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Article

Clinical and Microbiological Survey of *Serratia marcescens* Infection During HIV Disease

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Abstract Clinical charts of 2398 consecutive HIV-infected patients hospitalized over an 8-year period were reviewed retrospectively to identify all cases of *Serratia* infection and to evaluate the occurrence and outcome of these cases according to several epidemiological, clinical, and laboratory parameters. Seventeen of 2398 (0.71%) patients developed *Serratia marcescens* infections: nine had septicaemia, six had pneumonia, one had a lymph node abscess, and one had cellulitis. All patients were severely immunocompromised, as evidenced by a mean CD4+ lymphocyte count of <70 cells/μl and a frequent diagnosis of AIDS (13 patients). When compared with other disease localizations, septicaemia was related to a significantly lower CD4+ cell count and a more frequent occurrence of neutropaenia. Antibiotic, corticosteroid, or cotrimoxazole treatment was frequently carried out during the month preceding disease onset. Hospital-acquired *Serratia* spp. infection was more frequent than community-acquired infection and was significantly related to AIDS, neutropaenia, and sepsis. Antimicrobial sensitivity testing showed complete resistance to ampicillin and cephalothin but elevated susceptibility to ureidopenicillins, second- and third-generation cephalosporins, aminoglycosides, quinolones, and cotrimoxazole. An appropriate antimicrobial treatment attained clinical and microbiological cure in all cases, in absence of related mortality or relapses. Since only 13 episodes of HIV-associated *Serratia* spp. infection have been described until now in nine different reports (7 patients with pneumonia, 3 with sepsis, 1 with endophthalmitis, 1 with perifolliculitis, and 1 with cholecystitis), our series represents the largest one dealing with *Serratia marcescens* infection during HIV disease. *Serratia marcescens* may be responsible for appreciable morbidity among patients with HIV disease, especially when a low CD4+ cell count, neutropaenia, and hospitalization are present. The clinician and the microbiologist facing a severely immunocompromised HIV-infected patient with a suspected bacterial disease should consider the *Serratia* spp. organisms. In fact, a rapid diagnosis and an adequate and timely treatment can avoid disease relapses and mortality.

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Introduction

Serratia marcescens is a motile, encapsulated gram-negative bacillus belonging to the *Enterobacteriaceae* family (species *Klebsiellae*), usually recovered from environmental sources such as water and soil but also capable of colonizing the respiratory and urinary tracts of hospitalized adults and the gastrointestinal tract of neonates. It is found increasingly to cause bacteraemia

and respiratory or urinary tract infections (and, rarely, to cause meningitis, cellulitis, and surgical wound infections) in patients with underlying diseases or predisposing conditions such as extremes of age, malignancies, diabetes mellitus, kidney failure, neutropaenia, surgery, and i.v. drug addiction. Its opportunistic behaviour becomes more evident when hospitalization and instrumentation are of concern, so that nosocomial outbreaks have been recognized, particularly when contamination of medical fluids, disinfectants, or instruments has occurred [1–5]. The most common portals of entry are the lung, the genitourinary tract, and i.v. lines [1, 3].

In a recent survey of nosocomial bloodstream infections carried out in the USA, *Serratia marcescens* was responsible for 65 of the 4725 (1.38%) episodes assessed [5]. In a study of *Serratia* spp. bacteraemia, nosocomial infection accounted for 80.4% of 56 evaluated episodes, with 48.2% of the cases occurring in intensive care units; 25% of the episodes described had a lethal outcome [1]. Remarkable therapeutic problems stem from the unpredictable antimicrobial susceptibility profile of *Serratia* spp. organisms: though susceptibility to carbenicillin, ticarcillin-clavulanate, second- or third-generation cephalosporins, aztreonam, aminoglycosides, ciprofloxacin and cotrimoxazole is often found, elevated resistance to ampicillin, first-generation cephalosporins, and tetracyclines, and multiresistant strains are usually described in hospital setting [1, 5, 6].

The aim of this study was to evaluate the role of *Serratia* spp. infections within the setting of HIV disease, as studied over an 8-year period.

