

## Review of *Pasteurella Multocida* Infections over a Twelve-Year Period in a Tertiary Care Hospital

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**Abstract:** The aim of this study was to present the epidemiological, clinical and microbiological data, as well as the management and the outcome of 13 patients with documented *Pasteurella multocida* infections, diagnosed in the University hospital of Crete, Greece, between 1993 and 2004. Most patients (62%) were >70 years of age. Respiratory tract infections were most commonly encountered (61.5%), followed by soft-tissue infections (30.8%) and septicemia (7.7 %). Underlying diseases included malignancies, bullous pemphigoid, mitral valve stenosis, coronary disease, chronic obstructive pulmonary disease and intracranial hemorrhage. Antibiotic sensitivity testing showed that all *P. multocida* isolates were susceptible to beta-lactams, quinolones, chloramphenicol, tetracycline and trimethoprim/sulfamethoxazole. Antibiotics were administered to all 13 patients and a clinical response was observed in 77% of them. The overall mortality rate was 23% (3/13) but only 15.4% (2/13) died from the infection. Although rare, *P. multocida* infections should be suspected in patients reporting animal exposure, particularly in those with chronic underlying diseases.

**Key words:** *Pasteurella multocida*, infections, zoonoses, Greece

### INTRODUCTION

*Pasteurella multocida*, a Gram-negative coccobacillus, is a member of the normal flora of the upper respiratory and gastrointestinal tract of many domestic and wild animals<sup>[1]</sup>. Human infections due to *P. multocida* are strongly associated with animal exposure and usually involve soft-tissue sites after animal bites or scratches<sup>[2,3]</sup>. Respiratory tract infections and less frequently septicemia, endocarditis, meningitis, peritonitis, or other unusual types of infection due to this organism have also been described<sup>[4-8]</sup>. In this study we present 13 cases of *P. multocida* infection diagnosed in our hospital during a 12-year period.

### PATIENTS AND METHODS

This was a retrospective study, performed at a 650-bed university hospital that serves a population of 150,000 inhabitants in Crete, Greece. We reviewed the records of all patients who had positive cultures for *P. multocida* between 1993 and 2004.

Demographic, epidemiological and clinical data including age, sex, animal exposure, site of infection, underlying diseases, type of therapy and outcome were evaluated. All isolates were identified by standard conventional microbiological methods (cell morphology, cultural characteristics, colony morphology, biochemical tests) and by using the API 20NE system (bioMérieux, Marcy L' Etoile, France)<sup>[9]</sup>.

Antibiotic susceptibility testing was performed by the disk diffusion method onto Muller-Hinton agar supplemented with 5% sheep blood<sup>[10]</sup> and the MICs of fourteen antibiotics were determined by the E-test method according to the manufacturers' guidelines (Solna, Sweden).

### RESULTS

**Patients:** Over the 12-year period of the study, 13 cases of *P. multocida* infection were diagnosed at our center. The data of the patients are summarized in Table 1. The male to female ratio was 10:3. With the exception of a 3.5 years old boy, all patients were adults. The mean age was 64.4 years (range 3.5-79 years) and 8 (62%) of the patients were older than 70 years.

Respiratory tract was the most common site of infection (5 cases with pneumonia, 3 with tracheobronchitis). Septicemia secondary to severe pneumonia and septicemia without any other primary infection was detected in two and one patient, respectively. Cellulitis was diagnosed in three patients. Two of them were scratched by cats, the first on the left leg and the second on the right forearm. The third one was presented with a *P. multocida* wound infection after an injury. The last patient, a 64-year-old woman who had lost her own teeth and substituted them with a denture, presented with an inflammation in the left mandibula on the gingiva with purulent exudate.

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Table 1: *Pasteurella multocida* infections diagnosed between 1993 and 2004

Case no.	Sex	Age	Animal Exposure	Site of isolation	Infection	Underlying disease	Treatment	Outcome
1	M	55	Cat scratch	Right forearm	Wound	CBLL	Amoxicillin/ clavulanic acid	Recovered
2	M	78	Cat scratch	Blood	Septicemia	None	Ceftriaxone + netilmicin	Recovered
3	F	77	Unknown	Blood + BAL	Pneumonia, septicemia	Mitral valve stenosis	Cefuroxime+ netilmicin	Died
4	M	79	Cat and dog	BAL	Pneumonia	Bowel Ca, Bullous Pemphigoid	Piperacillin/tazobactam + Pefloxacin	Died
5	F	64	None(village)	Left mandible	Soft tissues	None	Amoxicillin + metronidazole	Recovered
6	F	48	Cat scratch	Left leg	Wound	None	Amoxicillin/ clavulanic acid	Recovered
7	M	72	None(village)	BAL	Pneumonia	Injured during agricultural work	Ceftriaxone	Recovered
8	M	76	None(village)	Sputum	Tracheobronchitis	Coronary disease	Amoxicillin/ clavulanic acid	Recovered
9	M	75	Dog	Blood	Pneumonia, septicemia	Larynx Ca	Ceftazidime+ netilmicin	Recovered
10	M	78	None(village)	Sputum	Tracheobronchitis	COPD	Amoxicillin/ clavulanic acid	Recovered
11	M	72	None	Sputum	Tracheobronchitis	Prostatic Ca, Bone and lung metastasis	Cefuroxime	Recovered from infection
12	M	60	Unknown (village)	BAL	Pneumonia	Intracranial hemorrhage, craniotomy	Meropenem	Died from his main disease
13	M	3.5	None (village)	Forehead	Wound	Injury	Cefotaxime+ metronidazole	Recovered

