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VETERINARY MICROBIOLOGY - RESEARCH PAPER

Klebsiella-induced infections in domestic species: a case-series study in 697 animals (1997–2019)

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Abstract

Klebsiella species, particularly *K. pneumoniae*, are well-known opportunistic enterobacteria related to complexity of clinical infections in humans and animals, commonly refractory to conventional therapy. The domestic animals may represent a source of the pathogenic and multidrug-resistant *Klebsiella* species to humans. Nevertheless, most studies involving *Klebsiella*-induced infections in domestic animals are restricted to case reports or outbreaks. We retrospectively investigated selected epidemiological data, clinical aspects, and in vitro susceptibility pattern of 697 non-repetitive *Klebsiella* infections in livestock and companion species (1997–2019). The isolates were obtained from different clinical disorders from dogs ($n=393$), cattle ($n=149$), horses ($n=98$), cats ($n=27$), pigs ($n=22$), sheep ($n=5$), goats ($n=2$), and buffalo ($n=1$), except four isolates from subclinical bovine mastitis. Urinary (223/697 = 32%), enteric (117/697 = 16.8%), mammary (85/697 = 12.2%), reproductive (85/697 = 12.2%), and respiratory disorders (67/697 = 9.6%) were the most common clinical manifestations. Other miscellaneous clinical pictures (116/697 = 16.6%) included abscesses, otitis, hepatitis, conjunctivitis, pyodermitis, sepsis, and encephalitis. Norfloxacin (183/245 = 74.7%) and gentamicin (226/330 = 68.5%) were the most effective antimicrobials. High in vitro resistance of the isolates was seen to ampicillin (326/355 = 91.8%), amoxicillin/clavulanic acid (25/62 = 40.3%), and trimethoprim/sulfamethoxazole (100/252 = 39.7), and multidrug resistance to ≥ 3 classes of antimicrobials was found in 20.4% (142/697) isolates. Wide variety of clinical manifestations of *Klebsiella*-induced infections was observed, with a predominance of urinary, enteric, mammary, reproductive, and respiratory tract disorders, reinforcing opportunistic behavior of agent. Poor in vitro efficacy was observed to some conventional antimicrobials and ~ 20% of isolates exhibited resistance pattern, reinforcing the need for proper use of drugs on therapy approaches in domestic animals to avoid multidrug-resistant bacteria, an emergent global concern.

Keywords *Klebsiella pneumoniae* · Livestock · Companion animals · Clinical and epidemiological aspects · Multidrug-resistant bacteria

Introduction

Klebsiella species are well-known rod-shaped gram-negative, non-motile, lactose-fermenting, facultatively anaerobic bacteria belonging to the *Enterobacteriaceae* family. The organism is found widely in the environment, i.e., soil, water, manure, and plants, as well as enteric tract, skin, and mouth microbiota of animals and humans [1–3]. Different routes of transmission are possible to *Klebsiella*-induced infections due to virulence potential and opportunistic nature of the bacterium, although ingestion of contaminated food and water [4], genitourinary, and intramammary [5] are common routes associated with the transmission of the pathogen in livestock [6] and companion animals [7].

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The pathogenicity of *Klebsiella* species, particularly *K. pneumoniae*, has been attributed to a set of virulence factors, including capsular serotypes (K1 and K2), adhesins (*fimH-1*, *mrkD*), iron-acquired systems (siderophores, *iucC*), lipopolysaccharides of cell wall, bacteriocins (*entB*), and serum resistance (*traT*) [8–10]. A great variety of clinical signs are related to *Klebsiella* infections in domestic animals, although urinary, respiratory, mammary, and reproductive tract disorders have been predominantly reported [5, 6, 11, 12].

In humans, *K. pneumoniae* is intimately associated with hospital-acquired infections [2, 13] causing mainly pneumonia, urinary tract disorders, and sepsis [4]. Neonates, elderly, and immunocompromised patients have been related to a significant morbimortality rate, caused mainly by multidrug-resistant *K. pneumoniae* isolates [2, 4], an emergent global One Health issue [14]. In addition, a dangerous hypervirulent *K. pneumoniae* variant has been increasingly reported in some countries, with the ability to develop serious life-threatening community-acquired infections related mainly to pneumonia, abscesses, sepsis, and encephalitis [15].

Besides a great variety of virulence mechanisms, genomic diversity, multidrug resistance to conventional antimicrobials, and public health relevance of *Klebsiella*-induced infections [2–4, 14], there are scarce comprehensive studies that have focused on the main epidemiological and clinical aspects related to the pathogen from the non-human origin [10], especially involving a great number of domestic animals. In addition, domestic species and food products and derivatives from animal origin may represent transmission sources of pathogenic *Klebsiella* species from animals to humans [3, 10]. In this scenario, we retrospectively investigated selected epidemiological and clinical aspects of 697 non-repetitive cases of *Klebsiella*-induced infections naturally acquired isolated from a great variety of clinical disorders from cattle, dogs, pigs, horses, cats, sheep, goats, and buffalo for 22 years (1997–2019), as well as in vitro susceptibility pattern of isolates.

