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Prognostic factors of *Pasteurella* infections: a single-center retrospective cohort study over a 14-year period (2005-2018)

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Running Title

Invasive *Pasteurella* infections

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1 **[Abstract]**

2 **Background:** *Pasteurella* spp. can lead to fatal infections in humans.

3 **Objective:** To assess prognostic factors of invasive pasteurellosis.

4 **Methods:** We conducted a single retrospective cohort study of local versus invasive *Pasteurella*
5 infections from January 1, 2005 to December 31, 2018 in the Amiens-Picardie University Hospital,
6 France.

7 **Results:** Forty-five (20.9%) invasive pasteurellosis and 22 (10.2%) complicated local infections
8 were reported among a total of 215 *Pasteurella* infections. The mortality rate among invasive
9 infections was 22.2% (10/ 45) while no death was recorded in local group. Non-drug-induced
10 prothrombin time test <70% of standard and platelet counts <100,000/mm³ were more frequent in
11 non-survivors than survivors ($p=0.005$ and $p=0.019$) in univariate analyses. A history of neoplasia
12 (adjusted OR=13.62, $p=0.020$), an evidence of bacteremia (adjusted OR=20.68, $p=0.025$) and
13 hemoglobin level <10 g/dL (adjusted OR=17.80, $p=0.028$) were identified as poor prognostic
14 factors in multivariate analyses.

15 **Conclusion:** Invasive pasteurellosis appears as a serious disease in vulnerable patients,
16 particularly if bacteremia and/or coagulopathies occur.

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Introduction

Described for the first time in 1881 by Louis Pasteur as the causative pathogen of fowl cholera (Harper et al., 2006), *Pasteurella* species are now well known to be responsible for possibly lethal zoonotic infections in humans (Christenson et al., 2015; Harper et al., 2006; Körmöndi et al., 2019; Wilson and Ho, 2013).

Pasteurella spp. are facultative anaerobic Gram-negative coccobacilli. These bacteria are found in the normal oral flora of 50-70% of dogs, 50- 90% of cats, and various other domestic and wild animals (Talan et al., 1999; Wilson and Ho, 2013). Most human infections are caused by *P. multocida subsp multocida* or *septica* (Harper et al., 2006; Holst et al., 1992; Wilson and Ho, 2013). Nevertheless, other species, including *P. canis*, *P. dagmatis*, and *P. stomatis* can also be implicated (Harper et al., 2006; Holst et al., 1992; Wilson and Ho, 2013).

Pasteurella are not usually considered as commensal bacteria in humans. However, colonization of the oropharynx and the respiratory tract is possible, particularly after inhalation of contaminated animal secretions (Ferreira et al., 2015; Giordano et al., 2015; Harper et al., 2006; Wilson and Ho, 2013). *Pasteurella* most commonly causes skin and soft tissue infections, typically following an infected animal bite or scratching or licking of chronic wounds by animals (Babovic et al., 2014; Escande and Lion, 1993; Giordano et al., 2015; Körmöndi et al., 2019; Nseir et al., 2009). These infections are often associated with a rapid occurrence of local inflammatory signs, lymphadenopathy and/or lymphangitis (Babovic et al., 2014; Escande and Lion, 1993; Giordano et al., 2015; Körmöndi et al., 2019; Nseir et al., 2009). Local complications such as tenosynovitis, abscess formation, or fistulas are possible, often in cases of treatment delay. Sometimes, more severe complications occur such as septic arthritis (SA), osteomyelitis, or extensive cellulitis (Giordano et al., 2015; Körmöndi et al., 2019; Nseir et al., 2009; Weber et al., 1984). More rarely, these bacteria can lead to invasive infections confirmed by a positive culture of any sterile body fluid, particularly among older patients with underlying

diseases (Chatelier et al., 2020; Christenson et al., 2015; Escande and Lion, 1993; Giordano et al., 2015; Kannangara et al., 2020; Körmöndi et al., 2019; Kumar et al., 1990; Nollet et al., 2016; Raffi et al., 1987; Weber et al., 1984). Mortality rates of *Pasteurella* invasive infections may be as high as 30% of cases (Chatelier et al., 2020; Kumar et al., 1990; Raffi et al., 1987).

In the present study, we report a large series of invasive *Pasteurella* infections, including several unusual clinical presentations. Predictive factors of poor prognosis, including in the most vulnerable patients, are assessed.

Methods

We conducted a single-center retrospective study of *Pasteurella* infections from January 1, 2005 to December 31, 2018 in the Amiens-Picardie University Hospital, France.

Data were extracted from computerized medical charts (DX-CARE software, Medasys, France), and each chart have been carefully read by the two first authors. Patients were included into two main groups:

i) Cutaneous infections, that either remained local in the skin tissue (uncomplicated), or spread to contiguous tendon sheaths, bone, or joints (complicated).

ii) Invasive infections, including two subgroups:

- pulmonary infections defined as isolation of *Pasteurella* in pulmonary samples (i.e. bronchial aspirates or bronchoalveolar lavage) with symptoms of respiratory tract infection,
- other invasive infections defined as positive culture from at least a sterile body fluid, with or without concomitant pulmonary infection.