*P. multocida* was isolated from the bronchoalveolar lavage (BAL) in 3 patients with severe pneumonia, from sputum in 3 patients with tracheobronchitis, from pus in 4 patients with local infections, from blood in 2 patients (one with pneumonia and the other with septicemia without any local infection) and from both blood and BAL in one patient with severe fatal pneumonia.

Underlying disease serving as predisposing factor for the development of *P. multocida* infection was present in 8 patients. Among them, 4 presented a kind of malignancy. Two patients suffered from solid tumors, one from chronic b-lymphocytic leukemia and another one had a history of bowel cancer successfully treated 9 years ago and a recent diagnosis of a bullous pemphigoid under treatment. Mitral valve stenosis, coronary disease, chronic obstructive pulmonary disease and intracranial hemorrhage with a craniotomy and celiotomy were the underlying diseases for the other 4 patients, respectively.

Treatment was successful in 10 cases. Among the three other patients with fatal outcome, a 77-year-old woman was admitted with severe pneumonia, developed ARDS and died within 20 hours, a 79-year-old man with a history of bullous pemphigoid was admitted with pneumonia and ARDS, was treated in the intensive care unit (ICU) where *P. multocida* was isolated from broncho-alveolar lavage in a concentration up to 10<sup>9</sup> cfu/ml and despite the appropriate therapy he died on the 11<sup>th</sup> day of multiple organ dysfunction syndrome and the third one was a 60-year-old man who was admitted with intracranial hemorrhage, underwent a craniotomy and celiotomy, was treated in the ICU where developed a *P. multocida* pneumonia on the 10<sup>th</sup> day and died after 7 days of his main disease. A period longer than 3 years separated these 3 fatal cases.

Regarding the animal exposure, only two of the patients developed the typical form of *P. multocida* soft tissue infection after cat scratches: a 48-year-old woman and a 55-year-old man admitted with cellulitis, developed purulent discharge on the left leg and the right forearm, respectively. Cat scratch was also the portal of entry for a 78-year-old man who was admitted with fever without any local infection and *P. multocida* was isolated from the blood. A retrospective epidemiological history revealed that he had three cats and two dogs at home and he had been scratched by one of his cats on his right forearm, one month ago. After local treatment the lesion healed completely and no signs of soft-tissue infection were present when the bacteremia appeared. A 72-year-old man with pneumonia had injured his left hand during agricultural work a month ago, but he denied any animal exposure. Two patients, one admitted with pneumonia and the other with pneumonia and septicemia owned a cat and a dog the first and a cat the second, but they did not reported bites or scratches. No epidemiological data were available for two fatal cases because of their crucial situation. The other 5 denied any known animal exposure although 4 of them lived in villages.

**Bacteriology:** All *P. multocida* isolates were similar in morphology, growth conditions, biochemical profile and antibiotic susceptibility. They were non-motile, gram-negative coccobacilli, well grown on blood and chocolate agar but not onto MacConkey agar. Colonies on blood agar were grey and nonhemolytic with a distinctive mousey odor. They were catalase and oxidase positive and the API 20NE system identified them as *P. multocida*. They fermented glucose, xylose, mannitol and sucrose and presented a similar antibiotic susceptibility profile. They were susceptible to beta-lactams (amoxicillin, amoxicillin/clavulanic acid,

cefepime, cefuroxime, ceftriaxone, imipenem and meropenem), quinolones (ciprofloxacin, norfloxacin, levofloxacin and sparfloxacin), chloramphenicol, tetracycline, trimethoprim/sulfamethoxazole. Beta-lactamase production using nitrocephin disks was negative in all thirteen isolates. Minimal inhibitory concentrations (MICs) of the antibiotics tested are given in Table 2.