Material and methods

Study design

A cross-sectional study of the clinical aspects and selected epidemiological data in 697 *Klebsiella*-induced infections isolated from domestic animals in the Laboratory of Microbiology at Veterinary Hospital of School of Veterinary Medicine and Animal Sciences (FMVZ) of the São Paulo State University (UNESP), Botucatu, SP, Brazil, from 1997 to 2019, was retrospectively investigated.

Animals, criteria for case selection and database of study

All six hundred ninety-seven cases of *Klebsiella* infections isolated from different disorders from dogs, cattle, horses, cats, pigs, sheep, goat, and buffalo recorded at Laboratory of Microbiology over a 22-year period were included in the study. All the *Klebsiella* isolates were recovered from non-repetitive 697 cases among domestic animals sampled. Only four subclinical cases of bovine mastitis were included in this trial. The animals enrolled came from the State of São Paulo, Paraná, and Minas Gerais, located in the southeast and southern regions of Brazil. The database of the study consisted exclusively of paper records analyzed manually.

Epidemiological and clinical data

Selected epidemiological data were represented by age, gender (male/female), and season of cases in the spring (September to November), summer (December to February), autumn (March to May), and winter (June to August). Due to the isolation of the pathogen from diverse breeds and cross-breeds among different domestic animals sampled, this data was not used to further analysis. Age of dogs was stratified as < 1 year old, 1 to < 5 years old, ≥ 5 to ≤ 10 years old, and > 10 years old, while livestock species were subdivided among < 3 years old, 3 to 10 years old, and > 10 years old.

The diagnosis was based on clinical data available in the medical records, complementary exams, and microbiological identification of *Klebsiella* isolates. Clinical specimens were obtained mainly from urine, feces, milk, semen, uterus secretion, bronchoalveolar lavage fluid, auditive and ocular secretions, abscesses content, cerebrospinal fluid, and different fragments of organs at necropsy. Some clinical manifestations from the same organic system were grouped as respiratory (sinusitis, pharyngitis, bronchitis, pneumonia, nasal fistula), urinary tract (cystitis, pyelonephritis, urethritis), and reproductive disorders (vaginitis, pyometra, abortion, seminal vesiculitis, prostatitis, epididymitis, and orchitis), while other various clinical abnormalities were grouped as miscellaneous. Clinical outcome (number of surviving and mortality) represented poor consistent or missing data and was not used to further analysis.

Bacteriological diagnosis

Along the retrospective study from 1997 to 2019, all the samples were plated on defibrinated sheep blood agar (5%)

and MacConkey agar, incubated aerobically at 37 °C for 72 h, and diagnosis of *Klebsiella* isolates in 697 cases was based on conventional biochemical tests [1].

Diagnosis of bovine mastitis and the clinical score of severity

Subclinical mastitis was diagnosed by conventional California mastitis test (1 + to 3 + scores) [6]. The clinical mastitis cases and three severity scores were diagnosed in quarter/animal level as follows: mild cases (or score 1) were characterized by the presence of macroscopic abnormalities in the milk appearance (e.g., flakes, pus, blood) using strip cup test; moderate cases (or score 2) when quarter of animals showed an altered appearance of milk and udder inflammation (redness to congestion, edema, swelling, and pain in the affected mammary gland); whereas animals with additional clinical signs of inappetence, fever, tachypnea, tachycardia, decubitus, or ruminal motility alterations were classified as severe cases (or score 3) [16]. When more than one quarter had been infected by *Klebsiella* sp., only one strain (*i.e.,* animal) was considered to analyze.

In vitro antimicrobial susceptibility test and multidrug-resistant isolates

Along 1997–2019, results of the in vitro antimicrobial disk diffusion test (Clinical and Laboratory Standards Institute guidelines, CLSI) [17, 18] from 697 *Klebsiella* isolates were retrospectively analyzed. Among these 22 years of retrospective study, 12 antimicrobials from six different classes were used as follows: (1) synthetic or derivative penicillins (ampicillin 10 µg, amoxicillin/clavulanic acid 30 µg), (2) cephalosporins (ceftiofur 30 µg, ceftriaxone 30 µg, cephalexin 30 µg), (3) fluoroquinolones (ciprofloxacin 5 µg, enrofloxacin 5 µg, norfloxacin 10 µg), (4) amphenicols (florfenicol 30 µg), (5) aminoglycosides (amikacin 30 µg, gentamicin 10 µg), and (6) sulfonamides (trimethoprim-sulfamethoxazole 25 µg). Isolates that exhibited simultaneous resistance to ≥ 3 different classes (groups) of antimicrobials were considered multiresistant [19]. Intermediate results of in vitro antimicrobial pattern were not included in analysis of multiresistant isolates.

Multiple antimicrobial resistance (MAR) indices were calculated by determining the ratio of the number of antimicrobial class(es) against which each isolate was resistant and the total number of tested classes [20].

Data analyses

The Chi-square (or Fisher's exact) test was used to compare the association between clinical manifestations and selected epidemiological data of *Klebsiella* isolates. Statistical analyses were conducted using SPSS version 14 for Windows (SPSS Inc., Chicago, IL, USA) and the level of statistical significance was set at 0.05.

