Urinary tract infection in men with AIDS

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Abstract

Objective—To investigate whether bacteriuria and, specifically, symptomatic urinary tract infection (UTI) occur with increased frequency in men with HIV infection.

Methods—In this cross-sectional study we investigated three groups of men, aged from 18 to 50 years. Group A was composed of patients with a diagnosis of AIDS; Group B, of patients without HIV infection, and group C of patients with asymptomatic HIV infection. Patients with any known predisposing factor for UTI were excluded from the study. A clean-catch midstream urine sample was collected from each patient on the first day of hospital admission (groups A and B) or during a visit to the outpatient clinic (group C). Bacteriuria was diagnosed when $\geq 100\,000$ colony forming units/ml, urine were grown.

Results—There were 415 patients, 151 in group A, 170 in group B and 94 in group C. Bacteriuria was significantly more frequent in group A (20 cases, 13.3%) than in groups B (3 cases, 1.8%, $p = 0.00007$) and C (3 cases, 3.2%, $p = 0.009$). Ten cases of bacteriuria in group A (6.6%) were symptomatic while no case of symptomatic UTI was seen in groups B ($p = 0.0004$) and C ($p = 0.008$). The frequency of UTI in homosexual men with AIDS (7 cases, 6.7%) was not significantly different from that observed in men with AIDS who denied homosexuality (3 cases, 6.5%). *E coli* was the predominant pathogen associated with UTI. Although adequate response to a two-week course of antibiotics was observed in most cases, an in-hospital mortality rate of 20% was found among AIDS patients with symptomatic UTI.

Conclusions—In the present study, the frequency of bacteriuria and symptomatic UTI was found to be increased in men with AIDS. *E coli* was the predominant pathogen in these cases. These data suggest that symptomatic UTI may represent a relevant cause of morbidity for men with AIDS.

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Introduction

In most Western countries, the Acquired Immunodeficiency Syndrome (AIDS) has

predominantly occurred in young adult or middle aged males¹, a population otherwise expected to be at very low risk for urinary tract infection (UTI).² However, some uncontrolled studies have suggested that men with AIDS may be at increased risk for bacteriuria³⁻⁵. Recently, a controlled longitudinal study showed that men infected with the Human Immunodeficiency Virus (HIV), the causative agent of AIDS, who had CD4 + lymphocyte counts below 200 cells/mm³ were at increased risk for bacteriuria when compared with other HIV-infected men but with higher CD4 + lymphocyte counts⁶. In spite of this elevation in the risk for bacteriuria, the frequency of symptomatic UTI has not yet been shown to be significantly increased among HIV-infected men, in comparison with a similar population without HIV infection. Furthermore, Welch *et al* suggested that most cases of asymptomatic bacteriuria in HIV infected men may be self-limited⁷. Thus, the clinical relevance of UTI as a cause of morbidity in male patients with HIV infection has not been established.

To investigate the frequency of bacteriuria and of symptomatic UTI in adult males with HIV infection, we conducted a controlled, cross-sectional study, comparing a group of men with AIDS with a group of male patients without HIV infection, both studied within 24 hours after hospital admission. A group of male outpatients with asymptomatic HIV infection was also studied.

Methods

This study was carried out in two Brazilian national referral centres for AIDS, Hospital Universitário Clementino Fraga Filho and Hospital Universitário Gaffrée e Guinle, from September 1991 up to August 1992. Male patients who were consecutively admitted to one of these hospitals, and whose age ranged from 18 to 50 years were grouped as follows: the first group included patients with a diagnosis of AIDS according to the 1987 criteria of the Centers for Disease Control⁸ (group A), and the second was composed of patients without HIV infection (group B). A third group included consecutive male individuals attending the outpatient clinic, with the same age range of the previous 2 groups, who had asymptomatic HIV infection (group C). Patients who reported any risk factor for HIV infection were not included in group B. All patients studied gave informed consent. Patients with a history of urinary lithiasis,