Patients and Methods

The clinical and microbiological records of 2398 consecutive HIV-infected patients hospitalised since 1991 were reviewed retrospectively in order to identify all cases of *Serratia* spp. infection and to assess the occurrence and outcome of such infections according to several epidemiological, clinical, and laboratory parameters. An infectious process was attributed to *Serratia* spp. when one of these organisms was isolated from blood, respiratory secretions, bronchoalveolar lavage fluid, or tissue biopsy concurrently with signs, symptoms, and laboratory and instrumental examinations consistent with those of a bacterial disease. In particular, septicaemia was defined by at least two consecutive microbial isolations from blood cultures or by one positive blood culture plus the presence of one localised focus of infection (as probable source of bacteraemia); respiratory secretion specimens were considered acceptable for culture according to their content of polymorphonuclear leucocytes and epithelial cells. *Serratia* spp. were isolated and identified according to conventional laboratory techniques.

Antimicrobial sensitivity testing was performed using a standardised agar diffusion method, according to the Kirby-Bauer technique and the National Committee for Clinical Laboratory Standards (NCCLS) guidelines. An episode of infection was considered nosocomial in origin when diagnosed after the first 72 h of admission. Student's *t* test or Fisher's exact test (where applicable) was used for statistical analysis, with significance levels set at $P<0.05$.

Results

Seventeen of 2398 (0.71%) patients, 11 males and six females aged 23–49 years (9 former i.v. drug users, 5 homo/bisexual men, and 3 heterosexuals), were diagnosed with *Serratia* spp. infections while hospitalised due to HIV-related disorders. Overall, *Serratia* spp. organisms caused 17 of 1933 (0.88%) episodes of nonmycobacterial bacterial infection and nine of 1072 (0.84%) episodes of HIV-associated septicaemia over the 8-year period studied (1991–1998). All episodes of *Serratia* spp. infection were diagnosed between 1991 and 1996, with the majority of cases occurring during 1995 (6 episodes) and 1991 (4 cases), always in the absence of time- and space-clustering. During the last 2 years (1997 and 1998), no further episodes occurred, probably as a result of the significant improvement of the natural history of HIV disease following the introduction of combined antiretroviral regimens containing HIV protease inhibitors.

The most frequent clinical syndromes were septicaemia (9 cases) and pneumonia (chest radiograph showing multiple bilateral infiltrates; 6 cases). One case each of lymph node abscess and cellulitis were observed, while no cases of urinary tract infection occurred. *Serratia marcescens* was the only species of *Serratia* identified in our patients with HIV disease: it was isolated from blood cultures in nine cases, from respiratory secretions or bronchoalveolar lavage fluid in six cases, and from lymph node or soft tissue biopsy in one case each. In eight of 17 (47.1%) cases, other microbial pathogens were cultured concomitantly from respiratory secretions ($n=5$), tissue specimens ($n=2$), or blood cultures ($n=1$): *Staphylococcus aureus* was recovered in three cases, *Xanthomonas maltophilia* in two, and *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, and *Candida albicans* in one case each.

All patients with *Serratia* spp. infections were immunocompromised, as evidenced by a mean CD4+ lymphocyte count of 69.5 ± 21.4 cells/μl (range 1–240 cells/μl); subjects who developed septicaemia showed a significantly lower mean CD4+ cell count (30.2 ± 16.3 cells/μl) compared with patients who had other disease localizations ($P<0.001$). Moreover, a total leucocyte count of <2500 cells/μl was observed in 12 of 17 patients, and an absolute neutrophil count of <1000 cells/μl was seen in ten of 17 subjects; again, leucopaenia and neutropaenia were more frequent among patients with *Serratia marcescens* bacteraemia than in subjects with other disease complications, with all nine cases of leucopaenia and eight of nine cases of neutropenia occurring in this group ($P<0.01$ and $P<0.02$, respectively). Thirteen of 17 (76.5%) patients

(8 of 9 with bacteraemia) had been previously diagnosed with full-blown AIDS, due to opportunistic ($n=11$) or neoplastic ($n=2$) complications of HIV disease. During the month preceding disease onset, ten and five patients, respectively, were treated with broad-spectrum antibiotics or corticosteroids, while 12 of 17 patients were given i.v. or oral cotrimoxazole treatment or prophylaxis for *Pneumocystis carinii* infection.

When considering the role of hospitalization, *Serratia marcescens* infection was acquired nosocomially in 11 of 17 (64.7%) patients; hospital-acquired infection was significantly related to a previous diagnosis of AIDS (all 11 cases) ($P<0.007$), underlying leucopaenia and/or neutropaenia (10 of 11 cases) ($P<0.03$), and clinical characteristics of sepsis/bacteraemia (8 of 11 cases) ($P<0.05$) compared with community-acquired *Serratia marcescens* infection. However, a central i.v. line was present in only two subjects who developed *Serratia marcescens* bacteraemia, and no cases were detected after mechanical ventilation, surgery, or hospitalization in an intensive care unit. Finally, no significant relationship was observed between the occurrence of this bacterial disease and either age, gender, or type of risk for HIV infection (including i.v. drug use) (data not shown).

