Schweizer Archiv für Tierheilkunde
© 2014 Verlag Hans Huber, Hogrefe AG, Bern
C. Callegari et al., Band 156, Heft 10, Oktober 2014, 499–503
DOI 10.1024/0036-7281/a000637

Pneumonia associated with *Salmonella* spp. infection in a cat receiving cyclosporine

C. Callegari[1], G. Palermo[1], M. F. Greco[2], M. Corrente[2], E. Piseddu[3], E. Auriemma[4], E. Zini[5]

[1]Department of Internal Medicine, Istituto Veterinario di Novara, Granozzo con Monticello, Italy, [2]Department of Veterinary Medicine, University of Bari, Bari, Italy, [3]Novara Day Lab – IDEXX Laboratories, Granozzo con Monticello, Italy, [4]Department of Diagnositc Imaging, Istituto Veterinario di Novara, Granozzo con Monticello, Italy, [5]Clinic for Small Animal Internal Medicine, Vetsuisse Faculty, University of Zurich, Switzerland

Summary

Salmonellosis is uncommon in cats, usually affects the gastrointestinal tract or skin, and can be fatal. This report describes a domestic shorthair cat with severe pneumonia caused by *Salmonella* spp. without accompanying gastrointestinal or skin manifestations, in which previous administration of cyclosporine may have played a permissive role in its development. Clinical and laboratory findings as well as follow-up are described from diagnosis until complete recovery. This unusual presentation serves to alert practitioners to consider *Salmonella* spp. as a possible cause of lung disease in cats, especially if immunocompromised.

Keywords: Salmonella, infection, pneumonia, cat, immunosuppression

Salmonella spp. Pneumonie bei einer Katze nach Cyclosporin-Behandlung

Salmonellose wird bei der Katze selten erwähnt, befällt häufig Darm oder Haut und kann lebensbedrohlich sein. Diese Arbeit beschreibt eine schwere Pneumonie, verursacht durch *Salmonella* spp. bei einer Kurzhaar-Hauskatze ohne gastrointestinale oder dermatologische Anzeichen, wobei Cyclosporin als Vorbehandlung ein Risikofaktor bei der Entwicklung der Lungenentzündung gespielt hat. Es werden die klinische Untersuchung, Laborbefunde sowie der Verlauf von der Diagnose bis zur Heilung beschrieben. Dieses seltene klinische Krankheitsbild soll Tierärzte informieren, dass *Salmonella* spp. als Ursache für eine Lungenerkrankung bei Katzen in Frage kommt, insbesondere wenn sie immunsupprimiert sind.

Schlüsselwörter: Salmonella, Infektion, Pneumonie, Katze, Immunsuppression

Introduction

Salmonella spp. are motile, non-spore-forming, gram-negative aerobic bacilli of the family Enterobacteriaceae. Although they are mainly harboured in the intestine, they can cause systemic disease and can be isolated from other organs and blood (Greene, 1990). Salmonellosis in cats is infrequent, often favoured by host immunosuppression, and usually associated with gastrointestinal signs (Dow *et al.*, 1989; Greene, 1990; Hall and German, 2010; Marks *et al.*, 2011). Lung involvement is extremely rare, and has only been reported in 3 cats so far (Rodriguez *et al.*, 1993; Barrs *et al.*, 1999, 2005; Foster *et al.*, 2004). This case report describes a unique presentation of this disease in a cat.

Clinical report

A 5-year-old, neutered male, 6.7 kg, body condition score 7/9, outdoor domestic shorthair cat was presented for evaluation of a nasal crust, sneezing and stertor of 4 weeks duration. Polyuria and polydipsia had occurred in the last month. The cat had been treated since 3 years with megestrol acetate (2,5 mg PO q 48 h) because of an eosinophilic keratoconjunctivitis. Abnormalities on physical examination included stertorous breathing, erythema and crusting of the nasal planum, and retromandibular lymph nodes enlargement. The cat appeared otherwise normal.