Results

Epidemiological and clinical data

Dogs (393/697 = 56.4%), cattle (149/697 = 21.4%), and horses (98/697 = 14.1%) were the domestic species most frequently affected by *Klebsiella*-induced infections, followed by a minor number of cases in cats (27/697 = 3.9%), pigs (22/697 = 3.1%), sheep (5/697 = 0.7%), goats (2/697 = 0.3%), and buffalo (1/697 = 0.1%). Data of clinical manifestations versus livestock and companion species infected by *Klebsiella* sp. are shown in Table 1. Out of 697 cases, urinary tract infections (223/697 = 32%), diarrhea (117/697 = 16.8%), clinical and subclinical mastitis (89/697 = 12.8%), reproductive abnormalities (85/697 = 12.2%), and respiratory infections (67/697 = 9.6%) were the most common disorders. Nevertheless, the pathogen was also isolated from other miscellaneous clinical conditions (116/697 = 16.6%), e.g., otitis (32/116 = 27.6%), abscesses (24/116 = 20.7%), hepatitis (20/116 = 17.2%), pyodermitis (8/116 = 6.9%), sepsis (4/116 = 3.4%), conjunctivitis (3/116 = 2.6%), encephalitis (1/116 = 0.9%), and from different fragments of organs at necropsy (24/116 = 20.7%).

Respiratory infections were clinically manifested by pneumonia (39/67 = 58.2%), bronchitis (17/67 = 25.4%), sinusitis (9/67 = 13.4%), pharyngitis (1/67 = 1.5%), and nasal fistula (1/67 = 1.5%). Urinary tract infections (UTI) were represented by cystitis (169/223 = 75.8%), pyelonephritis (32/223 = 14.3%), and urethritis (22/223 = 9.9%). Reproductive disorders were clinically observed predominantly as seminal vesiculitis (46/85 = 54.1%) and pyometra (29/85 = 34.1%), followed by low frequency of equine abortion (3/85 = 3.5%), vaginitis (2/85 = 2.3%), and isolated cases of bovine abortion (1/85 = 1.2%), equine orchitis (1/85 = 1.2%), ovine prostatitis (1/85 = 1.2%), ovine epididymitis (1/85 = 1.2%), and ovine orchitis (1/85 = 1.2%) (Table 1).

Of all animals enrolled, 57.2% (399/697) were female, 40.5% (282/697) male, and there was no information/missing data about the gender of 2.3% (16/697) animals.

The age of the 697 domestic animals ranged from 1 day to 20 years old, with mean age of 7.1 years. The most common age of canine pneumonia occurrence ranged from 1- to < 5 years old (23/46 = 50%), followed by < 1 year old (7/46 = 15.2%), ≥ 5 to ≤ 10 years old (8/46 = 17.4%), and > 10 years old (8/46 = 17.4%). Dogs that manifested enteritis were affected mainly < 1 year old (35/55 = 63.6%), followed by 1 to < 5 years old

Table 1 Clinical disorders caused by *Klebsiella*-induced infections in 697 companion and livestock species. Brazil, 1997–2019

Clinical manifestations	Mastitis[1]	Diarrhea	Respiratory infections[2]	Urinary infections[3]	Reproductive disorders[4]	Miscelaneous[5]	Total (%)
Animal species	N isolates (%)	N isolates (%)	N isolates (%)	N isolates (%)	N isolates (%)	N isolates (%)	
Dogs	-	55 (14)	46 (11.7)	204 (51.9)	13 (3.3)	75 (19.1)	393 (100)
Cattle	89 (59.7)	21 (14.1)	8 (5.4)	1 (0.7)	17 (11.4)	13 (8.7)	149 (100)
Horses	-	26 (26.5)	7 (7.1)	1 (1)	52 (53.1)	12 (12.3)	98 (100)
Cats	-	-	-	17 (63)	-	10 (37)	27 (100)
Pigs	-	13 (59.1)	4 (18.2)	-	-	5 (22.7)	22 (100)
Sheep	-	-	2 (40)	-	2 (40)	1 (20)	5 (100)
Goats	-	1 (50)	-	-	1 (50)	-	2 (100)
Buffalo	-	1 (100)	-	-	-	-	1 (100)
Total (%)	89 (12.8)	117 (16.8)	67 (9.6)	223 (32)	85 (12.2)	116 (16.6)	697

N number, % percentage

[1]Clinical ($n=85$), subclinical ($n=4$)

[2]Pneumonia ($n=39$), bronchitis ($n=17$), sinusitis ($n=9$), pharyngitis ($n=1$), nasal fistula ($n=1$)

[3]Cystitis ($n=169$), pyelonephritis (32), urethritis ($n=22$)

[4]Seminal vesiculitis ($n=46$), pyometra ($n=29$), equine abortion ($n=3$), vaginitis ($n=2$), bovine abortion ($n=1$), equine orchitis ($n=1$), prostatitis ($n=1$), ovine epididymitis ($n=1$), and ovine orchitis ($n=1$)