In vitro antimicrobial susceptibility assays performed on bacterial strains cultured from our patients showed 100% resistance to ampicillin and cephalothin, while 82.4–94.1% of all isolates were sensitive to piperacillin, cefotaxime, ceftriaxone, gentamicin, amikacin, netilmicin, fluoroquinolones, and cotrimoxazole (Table 1). Only one *Serratia marcescens* isolate cultured from a 36-year-old homosexual male with non-Hodgkin's lymphoma and hospital-acquired septicaemia was multiresistant (i.e., it was resistant to all above-mentioned compounds, plus aztreonam and tobramycin), though it remained susceptible to imipenem. Antimicrobial treatment was administered for 6–14 days with an antibiotic combination that included a second- or a third-generation cephalosporin plus an aminoglycoside in 14 patients, ceftazidime alone in two patients, and imipenem alone in the remaining patient (who was infected with the above-mentioned multiresistant bacterial strain). Indwelling i.v. catheters were removed in both patients with *Serratia* septicaemia. All patients were completely cured both clinically and microbiologically in 5–15 days, without related mortality or disease relapses.

Table 1 Results of in vitro antimicrobial susceptibility testing of all *Serratia marcescens* strains isolated from the 17 patients with HIV disease included in the study

Antimicrobial compound	Percentage (%) of strains susceptible
Ampicillin	0.0
Piperacillin	82.4
Cephalothin	0.0
Cefotaxime	88.2
Ceftriaxone	88.2
Ceftazidime	88.2
Gentamicin	94.1
Amikacin	94.1
Netilmicin	94.1
Cotrimoxazole	94.1
Ciprofloxacin	94.1

Discussion

Nonmycobacterial bacterial infections are still frequent in patients with advanced HIV disease, as a consequence of persisting risk factors such as prolonged survival with severe immunodeficiency, neutropaenia, frequent hospital admission, invasive diagnostic or therapeutic procedures, prolonged antimicrobial and steroid treatment, and lifestyle, i.e. i.v. drug addiction. Bacterial disease may be life-threatening when diagnosis and treatment are missed or delayed, when the patient affected is severely immunodeficient, and when multiresistant pathogens are of concern [7–9]. Series from different countries have shown remarkable variation in the profile of the organisms involved, which may be attributable to differences in underlying socioeconomic conditions, patients' lifestyle, and hospital standards. While early studies reported an increased incidence of encapsulated bacteria and staphylococci as leading AIDS-related bacterial pathogens [7, 9], recent surveys stressed a progressive upward trend of gram-negative bacilli as important agents of HIV-associated bacterial complications [7, 8, 10–25]. However, to our knowledge only 13 episodes of *Serratia marcescens* infection have been described in HIV-infected patients since 1987, in nine different reports [9, 10, 14, 25–30]: seven cases of pneumonia [10, 25, 30], three cases of septicaemia [9, 14, 28], and one case each of endophthalmitia [27], perifolliculitis [29], and bacteraemic cholecystitis [26]; no cases of urinary tract disease or infection due to non-*marcescens Serratia* spp. were reported. Unfortunately, these episodes have been reported as a part of large series dealing with bacterial complications of HIV disease (with most clinical and therapeutic details lacking) [9, 10, 14, 25, 30] or as anecdotal single-case observations [26–29].

McLoughlin et al. [26] first reported a case of *Serratia marscescens* acute bacteraemic cholecystitis complicated by perforation and bile peritonitis in an HIV-infected newborn treated with surgery; the infant died after 6 months due to multiple AIDS-related disorders and advanced liver disease [26]. In an older study of 44 cases of HIV-related bacteraemia, Krumholz et al. [9] described a homosexual male without neutropaenia who developed catheter-related sepsis due to *Serratia marcescens* and *Staphylococcus aureus*; a favourable outcome resulted after unspecified antimicrobial treatment. Later, an asymptomatic HIV-infected i.v. drug

user who developed *Serratia marcescens* endophthalmitis was described by Alvarez et al. [27]; pathogens isolated from vitreous humor culture were resistant to ampicillin and cephalothin but sensitive to third-generation cephalosporins, aminoglycosides, and fosfomycin Although combined treatment with cefriaxone, amikacin, and fosfomycin succeeded in controlling ocular infection in 3 weeks, complete blindness resulted as a severe sequela [27].