The complete blood count was unremarkable, and the results of enzyme-linked immunosorbent assay for fe-

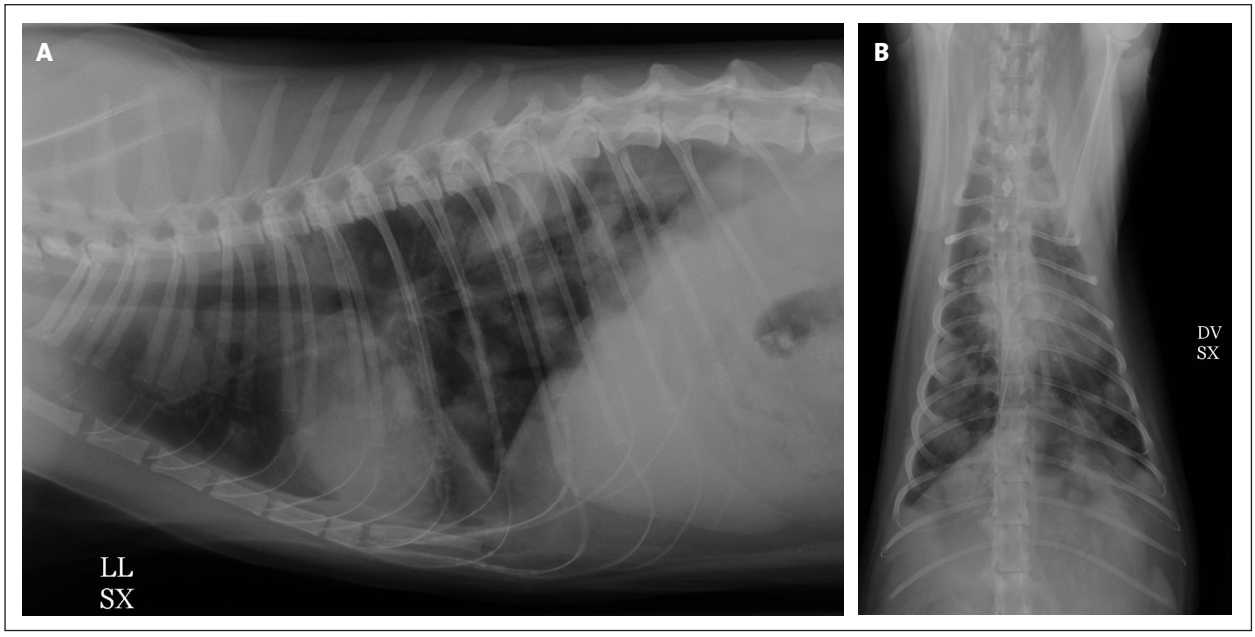

Figure 1: Left lateral (A) and dorsoventral (B) chest radiographs obtained at presentation. Multiple, widely distributed nodules of varying size can be identified throughout the lung fields.

line leukemia virus and feline immunodeficiency virus were negative. Serum biochemical profile revealed hyperglycemia (448 mg/dl; reference range, 72–162 mg/dl), hypertriglyceridaemia (736 mg/dl; reference range, 26–114 mg/dl) and increased fructosamine concentrations (487 µmol/l; reference range, 190–365 µmol/l). Urinalysis showed severe glycosuria without apparent ketonuria and low concentrated urine (specific gravity 1020). Fine needle aspirates from the nasal lesion and retromandibular lymph nodes were collected, and cytological features were consistent with eosinophilic inflammation and reactive lymphoid hyperplasia, respectively. A diagnosis of diabetes mellitus was made and insulin glargine (2 IU/cat, SC, q 12 h) was started; the administration of megestrol acetate was immediately interrupted because of its potential diabetogenic effect. Cyclosporine (5 mg/kg, PO, q 12 h) was prescribed for the treatment of the eosinophilic granuloma complex.