[5]Miscellaneous = otitis ($n=32$), abscesses ($n=24$), hepatitis ($n=20$), pyodermitis ($n=8$), sepsis ($n=4$), conjunctivitis ($n=3$), encephalitis ($n=1$), and from fragment of organs ($n=24$)

(9/55 = 16.4%), ≥ 5 to ≤ 10 years old (7/55 = 12.7%), and > 10 years old (4/55 = 7.3%). Canine urinary tract infection occurred predominantly among animals > 10 years old (108/204 = 53%), followed by ≥ 5 to ≤ 10 years old (61/204 = 29.9%), 1 to < 5 years old (27/204 = 13.2%), and < 1 year old (8/204 = 3.9%). Equine reproductive tract infections occurred mainly > 10 years old (27/52 = 52%) animals, followed by 3 to 10 years old (23/52 = 44.2%), and few cases < 3 years old (2/52 = 3.8%). Seventy-eight cases of clinical mammary infections occurred predominantly in cows between 3 and 10 years old (69/78 = 88.5%), followed by a minor number > 10 years old (4/78 = 5.1%) animals, while there was no information/missing data about age of 5 (5/78 = 6.4%) cows.

Eighty-five clinical cases of bovine mastitis occurred predominantly along with the summer (36/85 = 42.4%) and autumn (24/85 = 28.2%), followed by an equivalent number of cases in spring (13/85 = 15.3%) and winter (12/85 = 14.1%). Among forty-six dogs affected by pneumonia, the clinical manifestation occurred mainly in the winter (21/46 = 45.6%), followed by a minor number of cases in autumn (12/46 = 26.1%), spring (9/46 = 19.6%), and summer (4/46 = 8.7%). Fifty-five cases of canine enteritis occurred with an equivalent distribution throughout the summer (17/55 = 30.9%), spring (14/55 = 25.5%), autumn (13/55 = 23.6%), and winter (11/55 = 20%) periods. Among 204 canine urinary tract infections, the clinical manifestations occurred mainly in summer (68/204 = 33.3%), followed by winter (52/204 = 25.5%), spring (46/204 = 22.6%), and autumn (38/204 = 18.6%). Fifty-two cases of reproductive disorders in horses revealed an equivalent distribution of cases in winter (15/52 = 28.8%), spring (13/52 = 25%), summer (14/52 = 27%), and autumn (10/52 = 19.2%).

Diagnosis of bovine mastitis and the clinical score of severity

Among 89 isolates from bovine mastitis, 95.5% (85/89) and 4.5% (4/89) were clinical and subclinical cases, respectively. Of 78 clinical cases, data regarding clinical scores were available in 47 (60.2%) cases, of which 23.4% (11/47), 40.4% (19/47), and 36.2% (17/47) showed mild, moderate, and severe level, respectively.

In vitro antimicrobial susceptibility test and multidrug-resistant isolates

The most in vitro effective drugs against *K. pneumoniae* isolates were norfloxacin (183/245 = 74.7%) and gentamicin (226/330 = 68.5%). In contrast, high resistance rates of the isolates were observed mainly to ampicillin (326/355 = 91.8%), amoxicillin/clavulanic acid (25/62 = 40.3%), and trimethoprim/sulfamethoxazole (100/252 = 39.7) (Table 2). One hundred forty-two (142/697 = 20.4%) isolates from dogs ($n=82$), cattle ($n=37$), horses ($n=16$), pigs ($n=3$), cats ($n=2$), and small ruminants ($n=2$) exhibited simultaneous resistance to ≥ 3 antimicrobials of different groups of drugs and were

Table 2 In vitro antimicrobial susceptibility pattern of *Klebsiella* isolates from diseased companion animals and livestock. Brazil, 1997–2019