Given that uncomplicated local cases always progressed favorably after well-established care, we focused on the complicated cases (invasive systemic vs complicated local) to try to assess the initial prognostic factors.

We first described the population source (demographic characteristics, specimen sources, and microbiological data). Next, we collected medical history, clinical and biological data, underlying conditions, antibiotic therapies, surgeries performed, and outcomes for complicated local cases and all invasive infections.

In the descriptive analysis, categorical variables were expressed as number (percentage), and continuous variables were expressed as the mean±standard deviation (SD) or the median (range), depending on the data distribution. The Shapiro-Wilk test was used to determine whether data were normally distributed.

In bivariate group analyses, we compared complicated local cases against all invasive infections. We also carried out a subgroup analysis comparing pulmonary infections only versus other invasive infections. Continuous variables were compared using Student's t test or a Wilcoxon's rank sum test (depending on the data distribution). Categorical variables were compared using a chi-square test or Fisher's exact test when required.

To determine predictive factors of mortality among patients with an invasive infection or with a local complicated infection, univariate analyses were first performed using a chi-square test. Estimates were reported as odds ratio (OR) and 95% confidence interval (95% CI). Then, in multivariate analysis, variables included in the logistic regression models were those 1- considered clinically relevant, and 2- those with $p < 0.2$ in univariate analysis. Variables that perfectly discriminated the two possible responses were not included in the multivariable model in order to avoid instability. Multicollinearity was investigated using the variance inflation factor (18) and variables of the best-performing algorithm were selected through stepwise use of Akaike's information criterion (AIC).

We considered $p < 0.05$ the threshold for statistical significance. All analyses were performed using R software (version 3.6.0, R Foundation for Statistical Computing, Vienna, Austria).

This study was conducted in compliance with French legislation and the Declaration of Helsinki regarding ethics principles for medical research involving human subjects.

Results

We identified a total of 215 *Pasteurella* infections including 45 (20.9%) invasive infections and 170 (79.1%) local infections (Figure 1).

P. multocida was the most frequently isolated in all groups (169/215). *P. canis* was reported in a significant proportion of local infections (32/170). Other subspecies (*P. dagmatis*, *P. ureae*, *P. stomatis* and *P. erogenous*) were rarely recorded in local infections. Eleven patients (5.1%) had a co-infection by two different subspecies.

The mean age was 59.8 ± 18.0 years in patients with invasive infections and 49.1 ± 24.2 years in patients with local infections ($p=0.006$). Invasive pasteurellosis was more likely to affect men (29/45 vs 64/171, $p=0.001$). No statistically significant difference of age and sex was found between both groups (Table 1).

Exposure to an animal was described in the medical history of only about one-third of invasive cases whereas it was found for almost all patients with complicated local infections (21/22) ($p<0.001$). Most of the cases of local infections complicated by arthritis (21/22) were due to an animal bite, usually by a cat (17/21).

Underlying conditions were present for all patients with invasive infections or with complicated local infections, except for one patient (Table 1). In bivariate analysis, risk conditions significantly associated with invasive infection were obesity (22.7% vs 0%, $p=0.024$), diabetes (25% vs 0%, $p=0.012$), and cancer (blood malignancy and/or solid tumors) (20.5% vs 0%, $p=0.024$). Among invasive cases, more patients in the “pulmonary infections” subgroup (9/17) had chronic lung disease compared with patients with other invasive infections

(2/27) ($p=0.001$), particularly chronic obstructive pulmonary disease (COPD) ($p=0.025$). No evidence of other difference was shown between the two subgroups of invasive cases.

None of the patients with local infection had fever or sepsis, in contrast to 28 of 45 (62.2%) invasive cases ($p<0.001$) (Table 1). Patients in the “pulmonary infections” subgroup also presented with fever less often (6/17, 35.3%) than patients with other invasive infections (22/28, 78.6%) ($p=0.005$). Blood cultures were performed in 12 of the 22 complicated local infections and in 39 of the 45 invasive cases (Table 1). None of the patients with complicated local infection (0/12) and none of the patients in the “pulmonary infections” subgroup (0/12) had bacteremia. In contrast, 17 of the 27 (63%) patients with another invasive infection had positive blood culture. Moreover, for 14 of these 17 patients, *Pasteurella* was isolated in blood culture only: 8 patients had a dermohypodermatitis, one patient had local inflammation of a prosthetic knee joint, one patient had meningism and purpuric lesions, one had respiratory symptoms, and 3 patients had non-specific clinical symptoms of infection.

Among patients for whom biological data were available, all patients (41/41) with invasive infections had an inflammatory syndrome (i.e. CRP $>5\text{mg/L}$), and more than half (21/41) had a CRP rate greater than 100 mg/L, 29.3% (12/41) had a platelet count of less than 150,000/mm³, and 9 of them (22%) had fewer than 100,000/mm³. However, all patients with arthritis of small joints had a platelet count greater than 150,000/mm³ ($p=0.038$ compared to invasive cases). Nineteen of 40 patients (47.5%) in the “invasive disease” group had decreased prothrombin time test (PT less than 70% of standard) compared to none of the patients in the group of complicated local infections ($p=0.001$). Nine of 19 patients (47.4%) who had a low PT were being treated with oral anticoagulation, and three other patients (15.8%) had severe liver disease. We did not shown statistically significant differences in CRP levels, white blood cells and platelet counts, and PT between patients with exclusively pulmonary infections and other invasive cases.