Forty-five days later, insulin therapy could be discontinued because clinical remission had been achieved. One month later, the cat was brought back to visit for lack of appetite, lethargy and cough since the last week. On physical examination hyperthermia (40.1 °C) was present without evidence of other abnormalities. Complete blood count and serum biochemical profile were unremarkable. Thoracic radiography revealed a multifocal, nodular interstitial infiltrate (Fig. 1). Some of the documented lung nodules were subpleural and superficial, just beyond the chest wall edge, and ultrasound-guided fine needle aspirates were performed (Fig. 2). Cytological smears were highly cellular with predominance of neutrophils and macrophages, representing a pyogranulomatous inflammation. At high power field resolution numerous rod-shaped bacteria were observed in the cytoplasm of some macrophages and neutrophils (Fig. 3). Other fine needle aspirates from the same pulmonary lesion were then obtained and the material transferred to a tube with bacterial media for culture. Baermann fecal examination, from three different stool samples for identification of lungworms infection was negative for parasites. A diagnosis of bacterial pneumonia was made and doxycycline (10 mg/kg, PO, q 24 h) was started. The administration of cyclosporine was discontinued and no recrudescence of the eosinophilic disorder had been noticed thereafter. Cultural examination of pulmonary aspirates allowed the

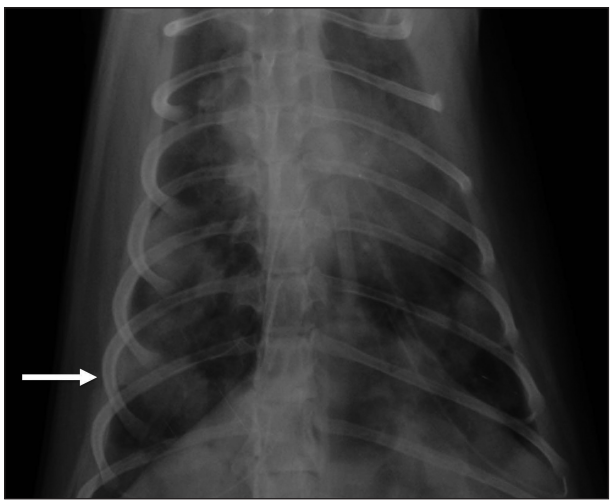

Figure 2: Detail of the dorsoventral view. The arrow shows the subpleural nodule from which the fine needle aspirates has been performed (3 ml syringe, 23 gauge and 25 mm length needle).

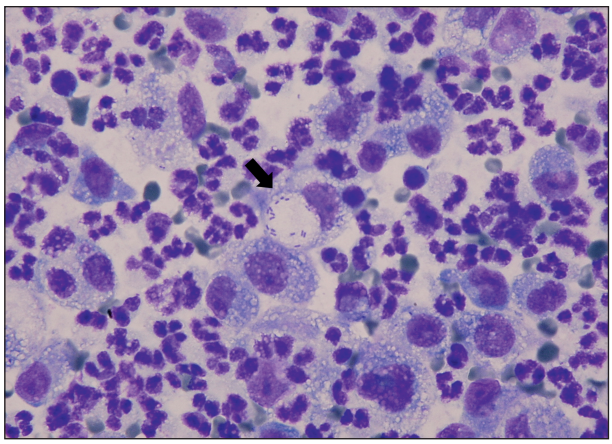

Figure 3: Fine-needle aspirate of a pulmonary nodule. Numerous markedly degenerated neutrophils associated with large foamy macrophages are present. The cytoplasm of some macrophages contains phagocytised neutrophils and bacterial rods (black arrow). May-Grunwald-Giemsa (×600).

isolation of *Salmonella* serogroup B. The antibiogram indicated a susceptibility to most of the antibiotics tested, including doxycycline which was therefore continued for 6 consecutive weeks. *Salmonella* spp. was also confirmed by polymerase chain reaction (PCR) using specific primers for the invA gene (Khan *et al.*, 2000) from cytological lung preparations, after DNA extraction. In addition, PCR was also performed to test whether the isolated *Salmonella* spp. belonged, within the serogroup B, to the serovar Typhimurium; the assay yielded negative results. During the following 6 weeks, clinical and radiographic re-evaluations showed gradual improvement until recovery with complete resolution of the pulmonary infiltrates (Fig. 4). For public health reasons, at 4 weeks from diagnosis, bacterial culture and PCR from oropharyngeal and rectal swabs were performed and resulted negative for *Salmonella* spp. At the time of writing, 14 months from diagnosis, the cat is still in good clinical conditions.