Animal species Classes of drugs	Antimicrobials	Dogs			Cattle			Horses			Pigs			Cats			Total		
		N of strains (%)			*N* of strains (%)			*N* of strains (%)			*N* of strains (%)			*N* of strains (%)			*N* of strains (%)		
		S	I	R	S	I	R	S	I	R	S	I	R	S	I	R	S	I	R
Aminoglycosides	Amikacin	33/66 (50)	8/66 (12)	25/66 (38)	-	-	-	28/44 (64)	7/44 (16)	9/44 (20)	-	-	-	-	-	-	61/110 (55.4)	15/110 (13.6)	34/110 (31)
	Gentamicin	99/155 (64)	9/155 (6)	47/155 (30)	78/101 (77)	15/101 (15)	8/101 (8)	43/65 (66)	10/65 (15)	12/65 (19)	5/6 (83)	-	1/6 (17)	1/3 (33)	-	2/3 (67)	226/330 (68.5)	34/330 (10.3)	70/330 (21.2)
Amphenicols	Florfenicol	20/67 (30)	9/67 (13)	38/67 (57)	57/88 (65)	11/88 (12)	20/88 (23)	19/26 (73)	2/26 (8)	5/26 (19)	3/7 (43)	1/7 (14)	3/7 (43)	-	-	-	99/188 (52.7)	23/188 (12.2)	66/188 (35.1)
Betalactams and derivatives	Amoxicillin/clavulanic acid	29/62 (46.8)	8/62 (12.9)	25/62 (40.3)	-	-	-	-	-	-	-	-	-	-	-	-	29/62 (46.8)	8/62 (12.9)	25/62 (40.3)
	Ampicillin	5/145 (3)	3/145 (2)	137/145 (95)	7/92 (8)	4/92 (4)	81/92 (88)	6/61 (10)	2/61 (3)	53/61 (87)	2/55 (3.6)	-	53/55 (96.4)	-	-	2/2 (100)	20/355 (5.6)	9/355 (2.6)	326/355 (91.8)
Cephalosporins	Cefalexin	56/131 (43)	21/131 (16)	54/131 (41)	45/70 (64)	10/70 (14)	15/70 (22)	-	-	-	-	-	-	1/3 (33)	-	2/3 (67)	102/204 (50)	31/204 (15.2)	71/204 (34.8)
	Ceftiofur	29/164 (18)	60/164 (36)	75/164 (46)	25/50 (50)	15/50 (30)	10/50 (20)	29/59 (49)	13/59 (22)	17/59 (29)	-	-	-	-	-	2/2 (100)	83/275 (30.2)	88/275 (32)	104/275 (37.8)
	Ceftriaxone	38/84 (45)	14/84 (17)	32/84 (38)	-	-	-	18/27 (67)	5/27 (18)	4/27 (15)	-	-	-	-	-	2/2 (100)	56/113 (49.6)	19/113 (16.8)	38/113 (33.6)
Fluoroquinolones	Ciprofloxacin	76/159 (48)	25/159 (16)	58/159 (36)	-	-	-	33/40 (83)	2/40 (5)	5/40 (12)	-	-	-	-	-	2/2 (100)	109/201 (54.2)	27/201 (13.4)	65/201 (32.4)
	Enrofloxacin	77/177 (44)	34/177 (19)	66/177 (37)	56/93 (60)	23/93 (25)	14/93 (15)	46/65 (71)	11/65 (17)	8/65 (12)	1/6 (17)	1/6 (17)	4/6 (66)	1/3 (33)	-	2/3 (67)	181/344 (52.6)	69/344 (20.1)	94/344 (27.3)
	Norfloxacin	122/180 (68)	9/180 (5)	49/180 (27)	-	-	-	60/63 (95)	1/63 (2)	2/63 (3)	-	-	-	1/2 (50)	-	1/2 (50)	183/245 (74.7)	10/245 (4.1)	52/245 (21.2)
Sulfonamides	Trimethoprim-sulfamethoxazole	78/153 (51)	8/153 (5)	67/153 (44)	19/33 (58)	2/33 (6)	12/33 (36)	36/57 (63)	2/57 (4)	19/57 (33)	4/6 (67)	2/6 (33)	-	1/3 (33)	-	2/3 (67)	138/252 (54.8)	14/252 (5.5)	100/252 (39.7)

N number, % percentage, *S* susceptible, *I* intermediate, *R* resistant

considered multiresistant. These multidrug-resistant isolates were recovered mainly from clinical mastitis (30/37 = 81.1%) and diarrhea in cattle (6/37 = 16.2%); urinary tract infections (25/82 = 30.5%), diarrhea (23/82 = 28%), and pneumonia (10/82 = 12.2%) in dogs; pyometra (5/16 = 31.2%), seminal vesiculitis (3/16 = 18.8%), and pneumonia (2/16 = 12.5%) in horses; and diarrhea in pigs (2/3 = 66.7%). MAR indices of cattle, dogs, horses, pigs, and cats were 0.413, 0.348, 0.272, 0.227, and 0.123, respectively.

Data analyses

No statistical association was observed between age and canine pneumonia ($p = 0.21$), age and canine enteritis ($p = 0.22$), age and canine urinary tract infection ($p = 0.26$), canine pneumonia and seasons ($p = 0.15$), and bovine mastitis and seasons ($p = 0.15$).

Discussion

This study revealed a great variety of clinical manifestations of *Klebsiella*-induced infections in domestic animals retrospectively investigated over 22 years, with a predominance of urinary, enteric, mammary, reproductive, and respiratory disorders, a fact that reinforces the pathogenicity and opportunistic nature of the organism [4], since this pathogen is found widely in the environment and enteric tract of livestock and companion animals [1, 2]. In addition, ~ 20% of the isolates revealed multidrug resistance to conventional antimicrobials, an emergent public health issue worldwide.

For decades, gram-positive contagious bacterium represented the major causes of bovine mastitis globally. Nevertheless, dairy farms that reached success on programs to control this group of pathogens facing a novel scenario targeted to control environmental pathogens, particularly coliforms, e.g., *Escherichia coli* and *K. pneumoniae* [21]. *K. pneumoniae* is a well-known pathogen of mammary infections in livestock, especially as a primary causal agent of clinical mastitis in cows. The organism is widely distributed in dairy farm environment [5], i.e., manure, feces, water, and different types of bedding (sand, sawdust, straw). In the current study, 87.6% of cows with mammary infections showed clinical manifestations, which agrees with studies published previously [22, 23], which described the predominance of clinical bovine mastitis-related *Klebsiella* infections.