Table 2: MICs of antibiotics against 13 human isolates of *P. multocida*

Antibiotic	MIC range (µg/ml)	Sucseptible no (%)
Amoxicillin	0.125 – 0.75	100
Amoxicillin/clanulanic acid	0.125 – 0.75	100
Cefuroxime	0.023-0.094	100
Cefepime	0.012-0.125	100
Ceftriaxone	<0.016	100
Imipenem	0.125-2	100
Meropenem	0.016-0.125	100
Ciprofloxacin	0.008-0.032	100
Norfloxacin	0.047-0.125	100
Sparfloxacin	0.003-0.012	100
Levofloxacin	0.008-0.032	100
Chloramphenicol	0.38-0.75	100
Trimethoprim/sulfamethoxazole	0.008-0.125	100
Tetracycline	0.125-0.5	100

## DISCUSSION

*P. multocida* infections in humans are well known as animal derived infections (zoonoses), as this organism is a commensal in mouth, throats, noses and gastrointestinal tract of many domestic or wild animals and birds<sup>[1]</sup>. Cats and dogs have the highest carriage rates at 70-90% and 20-50%, respectively<sup>[11]</sup>. This organism is distributed worldwide and is pathogenic in many animal species, causing serious epizootic infections. Human *P. multocida* infections occur most commonly after animal bites and scratches<sup>[2,3]</sup>. However, several cases have been reported in patients who denied any animal contact. Even without an obvious animal exposure, it is believed that animal secretions are the major source of human infections<sup>[12]</sup>.

Localized infection, secondary to a bite or scratch from an animal, is probably the best-known form of human infection. In our study, only two patients developed this typical form. Respiratory tract is the most common site in *P. multocida* infections unrelated to traumatic animal contact<sup>[12]</sup>. As the majority of our patients were not associated with animal trauma, respiratory tract was unsurprisingly the most common site of the infection (tracheobronchitis, 3; pneumonia, 5). Unusual sites such as endocarditis in native or prosthetic valves<sup>[5,13]</sup>, tonsillitis<sup>[14]</sup>, periocular abscess<sup>[15]</sup> and utero infection in pregnancy<sup>[16]</sup> have also been reported. There was also a case with an unexpected site of infection among our patients: the patient no. 5 who presented with soft tissue infection

with purulent discharge, localized on the gingiva of the left mandible.

It is of interest the preference of this microbe to the extreme ages<sup>[6]</sup>. With the exception of a child, the majority of our patients (8/13) were older than 70 years.

Serious systemic *P. multocida* infections may develop with the presence of different underlying diseases. Rheumatoid arthritis is associated with the development of septic arthritis<sup>[4,17]</sup>, liver dysfunction with septicemia or peritonitis<sup>[4,8,18]</sup>, craniofacial operations with meningitis or intracranial abscesses<sup>[6,19]</sup>, peritoneal dialysis with peritonitis<sup>[20,21]</sup> and chronic respiratory disease such as bronchitis, emphysema, or bronchiectasis may underlie in respiratory tract infections<sup>[4,12,22]</sup>. Diabetes mellitus<sup>[4,23,24]</sup>, systemic lupus erythematosus<sup>[17,25]</sup>, solid tumors and hematological malignancies<sup>[7,23,26]</sup> have also been described as underlying diseases in human *P. multocida* infections. Although *P. multocida* bacteremia is strongly associated with liver dysfunction none of our 3 bacteremic patients suffered of any liver disease. One among them suffered from larynx Ca that is considered a predisposing factor for the infection. A kind of malignancy was also present in other 3 patients.

Although susceptibility of human *P. multocida* isolates to beta-lactams is almost universal<sup>[27]</sup>, beta-lactamase production by some isolates has been reported and thus susceptibility testing should always be performed<sup>[28,29]</sup>. Susceptibility to tetracycline, chloramphenicol and ciprofloxacin has been demonstrated, while inconsistent clinical results may be found with aminoglycosides, erythromycin, clindamycin and vancomycin<sup>[4,19]</sup>. The results of the antibiotic susceptibility testing of our isolates demonstrated excellent in vitro susceptibility to beta-lactams, chloramphenicol, trimethoprim/sulfamethoxazole, quinolones and tetracycline.

Despite the susceptibility and the appropriate therapy, three of the patients died. Outcome is associated with the severity of the infection, the extent of the underlying disease and the early onset of the appropriate therapy<sup>[4,26]</sup>. Mortality is found to be 30% in meningitis and increased mortality with increasing age has been observed<sup>[19]</sup>. A mortality rate of 31% is reported in patients with bacteremia, with all fatalities occurring in patients with severe cirrhosis<sup>[26]</sup>. Among our patients with fatal outcome, patient no. 3 died within 24 hours and the other two after prolonged treatment in the ICU.

*Pasteurella multocida* must be considered as the possible etiology for a variety of infections, especially in patients reporting a history of animal exposure. Early and correct clinical and microbiological diagnosis will lead to the institution of the appropriate antibiotic treatment.

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