Discussion

Most serotypes of *Salmonella* spp. are ubiquitous and easily transmitted among animals and people, with a prevalence range in stray or shelter dogs and cats of 0–51.4 % (Marks *et al.*, 2011). Ingestion of contaminated food, water, or fomites is the most common source of infection. Occasionally, airborne transmission may occur with respiratory implication, due to the capacity of the organism to survive on dried airborne particles (Greene, 1990). Normally the intestinal tract is protected against *Salmonella* spp. colonization by acid stomach pH, intestinal motility, resident bacterial population and intestinal mucus, which contains humoral and cellular immune factors (Greene, 1990). Infected cats with normal defence mechanisms have subsequently transient or no clinical symptoms. The establishment of clinical illness depends on many factors such as age, nutritional aspects and many kind of stress, such as hospitalisation, anesthesia, surgical or medical therapy, and overcrowding (Greene, 1990; Hall and German, 2010; Marks *et al.*, 2011). The impairment of host immune defences plays an important role in increasing the chance of clinically overt salmonellosis. Indeed, as previously reported, immunosuppression likely contributed to the development of salmonellosis in 2 cats with feline leukemia virus infection and diabetes mellitus, respectively (Dow *et al.*, 1989). In addition, salmonellosis was also reported in 4 recently vaccinated kittens (Foley *et al.*, 1999), and in one cat with lymphoma (Hohenhaus *et al.*, 1990). Moreover, treatment with cyclosporine was shown to aggravate murine salmonellosis and impair the development of native resistance to salmonellosis in newly hatched chickens, most likely due to reducing T-

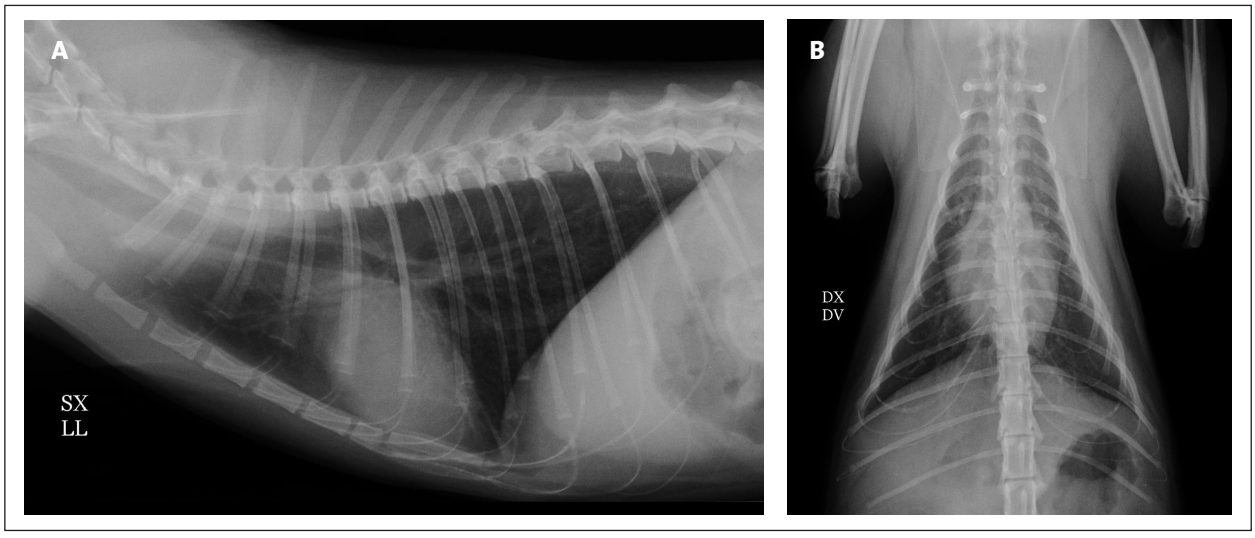

Figure 4: Left lateral (A) and dorsoventral (B) views of the thorax of the same cat after 6 weeks of antibiotic therapy. Complete resolution of the pulmonary lesions is observed.