E. coli and *K. pneumoniae* have been described as the main enterobacteria causing clinical bovine mastitis around the world [24], although differences in the pathogenicity have been noted among mammary infections induced by these enterobacteria [5]. High severity of clinical episodes, longer duration of infection, poor-to-moderate response to vaccination, inefficacy of antimicrobial therapy, and high risk of culling or death have been seen in mammary infections caused by *Klebsiella* species compared to *E. coli* [5, 25]. In addition, clinical severity scores of bovine mastitis have been traditionally investigated among mastitis-related *E. coli* infections [16], although the influence of virulence factors and the specific genes that determine the severity scores of clinical cases has not been fully determined [26]. In this regard, few comprehensive studies have addressed the severity scores of bovine clinical mastitis-related *Klebsiella* species [3]. A study that investigated the etiology of clinical mastitis in 50 large-scale dairy farms from the USA revealed 30.2% mild, 37.2% moderate, and 32.6% severe scores of mammary infections-related *K. pneumoniae* [22]. In this study, 23.4%, 40.4%, and 36.2% of cows from Brazil exhibited mild, moderate, and severe clinical scores, respectively, indicating a predominance of *Klebsiella* infections as a primary agent of moderate-to-severe clinical cases of bovine mastitis. In fact, the severity of bovine mammary infections-related *Klebsiella* species reinforces concern in dairy farms with clinical cases induced by this pathogen, which may need an emergency therapy approach [5, 27].

Classically, *Klebsiella* species are considered a causal agent of bovine mastitis from environment [5] and an opportunistic, non-contagious agent of bovine mastitis, which implicates that mammary infection is related to different sources of the dairy environment [28]. Nevertheless, a binary behavior, i.e., environmental and contagious nature, has been noted currently in *Klebsiella pneumoniae* [29, 30] and other pathogens (*Streptococcus uberis* and *Streptococcus agalactiae*) that cause bovine mastitis [31], which may represent a new challenge to the control and preventive approaches of bovine mastitis. Besides these new perceptions related to the ability of *K. pneumoniae* to infect bovine mammary glands, the optimization of the immune response of cows, milking hygiene practices, environmental hygiene conditions [5], and novel vaccines produced with modern purposes [32] remains as important measures to prevent/control bovine mastitis-related to this pathogen. In addition, the clinical cases of bovine mastitis by *Klebsiella* sp. in the current study predominantly ranged from 3- to 10 years old in summer and autumn. High frequency of mastitis along this period of age may be related to cow's production peak, which predisposes to mammary infections, particularly in the summer period due to the increase of pluviometry that may facilitate the proliferation and environmental contamination of enterobacteria, such as *Klebsiella* species [5, 21].

Klebsiella pneumoniae are well-known inhabitant of enteric microbiota of livestock and companion animals [1]. Besides multifactorial nature of enteritis in livestock [6, 33] and companion species [7, 34], which involves bacteria, virus, and/or protozoa as causal agents, little attention has been deserved to *Klebsiella* species as a potential cause of enteric disorders. Here, among domestic animals sampled,

enteric manifestations were seen as a major clinical sign of *Klebsiella*-induced infections in pigs (59.1%), as well as moderately frequent in horses (26.5%), cattle (14.1%), and dogs (14%), indicating that this pathogen should be considered in the diagnosis of enteric manifestations among these domestic species. Among dogs retrospectively studied, enteritis occurred mainly < 1 year old, a finding that agrees with similar studies where diarrhea has predominated in young animals [35]. Furthermore, no clear association between canine enteritis and season periods in the current study suggests that enteritis by the pathogen may occur along all year.

Pulmonary involvement is another clinical disorder caused by *Klebsiella* species in domestic animals. The pulmonary tract-related *K. pneumoniae* infections may occur by aerosols or secondary to systemic dissemination of the pathogen from other sites of infection [6, 7]. In this regard, *Klebsiella* spp. were reported as a primary cause of pneumonia in 46 horses from the USA [11]. In the current study, pulmonary infections by *Klebsiella* isolates, represented mainly by pneumonia, bronchitis, and sinusitis signs, were reported in sheep (40%), pigs (18.2%), dogs (11.7%), horses (7.1%), and cattle (5.4%), reinforcing the pathogenicity of the agent to the pulmonary tract of domestic animals. In addition, canine pulmonary infection occurred mainly along to winter (45.6%), whose transmission of the pathogen in this period could be favored by aerosolization [7] and cold temperatures that may reduce the immune response of the animals [36].