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known anatomic alterations of the urinary tract, recent (less than six months) urologic instrumentation (including urethral catheterisation), alterations of sphincter control, use of external urinary catheters, immunosuppressive therapy, granulocytopenia (defined as less than 1000 granulocytes/mm³) or diabetes mellitus were excluded from the study. Antibiotic therapy was a cause of exclusion for groups B and C. In group A, patients who were using anti-tuberculous drugs or sulphamethoxazole and trimethoprim (SMZ/TMP) for *Pneumocystis carinii* pneumonia prophylaxis were not excluded. Age, urological history and data about sexual behaviour were recorded in each case. A blood sample of each patient was tested for the presence of antibodies to HIV. The ELISA method (Organon) was employed as a screening test and an indirect immunofluorescence assay (Instituto de Tecnologia em Imunobiológicos, Bio-Manguinhos) was used as the confirmatory test.

A clean-catch mid-stream sample of urine was obtained from each enrolled patient on hospital admission (Groups A and B) or during the first out clinic visit after September 1991 (group C). Each sample was inoculated into agar-Brolacin (Merck) and cysteine lactose electrolyte deficient (agar-CLED, Difco Labs) plates after 1:100 and 1:10 000 dilutions. In symptomatic patients, a urine culture was considered positive when >10⁵ colony forming units were grown per ml. urine. In asymptomatic patients, cultures were considered positive only when >10⁵ CFU of a member of the *Enterobacteriaceae* family were grown⁹. UTI was considered symptomatic when associated with fever (if no other potential cause for hyperthermia was present), urinary frequency, urgency, dysuria or lumbar pain. Three blood samples were collected from patients with fever in groups A and B. These samples were inoculated in blood culture bottles containing brain-heart infusion (BHI, Difco Labs). Subcultures of each sample were routinely made onto chocolate blood agar plates (Merck). A microorganism grown in these blood cultures was considered identical to that found in the urine culture when both cultures yielded the same bacterial species with the same antibiotic sensitivity.

The Mann-Whitney test for unpaired data was used to compare mean age between groups. Chi square analysis of contingency tables and Fisher's exact test were used to compare frequency data between groups. Epi Info software version 5.01 (Centers for Disease Control, Atlanta, Georgia) was used for the statistical analyses. Differences were considered statistically significant when $p < 0.05$.

Results

Four hundred and fifteen patients were included in this study. Group A was composed of 151 patients. Groups B and C included, respectively, 171 and 94 patients.

Mean ages in the three groups were not significantly different (A = 33.5, SD 6.9, B = 35.1, SD 8.9 and C = 33.2, SD 7.2 years). In group A, 105 patients reported homosexual practices (69.5%) as well as 64 individuals in group C (68.1%), a difference that was not statistically significant. Since homosexuality was an exclusion criterion for group B, this group differed significantly from the other two in this respect. In group A, 87 patients (57.2%) were using antibiotics when the urine sample was collected. Thirty-two patients were using co-trimoxazole, 28 patients were under anti-tuberculous therapy (rifampicin, isoniazid, pyrazinamide—RIP) and 27 were using both co-trimoxazole and RIP.

Bacteriuria was found in 20 patients in group A (13.3%, 95% confidence interval 7.8 to 18.7%), in three patients in group B (1.8%, 95% confidence interval 0 to 3.8%) and in three cases in group C (3.2%, 95% confidence interval 0 to 6.8%). Bacteriuria was significantly more prevalent in group A than in groups B ($p = 0.00007$, $\chi^2 = 15.71$, odds ratio 8.6, 95% confidence interval 2.4 to 45.6) and C ($p = 0.009$, $\chi^2 = 6.81$, odds ratio 4.6, 95% confidence interval 1.3 to 24.9). The prevalence of bacteriuria in groups B and C was not significantly different. The microorganisms detected in group A patients were: *E coli* (14 cases, 70%), *Enterobacter* spp. (3 cases, 15%), *Citrobacter freundii* (2 cases, 10%) and *Klebsiella pneumoniae* (1 case, 5%). In group B, bacteriuria was caused by *E coli* (2 cases, 66.7%) and *Serratia marcescens* (1 case, 33.3%). Urine cultures in group C yielded *E coli* (2 cases, 66.7%) and *Proteus mirabilis* (1 case, 33.3%).