cell response (Nichterlein *et al.*, 1996; Ziprin *et al.*, 1996). Furthermore, in human medicine *Salmonella* spp. is one of the major organisms producing post transplant acute renal infection in patients treated with immune suppressive medicaments, such as with cyclosporine (Nampoory *et al.*, 2003). In the cat of the present report the administration of cyclosporine most probably played an important role by decreasing immune defences and favouring the infection. The permissive role of cyclosporine in the pathogenesis of other infections has been demonstrated in the previous literature, with three cats diagnosed with toxoplasmosis after cyclosporine treatment for atopy (Barrs *et al.*, 2006; Last *et al.*, 2004).

The most common clinical signs of salmonellosis in cats are gastrointestinal, with fever, malaise, and anorexia appearing initially, followed by vomiting, abdominal pain, and diarrhea (Dow *et al.*, 1989; Greene, 1990; Hall and German, 2010, Marks *et al.*, 2011). Bacteraemia and endotoxaemia, as well as localisation in extra intestinal organs, may also occur (Fox *et al.*, 1984; Dow *et al.*, 1989; Greene, 1990, Brain *et al.*, 2006). Lung infection with *Salmonella* spp. is very rare in cats, with only 3 cases yet documented (Barrs *et al.*, 1999, 2005; Foster *et al.*, 2004; Rodriguez *et al.*, 1993). The first case was a 8-year-old domestic shortair cat affected by *Salmonella* Choleraesuis with pneumonia but no enteric manifestation. The Salmonellae were cultured from bronchial brush samples (Rodriguez *et al.*, 1993). The second was a 14-week-old domestic shorthair kitten with a history of gastroenteritis, later diagnosed with bronchopneumonia and pleural effusion due to a concomitant infection with *Salmonella* Typhimurium and *Aelurostrongylus abstrusus*, both isolated from bronchial wash and pleural exudates (Barrs *et al.*, 1999, 2005; Foster *et al.*, 2004). Unfortunately, the latter case has only been briefly mentioned in a case series on feline lower respiratory tract infections, without detailed description (Foster *et al.*, 2004). *Salmonella* spp. pneumonia is also a rare condition in humans (Greene, 1990, Rodriguez *et al.*, 2006), and has been reported in elderly, children and if concurrent diseases are present (Mankhambo *et al.*, 2006; Gerona and Navarra, 2009; Graham *et al.*, 2011; Chen et al., 2012). In the immunocompetent patient pulmonary infection with *Salmonella* spp. is exceptionally rare (Genzen *et al.*, 2008).

In the present case, the clinical signs could be attributed entirely to a pulmonary disease and no gastrointestinal abnormalities were noted. Bacterial culture and PCR from oropharyngeal and rectal swabs yielded negative results, possibly confirming the fact that the gastrointestinal tract was not affected. However, these laboratory investigations were performed one month after diagnosis and under doxycycline treatment, not allowing a complete exclusion of a gastrointestinal involvement. In humans, lung salmonellosis is usually associated with previous or concomitant gastroenteritis or bacteremia (Rodriguez *et al.,* 2006), as it was in one of the 3 cats reported in the literature (Barrs *et al.,* 1999, 2005; Foster *et al.,* 2004). One possible explanation for the atypical localisation of *Salmonella* spp. in this free-roaming cat is an airborne transmission route. For instance, considering that phagocytic cells in the intestinal lymph nodes, liver, or spleen may harbour the organism persistently, even in the absence of shedding (Greene, 1990), a latent subclinical infection that reactivated due to immunosuppression and led to bacteraemia with lung involvement is possible. It has been shown in animals that reactivation of infection and clinical illness may occur after stress, immunosuppression, and crowding (Greene, 1990).

One of the previous cats with pulmonary salmonellosis described in the literature had a concurrent *Aelurostrongylus abstrusus* infection, and the seeding of the lungs with *Salmonella* was suspected to be a consequence of migration of *Aelurostrongylus abstrusus* from the gastrointestinal tract (Barrs *et al.*, 1999, 2005; Foster *et al.* 2004). In the cat of this report the Baermann test was negative, but the moderate sensitivity of this test does not allow its certain exclusion (Lacorcia *et al.*, 2009).