Urinary tract infections represent one of the most common infectious diseases in veterinary practices, which affects particularly older females of companion animals [7]. The disease is polymicrobial, although enterobacteria have been reported as the main group of pathogens, i.e., *E. coli*, *Klebsiella*, *Enterobacter*, and *Proteus* species. Various predisposing factors have been related to canine and feline UTIs, affecting animals that have disorders of the urinary tract or underlying conditions, including impaired immunity, chronic kidney diseases, diabetes, hyperthyroidism, lithiasis, neoplasia, anatomic abnormalities, and transurethral procedures (catheter) [37]. Typically, *K. pneumoniae* has been reported as a primary agent of UTI, which infects the domestic animals by fecal contamination of lower urinary tract from the perirectal region, contaminated environment, and, occasionally, spread of the pathogen from other diseased foci or intestines, since this pathogen may be found as an inhabitant of the enteric tract of domestic animals [1]. In Brazil, 67 K. *pneumoniae* isolated from different clinical manifestations from domestic animals and wildlife revealed a predominance of urinary abnormalities (11/67 = 16.4%), followed by enteric (10/67 = 14.9%) and pulmonary (9/67 = 13.4%) infections [12]. These data align with the current study since > 50% of dogs and cats enrolled showed UTI, represented predominantly by cystitis, pyelonephritis, and urethritis, reinforcing the pathogenicity of *Klebsiella* species to the urinary system, particularly to companion animals.

Most canine UTI in the current study occurred > 10 years old, male, and in the summer period. Likewise, a study revealed the predominance of urinary infections in older dogs, since this group of animals is more predisposed to underlying conditions, impaired immune response, or chronic diseases that affect the urinary system [37]. In fact, the proximity of the lower urinary tract of females with the perirectal region or fecal contamination from the environment of animals may predispose urinary infections by enterobacteria, including *Klebsiella* species. Similar to bovine mammary infections in this study, the high number of canine UTI cases in the summer period (33.3%) may have been influenced by the increase of rainfall that favors proliferation and environmental contamination of enterobacteria in this period.

Reproductive disorders in domestic males and females constitute another pathogenic manifestation of *K. pneumoniae*-induced infections [6]. Among domestic animals retrospectively studied, seminal vesiculitis (54.1%) and pyometra (34.1%) represented the most frequent reproductive disorders observed among horses and cows, respectively. The possibilities of fecal contamination of genitalia of females and ureteral canal of males, due to proximity with the perirectal region or by fecal contamination from the environment of livestock, are factors that may contribute to ascendent infection of enterobacteria, e.g., *Klebsiella* species, to genital organs of domestic males and females [38]. Also, only three mares and one cow developed abortion, showing that it is an uncommon clinical condition secondary to *K. pneumoniae* infections of the uterus. In this way, atypical coinfection by *Klebsiella oxytoca* and *Rhodococcus equi* has been reported in abortion of thoroughbred mare [39].

Miscellaneous clinical manifestations related to *Klebsiella* sp. were also reported among domestic animals retrospectively assessed, represented by otitis, abscesses, hepatitis, pyodermitis, sepsis, conjunctivitis, and encephalitis. This wide spectrum of pathogenicity of *Klebsiella* species may be credited to its opportunistic behavior, ability to evade the immune system response, and/or the presence of a set of virulence mechanisms, including capsular antigens, adhesins, iron-acquired systems, bacteriocins, serum resistance, lipopolysaccharides of cell wall structure [8, 9], and resistance to conventional antimicrobials [5, 10], indicating that, virtually, any organ or tissue of domestic animals may be infected by this pathogen. Few numbers of sheep, goats, and buffalos retrospectively investigated herein showed clinical diseases associated with *Klebsiella*-induced infections. This data could be attributed to less expressive breeds of these animal species in the studied region.

Fluoroquinolones, aminoglycosides, cephalosporins (third or higher generations), and amoxicillin-clavulanate appear to be the main groups of antimicrobials used in the therapy of domestic animals related to *Klebsiella*-induced infections [6, 7, 31, 37]. Likewise, norfloxacin (74.7%), a fluoroquinolone, and gentamicin (68.5%), an aminoglycoside, were the most effective antimicrobials against *Klebsiella* isolates recovered from most domestic animals retrospectively investigated here, indicating that they may be considered possibilities of drugs to therapy approach against the pathogen in livestock and companion animals. Despite in vitro susceptibility of our isolates to some antimicrobials, poor efficacy has been observed in therapy practices of *K. pneumoniae*-induced infections among domestic animals, particularly clinical bovine mastitis cases [5, 31], sepsis, pneumonia, and complicated UTI in companion animals [7, 36, 37]. The inefficacy of conventional therapy to *K. pneumoniae*-induced infections may be credited to a set of bacterial evasion mechanisms against the antimicrobials, including inactivation of enzymatic degradation of drugs, changes of membrane permeability, and modification of target site of antimicrobials by bacterial mutation [10].