Symptomatic UTI was found in 10 patients in group A (6.6%, 95% confidence interval 2.6 to 10.6%) while it was not present in any patient in groups B ($p = 0.0004$) and C ($p = 0.008$). Symptoms associated with UTI were: dysuria (8 cases), fever (8 cases), urinary frequency (4 cases) and lumbar pain (3 cases). Two patients presented with fever and other non-specific symptoms. In one of these cases, urinalysis showed leukocyte casts and a positive nitrite test. In the other patient, urinalysis was normal, but 2 blood cultures yielded the same microorganism (*E coli*) found in the urine culture. Most cases of symptomatic UTI were caused by *E coli* ($n = 9$, 90%). In the remaining patient, *Enterobacter* sp was found. Five patients with symptomatic bacteriuria were using antibiotics at the time of urine sample collection. Two patients were taking co-trimoxazole and RIP, two were taking RIP and one was only taking co-trimoxazole. There was no statistically significant difference in the frequency of bacteriuria or symptomatic UTI between group A patients who were taking and who were not taking antibiotics (data not shown).

Response to appropriate antibiotic treatment was documented in six cases (60%) of symptomatic UTI. Follow-up urine cultures, performed 7 to 15 days after the end of antibiotic treatment, confirmed the eradica-

Patients with symptomatic UTI in group A—Clinical and demographic characteristics

Age (years)	Sexual Behaviour	AT	Urinalysis	Aetiological Agent	Symptoms	Clinical Outcome
35	Homosexual	None	ND	<i>E coli</i>	Dysuria, frequency	Death
46	Homosexual	RIP	ND	<i>E coli</i>	Fever, dysuria	Cure
39	Heterosexual	co-trimoxazole	Nitrite +, pyuria	<i>E coli</i> *	Fever, dysuria, lumbar pain, frequency	Death
34	Homosexual	None	Pyuria, leukocyte casts	<i>E coli</i>	Fever, frequency, dysuria, lumbar pain	Cure
33	Homosexual	None	Pyuria, granular casts	<i>E coli</i>	Fever, dysuria, frequency	Remission of symptoms†
35	Homosexual	RIP	Pyuria, leukocyte casts	<i>E coli</i>	Fever	Cure
35	Heterosexual	RIP	Normal	<i>S faecalis</i>	Fever, dysuria	Cure
21	Heterosexual	co-trimoxazole	Normal	<i>E coli</i>	Fever, dysuria	Cure
28	Homosexual	RIP	Pyuria	<i>E coli</i> *	Fever	Cure
36	Homosexual	co-trimoxazole	Pyuria	<i>E coli</i>	Dysuria	Remission of symptoms†

AT = antimicrobial therapy, ND = not done.

*Blood cultures of these patients yielded the same bacterial strain found in urine culture.

†Follow-up urine cultures were not done in these cases.

tion of the infection in these cases. In 2 patients (20%) symptoms disappeared but follow-up urine cultures were not performed. Two patients (20%) died of septicaemia on the second day after hospital admission. Antibiotic sensitivity tests showed that the antibiotics empirically prescribed at admission were active against the bacteria grown in the urine cultures in both cases. In one of these cases, culture of three blood samples yielded the same strain of *E coli* that had grown in the urine culture. In the other patient, blood cultures were negative, but no other infectious focus related to septicaemia was apparent. Clinical data of patients with symptomatic UTI in group A are summarized in the table.

In group A, the prevalence of bacteriuria among patients reporting homosexual practices (16 cases, 15.2%, 95% confidence interval 8.3 to 22%) was not significantly different from that found among those denying these practices (four cases, 8.7%, 95% confidence interval 0.6 to 16.8). In the same group, seven out of 105 homosexual patients (6.7%, 95% confidence interval 1.9 to 11.5%) and three out of 46 heterosexual men (6.5%, 95% confidence interval 2.9 to 10.1%) had symptomatic UTI. This difference was not statistically significant. We also compared the frequency of bacteriuria and symptomatic UTI between homosexual patients in groups A and C. The prevalence of bacteriuria among homosexual males in group A (16 cases, 15.2%) was significantly higher than that found in homosexual men in group C (3 cases, 4.7%, $p = 0.035$, $\chi^2 = 4.44$, odds ratio = 3.66, 95% confidence interval 0.98 to 20.1). The frequency of symptomatic UTI was also significantly increased in homosexual males with AIDS (7 cases, 6.7%, 95% confidence interval 1.9 to 11.5%) in relation to homosexual men with asymptomatic HIV infection (no cases, $p = 0.045$).