All patients of the complicated local infections group (22/22) underwent a surgical intervention and received antimicrobial therapy, mainly amoxicillin-clavulanic acid (9/22) or associated with gentamicin (8/22) (Table 1). No death occurred and all patients recovered with no sequelae.

One (1/45) patient of the invasive infection group experienced such acute clinical deterioration that he died in the emergency room, and 14 of them (31.8%) required intensive care. For 4 patients (9.1%), no antibiotic was given because they died quickly. For the other patients, amoxicillin-clavulanic acid alone was the first-line therapy.

Surgical intervention was performed for 14 of 40 (35%) patients (Table 1). Surgical lavage was required for 5 patients who had infections of a large joint requiring replacement of the implant for 2 patients with prosthetic joint involvement. Moreover, an amputation of the lower limb was necessary for 3 patients. A skin graft was performed for two other patients. One patient with encysted pleuritis required a thoracoscopy.

The mortality rate was 22.2% (10/45), and for 7 of them the diagnosis of fatal infection was made post-mortem. One child born prematurely because of *Pasteurella* chorioamnionitis secondary to multisystem organ failure died at one month of life. No evidence of statistically significant differences in death rate or overall duration of hospital stay was found between the two subgroups of invasive cases.

Patients who died were older than survivors (65.9±16.2 years vs 53.8±20.1) but without statistical relevance (crude OR=1.71, 95% CI [0.43 – 6.85], $p=0.434$) (Table 2). Nevertheless, 6 of 10 patients had a low PT, and only one had oral anticoagulant therapy. Thus, non-drug-induced PT of less than 70% and platelet counts of less than 100,000/mm³ were significantly more frequent in patients who died than in survivors (crude OR=10.3, 95% CI [2.10 – 56.09], $p=0.005$ and crude OR=6.88, 95% CI [1.34 – 36.09], $p=0.019$, respectively, Table 2).

In the stepwise logistic regression model, a history of neoplasia (adjusted OR=13.62, 95% CI [1.78 – 168.62], $p=0.020$), evidence of bacteremia (adjusted OR=20.68, 95% CI [2.18 – 604.67], $p=0.025$) and hemoglobin level below 10 g/dL (adjusted OR=17.80, 95% CI [1.76 – 458.40], $p=0.028$) were identified as poor prognostic factors by multivariable analysis (Figure 2).

Discussion

We report a series of 45 (20.9%) invasive pasteurellosis and 22 (10.2%) complicated local infections among a total of 215 *Pasteurella* cases. The diagnosis of local *Pasteurella* infection is often considered in emergency units because it is one of the most common bacterial pathogens involved in infected wounds caused by dogs or cats (Babovic et al., 2014; Wilson and Ho, 2013). In a large cohort, Körmöndi *et al.* nevertheless recorded severe complications in 23 of 114 (20.2%) local cutaneous infections including functional disability, lymphangitis, and amputations (Körmöndi et al., 2019). However, no death was recorded (Giordano et al., 2015; Körmöndi et al., 2019; Nseir et al., 2009).

Invasive infections do not result from worsening of local conditions and their management is not as straightforward as local infections. First, injury caused by an animal is usually absent (Kannangara et al., 2020; Körmöndi et al., 2019; Nollet et al., 2016). In this study, an injury-free exposure to an animal was described in the medical history in about one-third of invasive cases. As previously described, no exposure to animals was noted for 90% of the deaths among invasive cases (Körmöndi et al., 2019; Nollet et al., 2016). A weaker bacterial inoculum and different types of exposure to the bacteria could be involved in the pathogenesis of non-bite-related cases which often occur in immunocompromised patients (Chatelier et al., 2020; Fayyaz, 2018; Kannangara et al., 2020; Weber et al., 1984). According to two series,

advanced age and some underlying conditions (neoplasia, chronic liver disease, cardiovascular disease, and diabetes mellitus) seem to be the risk factors for invasive pasteurellosis (Körmöndi et al., 2019; Nollet et al., 2016). In our study, only half of *Pasteurella* cases in the “pulmonary infections” group and one-third of other invasive cases were over 65. A history of cancer and diabetes were more frequently found in the group of invasive infections. Obesity could be another risk factor that has not been previously described. This can be explained in part by the increased susceptibility to type 2 diabetes in these patients. Moreover, obesity is associated with several types of dysregulation of innate and adaptative immune responses (Dobner and Kaser, 2018). Furthermore, only 11.4% of patients with invasive infections had chronic liver disease in our study whereas Nollet *et al.* reported 47% (Nollet et al., 2016).

Several studies have emphasized the high risk of fatal outcomes of invasive pasteurellosis (Chatelier et al., 2020; Giordano et al., 2015; Körmöndi et al., 2019; Raffi et al., 1987). We report a death rate for all invasive infections of 22.2%, and several cases of fulminant progression. In multivariate analysis, we identified that mortality was higher in case of history of neoplasia, anemia and in blood culture positive. These results should be taken with caution, the wide confidence intervals resulting from the small sample size of our population. Further studies with larger sample size are needed to explore this point.

