increase the circulating levels of endotoxins (Kruth 2006). In the present study, the combination of enrofloxacin with amoxycillin/clavulanic acid revealed the best overall efficacy of 85% and can be recommended as the drug combination of choice to treat cats with suspected sepsis.

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