Discussion

Most infectious complications in patients with AIDS are due to opportunistic

pathogens. Nevertheless, infections caused by common bacterial pathogens may represent additional causes of morbidity and mortality for HIV-infected individuals.¹⁰⁻¹⁶ Bacterial infections were found in 52 to 83% of the cases in some necropsy series.¹⁰⁻¹² In one series, these bacterial infections were the immediate cause of, or significantly contributed to death in 37% of the patients.¹²

Though pyelonephritis was reported in 10 to 15% of the cases in some necropsy series,^{10,11} few studies concerning UTI among HIV-infected patients have been published. Most of these are retrospective or uncontrolled.³⁻⁵ In the only controlled longitudinal study reported,⁶ it was found that the risk for bacteriuria was increased in HIV infected patients with CD4+ lymphocyte counts below 200 cells/mm³ when compared with two other groups of HIV infected patients with higher CD4+ lymphocyte counts.

In the present study, the prevalence of bacteriuria upon hospital admission in young male patients with AIDS was significantly higher than that observed in hospitalized men of similar age but without HIV infection. The prevalence of bacteriuria in AIDS patients was also significantly increased in comparison with that observed in a group of asymptomatic HIV-infected outpatients. Such significant differences were observed despite the fact that approximately one third of the patients in group A were using co-trimoxazole, which may have caused an underestimation of the true prevalence of bacteriuria in these patients. The prevalence of bacteriuria found in outpatients with asymptomatic HIV infection was not significantly different from that found among men without HIV infection. In accordance with the results of other studies,³⁻⁶ these data suggest that the prevalence of bacteriuria is significantly increased in patients with HIV infection who have developed clinical manifestations of immunodeficiency.

Although an increased predisposition for bacteriuria had already been recognised,⁶ no significant increase in the frequency of symptomatic UTI has been demonstrated in AIDS

patients. In this study, the frequency of symptomatic UTI in recently admitted young male patients with AIDS was significantly higher than that found in the other two groups. In fact, only patients with AIDS had symptomatic UTI. The absence of symptomatic UTI in the other 2 groups is in accordance with the expected very low risk of these infections among young immunocompetent males.² In most patients, the presence of UTI was suggested by symptoms related to the urinary tract. In two cases, however, fever was the only clinical manifestation of UTI. Similar cases have been reported by other authors.^{6,7} The relatively high frequency of UTI found in AIDS patients in this study and the occasional non-specificity of its clinical manifestations suggest that UTI must be considered in patients with AIDS who present with fever.

As has been observed in immunocompetent patients with community acquired UTI,¹⁷ *E coli* was the predominant pathogen found in AIDS patients with symptomatic UTI.

Clinical response to a two-week course of antibiotics was adequate in most patients with symptomatic UTI. However, an in-hospital mortality rate of 20% was observed due to the rapid development of sepsis, despite the appropriately selected empirical antibiotic therapy, in two patients.

The possible role of homosexual behaviour as a risk factor for UTI in males is controversial.^{18,19} The significant increase in the frequency of bacteriuria and, particularly, symptomatic UTI, observed in patients with AIDS when compared with patients without HIV infection might be related to the absence of homosexual patients in the latter group. However, bacteriuria and symptomatic UTI were also significantly more frequent in AIDS patients than in the group of men with HIV infection but without immunodeficiency, even though the proportion of homosexual patients included in both groups did not differ. In addition, bacteriuria and symptomatic UTI were significantly more frequent in homosexual men with AIDS than in homosexuals with asymptomatic HIV infection. Again, one may argue that these results might derive from a selection bias, since a group of recently hospitalised patients was compared with a group of outpatients. However, bacteriuria and symptomatic UTI in homosexual men in group A were not significantly more frequent than in heterosexual males of the same group. Although the study was not designed to address this point, the increased frequency of UTI among male patients with AIDS found in our study, irrespective of sexual orientation, suggests that UTI is not related to sexual preferences. Thus, our results are similar to those described by Hoepelman, *et al*⁶ who found that the increased frequency of bacteriuria in HIV-infected males was not related to the frequency of active or passive anal intercourse, but to the extent of CD4+ lymphocyte depletion.