In this study, 37.8% of all invasive cases had a positive blood culture whereas the proportion ranges from 7.8% to 57% in the literature (Escande and Lion, 1993; Giordano et al., 2015; Nollet et al., 2016; Nseir et al., 2009). *Pasteurella* bacteremia seems to be more frequent in patients with cirrhosis and metastatic cancer (Chatelier et al., 2020; Giordano et al., 2015; Körmöndi et al., 2019; Nollet et al., 2016; Raffi et al., 1987), and mortality rates vary widely from 14% to 31% (Chatelier et al., 2020; Escande and Lion, 1993) and even up to 37% based on a meta-analysis conducted on patients who had severe liver disease (Raffi et al., 1987). The

involvement of the central nervous system by the bacteria seems to be particularly serious in adults (Green et al., 2002; Kumar et al., 1990), but accounts for only less than 1% of all *Pasteurella* infections (Escande and Lion, 1993), which is consistent with our study.

We also emphasize the potential severity of *Pasteurella* maternal-fetal transmission. Only two cases of *Pasteurella* chorioamnionitis with bacteriological evidence have been described. Neonatal sepsis was documented and led to early death of the newborn child (Strand and Helfman, 1971; Wong et al., 1992).

We attempted to identify pertinent biological blood tests in routine practice that would allow early evaluation of the severity of any *Pasteurella* infection and would warrant admission to an intensive care unit. In our study, non-drug-induced PT of less than 70% and a platelet count of less than 100,000/mm³ were significantly more frequent in dead patients. Molecular and cellular processes driving coagulation and inflammation are intricately linked, and coagulation abnormalities are commonly observed in septic patients (Angus and van der Poll, 2013; Iba and Levy, 2018). The rapid and fatal progression of most serious *Pasteurella* invasive infections might be related to the occurrence of undiagnosed widespread thrombosis or internal hemorrhaging from DIC, as has been established for meningococemia (Melican and Dumenil, 2012). *Pasteurella* and *Neisseria meningitidis* are both Gram-negative bacteria with the same structural characteristics including the presence of LPS into their wall (Harper et al., 2006; Hart et al., 2003). During the first steps of invasion from the nasopharynx epithelium, *N. meningitidis* colonizes the vascular endothelium and through LPS, is recognized by the host's immune system via the Toll-like receptor 4 (TLR4) (Melican and Dumenil, 2012). The interactions between the bacteria and host cells can induce the secretion of large amounts of pro-inflammatory cytokines. This cytokine storm can induce DIC, then subsequent microvascular thrombosis and bleeding (Melican and Dumenil, 2012). A case report in a neutropenic patient is consistent with our hypothesis (Yokose and Dan, 2007).

We recorded several fatal outcomes among invasive *Pasteurella* infections despite appropriate antibiotic therapy. *Pasteurella* possesses numerous virulence factors enabling it to escape the action of the human immune system and cause systemic diseases. Its capsular material and LPS can prevent phagocytosis and afford resistance against complement lysis (Harper et al., 2006; Wilson and Ho, 2013). Some species are also able to produce extracellular matrix-degrading enzymes, such as neuraminidase, hyaluronidase, and protease, facilitating bacterial dissemination (Harper et al., 2006; Wilson and Ho, 2013). Comparing pasteurellosis with *N. meningitis* infections, we could also suggest a possible genetic susceptibility to developing severe forms of pasteurellosis for some predisposed individuals. In fact, the occurrence of mutations can cause TLR4 dysfunction and exposure to a high risk of septic shock in patients with meningococemia (Lorenz et al., 2002). Interestingly, TLR4 plays a key role in the protective reaction of macrophages against *P. pneumotropica* in murine models (Hart et al., 2003).

Since deaths may occur despite optimal medical management, some authors advise the use of preventive measures for immunocompromised patients (Christenson et al., 2015; Kannangara et al., 2020; Körmöndi et al., 2019). Although pets undoubtedly have a positive psychological impact on many people, it might be prudent for elderly individuals and/or patients with cancer to avoid contact with them (Kannangara et al., 2020; Körmöndi et al., 2019).

Our results have several biases inherent to the retrospective study design including some missing data in medical records. According to a marketing study, the number of pets, in particular cats, has increased gradually over the last 20 years in France (Les chiffres pour tout savoir sur le marché du petfood, n.d.). More exposures to an animal could have occurred but were not reported, because a contact with any animal was likely less investigated in absence of bite-induced wound. Moreover, the small size of our population due to the rarity of the disease prevents us from properly interpreting the results of univariate and multivariate analyses.

Conclusion

The diagnosis of invasive pasteurellosis must be suspected in patients with underlying conditions who have severe pneumonia and sepsis, even if no traumatic signs of animal contact have been found. An increasing tendency of invasive pasteurellosis could be observed in the coming years because of an increasing number of pets and immunocompromised individuals.