Diagnosis of salmonellosis in humans and in cats has been mostly based on the isolation of *Salmonella* spp. organisms from cultured feces, blood, bronchial brushing and effusions (Greene, 1990; Hall and German, 2010, Marks *et al.*, 2011). Positive culture from lung aspirates is an exceptional condition, rarely described in humans (Mankhambo *et al.*, 2006; Graham *et al.*, 2011), and documented for the first time in the feline species. In the present case, the nodular interstitial pattern has probably permitted a more accurate sampling. These findings suggest that in some pneumonia cases in cats isolation of bacteria may be achieved through fine needle aspirates, avoiding more stressful procedures requiring anesthesia.

Salmonella spp. organisms have an important zoonotic potential, possibly causing significant illness in humans, especially in the aged population, children, and in immunocompromised patients (Mankhambo *et al.*, 2006; Genzen *et al.*, 2008; Gerona and Navarra, 2009; Graham *et al.*, 2011; Chen *et al.*, 2012). Salmonellosis due to multidrug-resistant *Salmonella* serovar Typhimurium is a major concern for the public health with an estimated 30 million cases and 600'000 deaths annually (Ahmed *et al.*, 2006). For this reason determination of the infective serovar seems advisable. In conclusion, the present case report describes an unusual clinical presentation of salmonellosis in a cat, in which cyclosporine administration may have played a permissive role in its pathogenesis. *Salmonella* should be considered among pathogens responsible for pneumonia in immunocompromised cats.

References

Ahmed D., D'Costa L. T., Alam K., et al.: Multidrug-resistant *Salmonella* enterica serovar typhi isolates with high-level resistance to ciprofloxacin in Dahaka, Bangladesh. Antimicrob. Agents Chemoteher. 2006, 50: 3516–3517.

Barrs V. R., Swinney G. R., Martin P., et al.: Concurrent *Aelurostrongylus abstrusus* infection and salmonellosis in a kitten. Aust. Vet. J. 1999, 77: 229–232.

Barrs V. R., Graeme S. A., Martin P., et al.: Feline pyothorax: a retrospective study of 27 cases in Australia. J. Feline Med. Surg. 2005, 7: 211–222.

Barrs V. R., Martin P., Beatty J. A.: Antemortem diagnosis and treatment of toxoplasmosis in two cats on cyclosporine therapy. Aust. Vet. J. 2006, 84: 30–35.

Brain P. H., Barrs V. R., Martin P., et al.: Feline cholecystitits and acute neutrophilic cholangitis: clinical findings, bacterial isolates and response to treatment in six cases. J. Feline Med. Surg. 2006, 8: 91–103.

Chen P. L., Li C. Y., Hsieh T. H., et al.: Epidemiology, disease spectrum and economic burden of non-typhoidal *Salmonella* infections in Taiwan, 2006–2008. Epidemiol. Infect. 2012, 6: 1–8.

Chen P. L., Lee H. C., Lee N. Y., et al.: Non-typhoidal *Salmonella* bacteraemia in elderly patients: an increased risk for endovascular infections, osteomyelitis and mortality. Epidemiol. Infect. 2012, 140: 2037–2044.

Dow S. W., Jones R. L., Henik R. A., et al.: Clinical features of salmonellosis in cats: six cases (1981–1986). J. Am. Vet. Med. Assoc. 1989, 194: 1464–1466.

Fox J. G., Beaucage J. C., Niemi S. M.: Experimental *Salmonella*-associated conjunctivitis in cats. Can. J. Comp. Med. 1984, 48: 87–91.

Foley J. E., Orgad U., Hirsh D. C., et al.: Outbreak of fatal salmonellosis in cats following use of a high-titer modified-live panleukopenia virus vaccine. J. Am. Vet. Med. Assoc. 1999, 214: 67–70.

Foster S. F., Martin P., Allan G. S., et al.: Lower respiratory tract infections in cats: 21 cases (1995–2000). J. Feline Med. Surg. 2004, 6: 167–180.