Multidrug-resistant *K. pneumoniae* isolates have been referred as an emergent human [4, 14] and animal [10, 40] global concern [14]. Conversely, few comprehensive studies have been addressed to antibiotic resistance of *Klebsiella* species from a non-human origin [10, 40]. In this regard, in vitro antimicrobial susceptibility pattern of 67 K. *pneumoniae* isolated from domestic and wildlife species from Brazil revealed high resistance of the isolates to metronidazole (65/67 = 97%), ampicillin (65/67 = 97%), amoxicillin (62/67 = 93%), and sulfonamides (62/67 = 93%) [12]. Likewise, high in vitro resistance rates of our *Klebsiella* isolates were observed mainly to ampicillin (91.8%), amoxicillin/clavulanic acid (40.3%), and trimethoprim/sulfamethoxazole (39.7%). Herein, the high resistance of isolates to ampicillin and trimethoprim/sulfamethoxazole may be credited by the rise of selective pressure of resistant bacteria [19] because these drugs have been used for more than 30 years in different veterinary therapy approaches. In turn, high resistance of our isolates to amoxicillin/clavulanic acid obtained from dogs was not expected, because this combination of drugs has been recommended to therapy of *Klebsiella*-induced infections in domestic animals, particularly companion animals [36, 37]. These findings reinforce that antimicrobial therapy of *Klebsiella* infections in domestic animals should be, if possible, based on microbiological culture and in vitro antimicrobial profile, which enables rational use of antimicrobial agents and continuous epidemiological vigilance of multiresistant bacteria [37, 40]. In fact, the responsible use of antimicrobials for therapy approaches of bacterial infections from animal origin is an emergent issue [3, 10], avoiding unnecessary use of some antimicrobials in animals [41] that are critically important to humans [14].

Approximately 20% of the *Klebsiella* isolates retrospectively investigated in the current study exhibited in vitro simultaneous resistance to ≥ 3 classes of antimicrobials tested, being classified as multidrug-resistant strains. The isolates were recovered predominantly from clinical bovine mastitis (81.1%), urinary tract infections (30.5%), diarrhea (28%), and pneumonia (12.2%) in dogs, and pyometra (31.2%) in horses, which is consistent with other studies published elsewhere, which revealed in vitro resistance pattern and/or poor treatment efficacy of *Klebsiella*-induced infections related to clinical bovine mastitis [5, 31], sepsis [7], pneumonia [36], and complicated UTI in companion animals [37]. In addition, the major MAR index among animals retrospectively studied was seen in cattle, dogs, and horses, indicating that these species may be potential sources of transmission of isolates harboring resistance genes of antimicrobials [20].

The increase transmission of pathogenic bacteria from animal to humans by foods or direct contact represents a worldwide problem and a matter of One Health concept. One Health is a collaborative, multisectoral, and multi-professional worldwide effort aiming to achieve optimal health and well-being outcomes recognizing the interconnections between people, animals, plants, and their environment [42]. Food safety, the control potential zoonotic agents, and multidrug-resistant bacteria are areas particularly relevant in One Health approaches, which includes infections by *Klebsiella* species in domestic animals [14]. Nevertheless, minor attention has been deserved to *Klebsiella* species as a foodborne pathogen [10], besides its presence as a primary agent of bovine mastitis and elimination by milk [5, 31]. In addition, the close contact of owners and their companion animals in modern society increases the risk of interspecies transmissions of pathogens, including by *Klebsiella* species. A study in Portugal described evidence of dogs as a reservoir of pathogenic *K. pneumoniae* to humans, since dogs shared isolates that were genetically indistinguishable based on pulse-field gel electrophoresis and multilocus sequencing typing [43]. In this way, mammary infections of cows and diarrhea and UTIs in dogs were seen as the most common *Klebsiella*-induced infections in the current study, highlighting human risks represented by this pathogen as a contaminant of milk and derivatives, as well as an agent that may be eliminated by feces, urine, and other organic humors of companion animals, potentially infective to their owners due to close contact.

No speciation by the polymerase chain reaction, mass spectrometry (MALDI-TOF MS), or sequencing methods was used to diagnosis *Klebsiella* isolates, which may be considered a limitation of the current study.

Overall, we highlight the variety of clinical manifestations and opportunistic nature of *Klebsiella*-induced infections among domestic animals retrospectively studied, with a predominance of urinary, enteric, mammary, reproductive, and respiratory infections, reinforcing the opportunistic nature of the pathogen. In addition, low in vitro efficacy of some conventional antimicrobial agents was observed, and ~ 20% of isolates exhibited a multiresistant pattern, which reinforces the need for rational use of antimicrobials in therapy approaches to avoid the increase of bacterial resistance, an emerging One Health issue worldwide.

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Author contribution MGR made a substantial contribution to the conceptualization, interpretation of data, and article writing. ABCM, ACA, CADB, CLP, FVRP, GNJ, GHBL, LSAM, LSM, RMR, STG, TSB, AKS, ABB, FJPL, LFGS, and ACP made a substantial contribution to the collection, analysis, and/or interpretation of data. CADB and STG made a substantial contribution to the statistical analysis. All the authors approved and revised critically the final version of the manuscript.

Declarations

Ethics approval This study was carried out in accordance with guidelines for the ethical use of animals approved by the Ethics Committee on Animal Use (CEUA) of the School of Veterinary Medicine and Animal Sciences, São Paulo State University, UNESP, Botucatu, SP, Brazil (protocol number 0136/2017).

Competing interests The authors declare no competing interests.

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