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[Figure legends]

Figure 1. Distribution of local and invasive *Pasteurella* infections

IP: interphalangeal, MCP: metacarpophalangeal

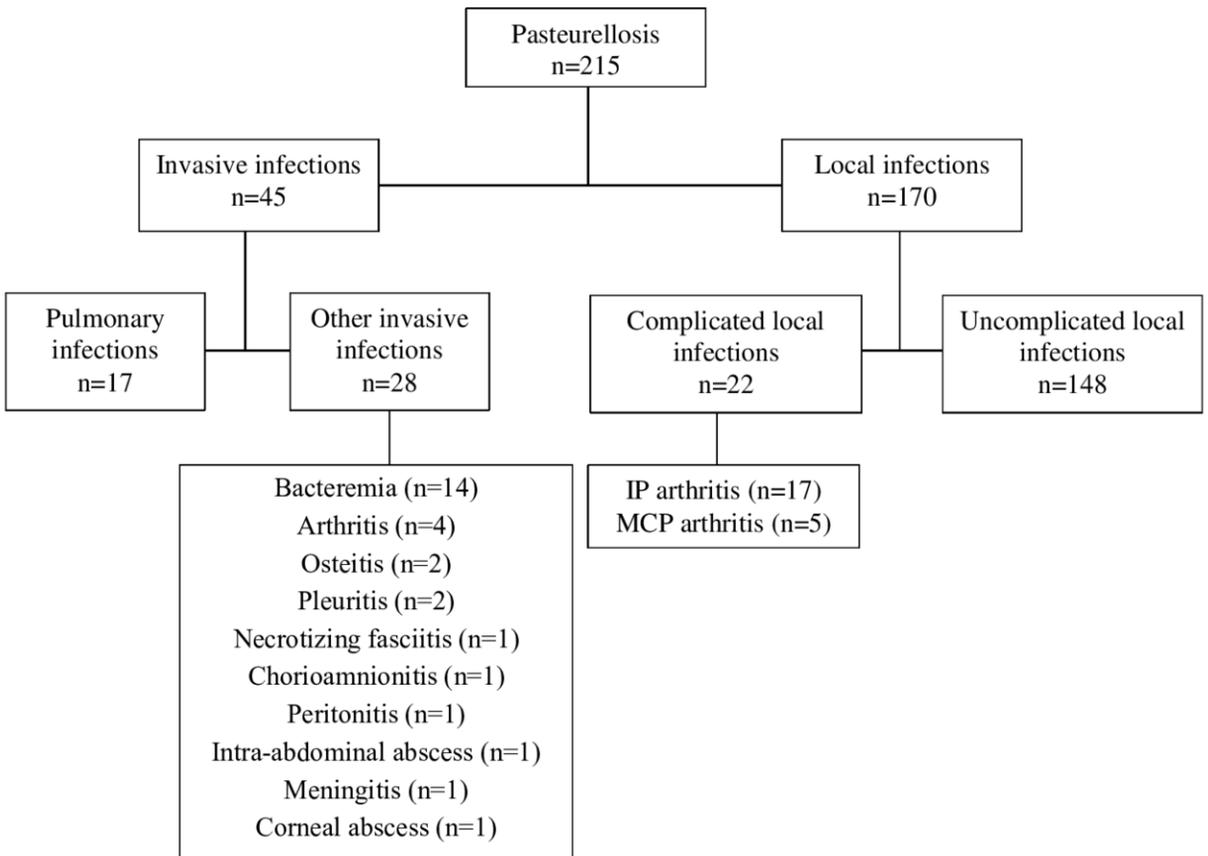
Figure 2. Prognostic factors of mortality in patients with *Pasteurella* invasive infections and patients with complicated local infections (stepwise logistic regression)

Variables initially included in the model: age, chronic renal failure, hepatic disease, history of neoplasia, fever, septic shock, bacteremia, platelet level, hemoglobin level, serum creatinine level.

Fever and serum creatinine level were first removed from the model (variance inflation factor > 5).

Retained variables of the best-performing algorithm selected through stepwise use of Akaike's information criterion were: history of neoplasia, bacteremia and hemoglobin level.

Twenty-one patients were excluded from the model due to missing data.