In 1994 Burack et al. [10] reported three cases of community-acquired pneumonia caused by *Serratia marcescens* in a series of 162 episodes; all bacterial isolates were resistant to cefuroxime but susceptible to ceftazidime and cotrimoxazole, and in two cases three other pathogens were present concomitantly [10]. In 1994 O'Connell [28] reported a case of recurrent *Serratia marcescens* sepsis favourably treated with ceftazidime and possibly related to the surprising resolution of concomitant Kaposi's sarcoma in a homosexual male with an extremely low CD4+ cell count and multiple AIDS-related disorders. Three more cases of *Serratia marscescens* pneumonia were described in 1995 in a series of 89 cases of microbiologically confirmed pneumonia; a positive culture was obtained from sputum in two cases and from bronchoalveolar lavage fluid in the remaining case [25]. Again in 1995, one more case of *Serratia marcescens* sepsis was reported in a series of 63 episodes of HIV-related bacteraemia observed in hospitalised patients [14]. One case of disseminated papular eruption described as acute *Serratia marcescens* perifolliculitis was reported in 1996 in an i.v. drug user with a relatively high CD4+ lymphocyte count (465 cells/μl); despite in vitro resistance of the isolate to ampicillin, chloramphenicol, and numerous cephalosporins, complete cure was obtained with oral doxycycline treatment [29]. More recently, in 1997, one additional case of *Serratia marcescens* pneumonia was reported in an Italian series that included 132 episodes of radiologically confirmed HIV-related pneumonia [30].

As a consequence, our series of HIV-associated *Serratia marcescens* disease is the largest reported to date (17 episodes on the whole, compared with the 13 cases described in 9 different reports until now) and the only one in which risk factors are analysed, antimicrobial susceptibility levels of the infecting isolates are reported, and outcome of treatment is described. Our experience demonstrates that *Serratia* spp. infection is responsible for appreciable morbidity among patients with HIV infection, causing slightly less than 1% of all bacterial complications and episodes of septicaemia occurring in our population of HIV-infected patients, even though no additional cases occurred after the introduction of highly active antiretroviral treatment.

As in other immunocompromised patients [1, 2, 4], bacteraemia and pneumonia accounted for the majority of infections caused by *Serratia* spp. in the setting of HIV disease, although two localizations not previously recorded in AIDS patients were observed in our series (1 lymph node abscess and 1 case of acute cellulitis). On the other hand, like others who reported previous experience with HIV-infected patients [9, 10, 14, 25–30], we did not observe any episodes of urinary tract infection. Nearly 50% of episodes in our series were polymicrobial in origin (others were described in 3 previous reports) [9, 10, 25], making the assessment of the pathogenetic potential of *Serratia* spp. organisms more difficult. Bacteraemia was the most frequent event in our series and occurred in association with indwelling central i.v. devices in two cases (this association was previously reported only once) [9]. As described in previous reports [10, 25, 30], pneumonia accounted for a relevant number of *Serratia* spp. complications in our series, usually with multiple, diffuse infiltrates observed on chest radiographs.

Among the potential risk factors for *Serratia* spp. disease in HIV-infected patients, a prior diagnosis of AIDS, the presence of other HIV-associated disorders, a low mean CD4+ lymphocyte count (<70 cells/μl), and leucopaenia/neutropaenia were confirmed by our experience. In particular, bacteraemia was associated with a significantly lower CD4+ cell count, a more frequent diagnosis of full-blown AIDS, and evidence of leucopaenia/neutropaenia when compared with pulmonary infection or infection at other sites. Prior reports suggested some relationship between the occurrence of *Serratia* spp. infection and full-blown AIDS or a low CD4+ lymphocyte count [26, 28] as well as prolonged hospitalization. In fact, hospital admission seems to play a promoting role through duration of hospitalization, drug administration, and diagnostic or therapeutic instrumentation, particularly the use of central i.v. lines [1, 2, 4, 9, 14]. In our series, nosocomial infections largely prevailed over community-acquired ones and showed significant correlation with an advanced underlying disease, granulocytopaenia, and the development of septicaemia, but a relapsing course and lethal outcome were not found. However, the majority of episodes of bacteraemia in our patients with *Serratia marcescens* pneumonia were not related to the use of indwelling intravascular catheters, mechanical ventilation, or instrumentation, and i.v. drug addiction did not seem to represent a significant risk factor (a finding that differs from those of 2 previously published case reports) [27, 29]. Finally, we also found an increased rate of prior antibiotic, steroid, or cotrimoxazole use among HIV-infected patients who developed *Serratia* spp. infection.