Genzen J. R., Towle D. M., Kravetz J. D., et al.: *Salmonella* Typhimurium pulmonary infection in an immunocompetent patient. Conn. Med. 2008, 72: 139–142.

Gerona J. G., Navarra S. V.: *Salmonella* infections in patients with systemic lupus erythematosus: a case series. Int. J. Rheum. Dis. 2009, 12: 319–323.

Graham S. M., Mankhambo L., Phiri A., et al.: Impact of human immunodeficiency virus infection on the etiology and outcome of severe pneumonia in Malawian children. Pediatr. Infect. Dis. J. 2011, 30: 33–38.

Greene C. E.: Salmonellosis. In: Infectious Disease of the dog and cat. 3rd edn. Ed. C. E. Greene, Saunders, Philadelphia, 1990, 355–360.

Hall E. J., German A. J.: Diseases of the small intestine. In: Veterinary Internal Medicine. 7th edn. Eds. S. J. Ettinger and E. C. Feldman, Elsevier, St. Louis, 2010, 1548.

Heinrich N. A., McKeever P. J., Eisenschenk M. C.: Adverse events in 50 cats with allergic dermatitis receiving ciclosporin. Vet. Dermatol. 2011, 22: 511–520.

Hohenhaus A. E., Rosenberg M. P., Moroff S. D.: Concurrent lymphoma and salmonellosis in a cat. Can. Vet. J. 1990, 31: 38–40.

Khan A. A., Nawaz M. S., Khan S. A., et al.: Detection of multidrug-resistant *Salmonella* Typhimurium DT104 by multiplex polymerase chain reaction. FEMS Microbiol. Lett. 2000, 182: 355–360.

Lacorcia L., Gasser R. B., Andreson G. A., et al.: Comparison of bronchoalveolar lavage fluid examination and other diagnostic techniques with the Baermann technique for detection of naturally occurring *Aelurostrongylus abstrusus* infection in cats. J. Am. Vet. Med. Assoc. 2009, 235: 43–49.

Last R. D., Suzuki Y., Manning T. et al.: A case of fatal systemic toxoplasmosis in a cat being treated with cyclosporine A for feline atopy. Vet. Dermatol. 2004, 15: 194–198.

Mankhambo L. A., Chiwaya K. W., Phiri A., et al.: Lobar pneumonia caused by Nontyphoidal *Salmonella* in a Malawian child. Pediatr. Infect. Dis. J. 2006, 25: 1190–1192.

Marks S. L., Rankin S. C., Byrne B.A., et al.: Enteropathogenic bacteria in dogs and cats: diagnosis, epidemiology, treatment, and control. J. Vet. Intern. Med. 2011, 25: 1195–1208.

Nampoory M. R., Johny K. V., Costandy J. N., et al.: Infection related renal impairment: a major cause of acute allograft dysfunction. Exp. Clin. Transplant. 2003, 1: 60–64.

Nichterlein T., Kretschmar M., Geginat G., et al.: Effects of FK-506 on the course of murine salmonellosis. J. chemother. 1996, 8: 449–456.

Rodriguez C. O. Jr, Moon M. L., Leib M. S.: *Salmonella* Choleraesuis pneumonia in a cat without signs of gastrointestinal tract disease. J. Am. Vet. Med. Assoc. 1993, 202: 953–955.

Rodriguez M., De Diego I., Martinez N., et al.: Nontyphoidal Salmonella causing focal infections in patients admitted at a Spanish general hospital during an 11-year period (1991–2001). Int. J. Med. Microbiol. 2006, 296: 211–222.

Ziprin R. L., Corrier D. E., Elissalde M. H.: Maturation of resistance to salmonellosis in newly hatched chicks: inhibition by cyclosporine. Poult. sci. 1989, 68: 1637–1642.

Corresponding author

Dr. Carolina Callegari
Istituto Veterinario di Novara
Strada Provinciale 9
28060 Granozzo con Monticello
Italy
carolina.callegari@istitutoveterinarionovara.it

Received: 30 November 2013
Accepted: 14 March 2014