IP: interphalangeal, MCP: metacarpophalangeal

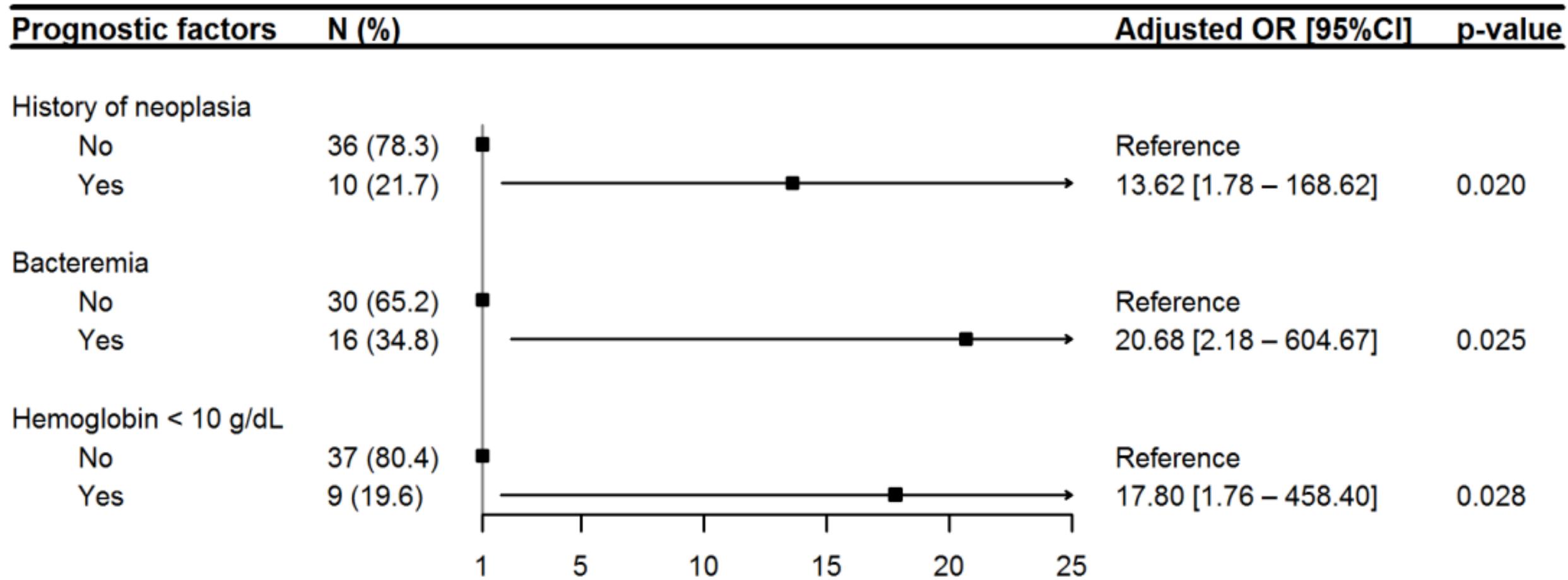


Table 1. Clinical and biological features, treatments, and outcomes of patients with *Pasteurella* invasive infections and patients with complicated local infections.

	Invasive infections N = 45		Complicated local infections N = 22	<i>p</i> -value ⁽¹⁾			
	Pulmonary N = 17	Others N = 28					
Female, n/N (%)	4/17 (23.5)	12/28 (42.9)	10/22 (45.5)	0.607			
Age (years), mean ± SD	63.2 ± 17.5	57.6 ± 18.3	47.2 ± 21.3	0.014			
>65, n/N (%)	9/17 (52.9)	10/28 (35.7)	4/22 (18.2)	0.095			
<18, n/N (%)	0/17 (0)	1/28 (3.6)	2/22 (9.1)	0.249			
Exposure to an animal, n/N (%)							
Reported in medical history	6/17 (35.3)	10/28 (35.7)	21/22 (95.5)	< 0.001			
Traumatic contact	0/6 (0)	5/10 (50)	21/21 (100)	0.002			
Animal type ⁽²⁾							
Cat	3/6 (50)	8/10 (80.0)	17/21 (81.0)	0.458			
Dog	5/6 (83.3)	3/10 (30.0)	3/21 (14.3)	0.030			
Rodent	0/6 (0)	0/10 (0)	1/21 (4.8)	1			
Inpatients, n/N (%)	15/17 (88.2)	27/28 (96.4)	22/22 (100)	0.545			
Medicine department	6/17 (35.3)	14/28 (50.0)	0/22 (0)	<0.001			
Surgery department	1/17 (5.9)	7/28 (25.0)	22/22 (100)	<0.001			
ICU	8/17 (47.1)	6/28 (21.4)	0/22 (0)	0.003			
Risk factors, n/N (%)	15/17 (88.2)	22/27 (81.5)	12/22 (54.5)	0.022			
Tobacco	8/17 (47.1)	12/27 (44.4)	10/22 (45.5)	1			
Chronic alcohol consumption	3/17 (17.6)	10/27 (37.0)	4/22 (18.2)	0.486			
Obesity	2/17 (11.8)	8/27 (29.6)	0/22 (0)	0.024			
Diabetes	2/17 (11.8)	9/27 (33.3)	0/22 (0)	0.012			
COPD	5/17 (29.4)	1/27 (3.7)	0/22 (0)	0.167			
Other chronic respiratory failure	4/17 (23.5)	1/27 (3.7)	0/22 (0)	0.161			
Chronic renal failure	2/17 (11.8)	5/27 (18.5)	1/22 (4.5)	0.252			
Hepatic disease	0/17 (0)	5/27 (18.5)	0/22 (0)	0.161			
Cardiopathy	3/17 (17.6)	6/27 (22.2)	1/22 (4.5)	0.146			
Autoimmune disease	1/17 (5.9)	0/27 (0)	1/22 (4.5)	0.293			
Malignancy	5/17 (29.4)	8/27 (29.6)	0/22 (0)	0.003			
Immunosuppressive drugs	5/17 (29.4)	3/27 (11.1)	0/22 (0)	0.046			
Pregnancy	0/17 (0)	1/27 (3.7)	0/22 (0)	1			
Joint prosthesis	0/17 (0)	2/27 (7.4)	0/22 (0)	0.549			
Clinical features							
Meningeal irritation	0/17 (0)	2/28 (7.1)	0/22 (0)	1			
Fever	6/17 (35.3)	22/28 (78.6)	0/22 (0)	<0.001			
Skin involvement	0/17 (0)	8/28 (28.6)	9/22 (40.9)	0.071			
Acute respiratory distress	7/17 (41.2)	1/28 (3.6)	0/22 (0)	0.046			
Septic shock	1/17 (5.9)	5/28 (17.9)	0/22 (0)	0.167			
Multiple organ failure	0/17 (0)	3/28 (10.7)	0/22 (0)	0.545			
Bacteremia, n/N (%)	0/12 (0)	17/27 (63.0) ⁽³⁾	0/12	0.004			
Biological data, median [IQR]	<i>n</i>		<i>n</i>				
WBC (10 ³ per mm ³)	16	9.95 [4.8]	26	12 [7.7]	18	10.1 [1.6]	0.153
Platelets (10 ³ per mm ³)	15	200 [107]	26	194.5 [161.8]	16	256.5 [166.2]	0.014
Hemoglobin (g/dL)	15	11.7 [3.2]	26	10.9 [2.9]	17	13.9 [2.3]	<0.001
CRP (mg/L)	15	100 [24.5]	26	155.5 [191]	18	17 [29]	<0.001
PCT (μg/L)	4	0.45 [17.7]	2	22.7 [9.9]	0	-	-
PT (%)	15	84 [31.5]	25	67 [34]	15	92 [12]	0.001
AST (UI/L)	11	61 [40.5]	20	49 [80.5]	2	29.5 [60]	0.293
ALT (UI/L)	11	26 [26]	20	33.5 [27.3]	2	17.5 [31]	0.163
Serum creatinine (μmol/L)	15	88 [61]	26	98 [131.2]	16	71 [79]	0.062