The variable pattern of antimicrobial resistance shown by *Serratia* spp. organisms makes antibiotic selection difficult [4–6]. When considering in vitro susceptibility levels of organisms isolated in the setting of HIV disease, very limited data are available: in an early

study from our institution, bacterial organisms cultured from HIV-infected individuals showed a significantly reduced mean resistance to most antimicrobial agents compared with the same organisms isolated from non-HIV-infected patients followed up at our general hospital [18]. In the above-mentioned reports of HIV-related *Serratia* spp. infections, only five strains were tested, confirming extensive resistance to ampicillin, first-generation cephalosporins, and some second-generation cephalosporins [10, 27, 29], but susceptibility to many third-generation cephalosporins and aminoglycosides [10, 27] as well as to cotrimoxazole [10] remained favourable. In our present experience with 17 *Serratia marcescens* isolates, acceptable susceptibility to ureidopenicillins, second- and third-generation cephalosporins, all aminoglycosides tested, systemic quinolones, and cotrimoxazole was observed, while elevated resistance to ampicillin and first-generation cephalosporins was confirmed. Furthermore, only one nosocomially acquired multiresistant strain was detected. Recommended treatment of *Serratia marcescens* infection should include third-generation cephalosporins, or aminoglycosides, carbapenems, fluoroquinolones, ticarcillin-clavulanate, piperacillin-tazobactam, aztreonam [6].

In the present clinical series, treatment with a second- or third-generation cephalosporin plus an aminoglycoside, with a third-generation cephalosporin, or with imipenem alone was effective both clinically and microbiologically. The protective role of cotrimoxazole prophylaxis against bacteraemia and other invasive bacterial complications in the setting of HIV disease is still uncertain [24]. Although cotrimoxazole resistance does not seem common among *Serratia* spp. strains isolated from HIV-infected patients, cotrimoxazole treatment or prophylaxis failed to prevent *Serratia* spp. infection in 12 of our 17 (70.6%) patients. On the other hand, removal of intravascular devices appears necessary in most catheter-related cases of bacteraemia, while surgery was needed in one reported case of cholecystistis [26]. In the majority of HIV-infected patients who developed *Serratia marcescens* infections but were given appropriate and timely antimicrobial therapy, a good clinical and microbiological response was obtained [9, 10, 27–29], with a surprisingly low recurrence rate (1 case only) [28] when compared with other bacterial complications associated with AIDS [7–9]. Complete clinical and microbiological cure without related mortality or disease relapse was obtained within 15 days in all of our patients. Like others who previously described cases of HIV-associated *Serratia marcescens* infections, we found no mortality directly related to *Serratia* spp. infection; there has, however, been one report of blindness that occurred as a result of severe endophthalmitis [27].

In conclusion, *Serratia* spp. organisms are responsible for appreciable morbidity among patients with advanced HIV infection and may pose relevant problems to both clinicians and bacteriologists involved in the care of HIV-infected patients. A broad spectrum of localizations and an association with advanced HIV disease, a low CD4+ cell count, the presence of leucopaenia/neutropaenia, and hospitalization were observed. Furthermore, prior antibiotic and steroid use were found frequently, and cotrimoxazole prophylaxis did not seem to prevent *Serratia marcescens* infection. In particular, septicaemia was significantly associated with a prior diagnosis of AIDS and lower CD4+, leucocyte, and neutrophil counts compared with other *Serratia* spp. localizations.

Hospital-acquired episodes accounted for the majority of cases, and a significant relationship between HIV-associated nosocomial *Serratia* spp. infection and a diagnosis of AIDS, neutropaenia, and the occurrence of septicaemia was demonstrated. Bacterial isolates had a better sensitivity profile than expected [1, 5, 6], so that all patients were cured, with no mortality or recurrences and apparently limited consequences on the course of HIV disease. However, due to the unpredictable resistance pattern exhibited by these microorganisms, antimicrobial treatment needs to be carefully selected on the basis of the results of susceptibility testing. The combination of a third-generation cephalosporin and an aminoglycoside seems an appropriate empiric choice when these organisms are of concern, pending the results of in vitro sensitivity assays. Increased suspicion for these infections is always warranted in patients with advanced HIV disease and a suspected bacterial complication: early recognition of a *Serratia* spp. infection may play a key role, since a timely intervention with appropriate therapy can lead to a rapid clinical and microbiological cure.

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