Co-infection, n/N (%)							
Bacterial		9/17 (52.9)		7/28 (25.0)		4/22 (18.2)	0.168
Viral		2/17 (11.8)		0/28 (0)		0/22 (0)	0.778
Antibiotics							
Intravenous (IV), n/N (%)		17/17 (100)		23/27 (85.1)		22/22 (100)	0.12
Oral, n/N (%)		12/17 (70.1)		18/27 (66.7)		21/22 (95.5)	0.013
Duration (days), median [IQR]	<i>n</i>	7/16 (43.8)		13/24 (54.2)		22/22 (100)	<0.001
IV	<i>n</i>		<i>n</i>		<i>n</i>		
Overall	12	8 [5]	18	7 [10.8]	20	1 [1.25]	<0.001
	16	10 [4]	21	21 [14]	20	35 [21]	<0.001
Surgery, n/N (%)		0/17 (0)		14/28 (50)		22/22 (100)	<0.001
Death, n/N (%)							
Time to death relative to admission (days), median [IQR]	<i>n</i>	2/17 (11.8)		8/28 (28.6)		0/22 (0)	0.024
	2	11.5 [7.5]	8	1.5[1.5]	-	-	-
Hospital stay (days), median [IQR]	<i>n</i>		<i>n</i>		<i>n</i>		
	16	18 [14]	27	4 [9]	22	2.5 [2]	<0.001

ICU: intensive care unit, IQR: interquartile range, WBC: white blood cells, CRP: C-reactive protein, PCT: procalcitonin, PT: prothrombin time

⁽¹⁾ Comparison of all invasive infections *versus* complicated local infections. Statistical analyses were performed by Student's t test or a Wilcoxon's rank sum test (depending on the data distribution determined by the Shapiro-Wilk test) for continuous variables and by a chi-square test or Fisher's exact test for categorical variables.

⁽²⁾ Exposure to different animals reported for three patients

⁽³⁾ Not performed for the patient with a cornea abscess

Table 2. Prognostic factors of mortality in patients with *Pasteurella* invasive infections and patients with complicated local infections (univariate analyses)

Variable	Total patients N = 67	Survivors N = 57	Non survivors N = 10	Univariate analysis		
				Crude OR	[95% CI]	p-value
Female, n/N (%) (ref. = Male)	26/67 (38.8)	21/57 (36.8)	5/10 (50.0)	1.71	[0.43 – 6.85]	0.434
Age (years), mean ± SD	55.6 ± 19.9	53.8 ± 20.1	65.9 ± 16.2	1.03	[0.99 – 1.09]	0.082
Risk factors						
Tobacco, n/N (%) (ref. = No)	30/66 (45.5)	27/57 (47.4)	3/9 (33.3)	0.56	[0.11 – 2.32]	0.436
Chronic alcohol consumption, n/N (%) (ref. = No)	17/66 (25.8)	14/57 (24.6)	3/9 (33.3)	1.54	[0.29 – 6.67]	0.578
Obesity, n/N (%) (ref. = No)	10/66 (15.2)	8/57 (14.0)	2/9 (22.2)	1.75	[0.23 – 8.96]	0.528
Diabetes, n/N (%) (ref. = No)	11/66 (16.7)	8/57 (14.0)	3/9 (33.3)	3.06	[0.56 – 14.40]	0.164
COPD, n/N (%) (ref. = No)	6/66 (9.1)	5/57 (8.8)	1/9 (11.1)	1.30	[0.06 – 9.58]	0.821
Other chronic respiratory failure, n/N (%) (ref. = No)	5/66 (7.6)	5/57 (8.8)	0/9	NA	NA	-
Chronic renal failure, n/N (%) (ref. = No)	8/66 (12.1)	5/57 (8.8)	3/9 (33.3)	5.20	[0.89 – 27.53]	0.052
Hepatic disease, n/N (%) (ref. = No)	5/66 (7.6)	3/57 (5.32)	2/9 (22.2)	5.14	[0.60 – 36.80]	0.101
Cardiopathy, n/N (%) (ref. = No)	10/66 (15.2)	8/57 (14.0)	2/9 (22.2)	1.75	[0.23 – 8.96]	0.528
Autoimmune disease, n/N (%) (ref. = No)	2/66 (3.0)	2/57 (3.5)	0/9	NA	NA	-
Malignancy, n/N (%) (ref. = No)	13/66 (19.7)	8/57 (14.0)	5/9 (55.6)	7.66	[1.70 – 37.41]	0.008
Immunosuppressive drugs, n/N (%) (ref. = No)	8/66 (12.1)	7/57 (12.3)	1/9 (11.1)	1.06	[0.05 – 7.46]	0.958
Pregnancy, n/N (%) (ref. = No)	1/66 (1.5)	1/57 (1.58)	0/9	NA	NA	-
Joint prosthesis, n/N (%) (ref. = No)	2/66 (3.0)	2/57 (3.5)	0/9	NA	NA	-
Clinical features						
Invasive infection, n/N (%) (ref. = complicated local infection)	45/67 (67.2)	35/57 (67.2)	10/10 (100)	NA	NA	-
Meningeal irritation, n/N (%) (ref. = No)	2/67 (3.0)	0/57	2/10 (20.0)	NA	NA	-
Fever, n/N (%) (ref. = No)	28/67 (42.4)	20/57 (35.7)	8/10 (80.0)	7.20	[1.62 – 50.88]	0.019
Skin involvement, n/N (%) (ref. = No)	17/67 (25.4)	14/57 (24.6)	3/10 (30.0)	1.31	[0.07 – 0.34]	0.716
Acute respiratory distress, n/N (%) (ref. = No)	8/67 (11.9)	6/57 (10.5)	2/10 (20.0)	2.13	[0.28 – 11.29]	0.403
Septic shock, n/N (%) (ref. = No)	6/67 (9.0)	1/57 (1.8)	5/10 (50.0)	56.00	[7.30 – 1194.93]	<0.001
Multiple organ failure, n/N (%) (ref. = No)	3/67 (4.5)	0/57	3/10 (30.0)	NA	NA	-
Bacteremia	17/51 (33.3)	10/42 (23.8)	7/9 (77.8)	11.2	[2.29 – 83.93]	0.006
Biological data						
WBC > 10,000 per mm ³ , n/N (%) (ref. < 10,000)	35/60 (58.3)	28/51 (54.9)	7/9 (77.8)	2.88	[0.62 – 20.57]	0.214
Platelets < 100,000 per mm ³ , n/N (%) (ref. > 100,000)	9/57 (15.8)	8/48 (16.7)	4/9 (44.4)	6.88	[1.34 – 36.09]	0.019
Hemoglobin < 10 g/dL, n/N (%) (ref. > 10 g/dL)	9/58 (15.5)	5/49 (10.2)	4/9 (44.4)	7.04	[1.38 – 36.9]	0.017
CRP > 100 mg/L, n/N (%) (ref. < 100 mg/L)	21/59 (35.6)	17/50 (34.0)	4/9 (44.4)	1.55	[0.35 – 6.63]	0.549
Non-drug-induced PT < 70 %, n/N (%) (ref. > 70%)	10/55 (18.2)	5/46 (10.9)	5/9 (55.6)	10.3	[2.10 – 56.09]	0.005
AST (IU/L), median [IQR]	48 [52.8]	49 [45]	47 [124]	1.00	[0.99 – 1.00]	0.635
ALT (IU/L), median [IQR]	32 [31]	34 [32]	25.5 [16.8]	0.98	[0.93 – 1.00]	0.419
Serum creatinine (μmol/L), median [IQR]	83 [51]	73.5 [38]	302 [199]	1.01	[1.00 – 1.01]	0.001
Co-infection						
Bacterial, n/N (%) (ref. = No)	20/67 (29.9)	16/57 (28.1)	4/10 (40.0)	1.71	[0.39 – 6.81]	0.450
Viral, n/N (%) (ref. = No)	2/67 (3.0)	2/57 (3.5)	0/10	NA	NA	-

ALT, alanine aminotransferases; AST, aspartate aminotransferase; CI, confidence interval; COPD, chronic obstructive pulmonary disease; CRP, C-reactive protein; NA, coefficients are not applicable when the variable of interest perfectly predicts the response; PT, prothrombin time test; OR, odds ratio; SD, standard deviation; WBC, white blood cells.