The mechanisms associated with HIV

infection that may be responsible for the observed increase in the frequency of UTI remain to be established. It is recognised that local antibody production can afford some protection against bacterial invasion of the urinary tract in immunocompetent patients.^{17,20} Although polyclonal activation of B lymphocytes and hypergammaglobulinaemia are frequently found in patients with AIDS,²¹ antibody response to T cell dependent and independent antigens is commonly inadequate.²²⁻²⁵ This impairment in the humoral immune response to bacterial antigens may facilitate the adhesion of pathogenic bacteria to the urothelium of patients with AIDS.

In conclusion, our results suggest that the frequency of bacteriuria and symptomatic UTI are increased among recently hospitalised men with AIDS without any known predisposing factor for UTI. Symptomatic UTI, usually caused by *E coli*, seems to be a relevant cause of morbidity for these patients.

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- 1 Mann JM, Welles SL. Global aspects of the HIV epidemic. In: De Vita VT, Hellmans S, Rosenberg SA. (eds) *AIDS. Etiology, Diagnosis, Treatment and Prevention*. Philadelphia, J.P. Lippincott Company, 3rd ed., 1992; p. 89-98.
- 2 Lipsky, B. Urinary tract infections in men. Epidemiology, pathophysiology, diagnosis and treatment. *Ann Intern Med* 1989;110:138-50.
- 3 Pinho AMF, Marangoni DV, Moreira BM, *et al*. Bacteriuria in patients with CDC group IV manifestations: a prospective study. *AIDS* 1991;5:342.
- 4 Santos OR, Lopes GS, Costa JLF, Lacerda MR, Haringer J, Faria RB. Urinary tract infection in men with HIV infection: results of a pilot uncontrolled study. 6th International Conference on AIDS. San Francisco, 1990; abstract FB 535.
- 5 Kaplan MS, Weschler M, Benson MC. Urologic manifestations of AIDS. *Urology* 1987;30:441-4.
- 6 Hoepelman AIM, Van Buren M, Van Den Broek J, Borleffs JCC. Bacteriuria in men with HIV-1 is related to their immune status (CD4+ cell count). *AIDS* 1992; 6:179-84.
- 7 Welch J, Pilkington H, Bradbeer C. Urinary infections in men. *BMJ* 1989;299:184.
- 8 Centers for Disease Control. Revision of the CDC surveillance case definition for acquired immunodeficiency syndrome. *MMWR* 1987;36 (Suppl. 1):1-15.
- 9 Gleckman R, Esposito A, Crowley M, Natsios GA. Reliability of a single urine culture in establishing diagnosis of asymptomatic bacteriuria in adult males. *J Clin Microbiol* 1979;9:596-7.
- 10 Falks S, Schmidts HL, Muller H. Autopsy findings in AIDS—a histopathological analysis of fifty cases. *Klin Wochenschr* 1987;65:654-63.
- 11 Niedt GW, Schinella RA. AIDS: clinicopathologic study of 56 autopsies. *Arch Pathol Lab Med* 1985;109: 727-34.
- 12 Nichols L, Balogh K, Silverman M. Bacterial infections in the AIDS. Clinicopathologic correlations in a series of autopsy cases. *Am J Clin Pathol* 1990;92:787-90.
- 13 Whimbey E, Gold JWM, Polsky B. Bacteremia and fungemia in patients with AIDS. *Ann Intern Med* 1986; 104:511-4.
- 14 Casadeval A, Dobroszycki J, Small C, Pirofski L-A. *Haemophilus influenzae* type b bacteremia in adults with AIDS and at risk for AIDS. *Am J Med* 1992;92:587-90.
- 15 Franzetti F, Cernuschi M, Esposito R, Moroni M. *Pseudomonas* infections in patients with AIDS and AIDS-related complex. *J Intern Med* 1992;231:437-43.
- 16 Garcia-Leoni ME, Moreno S, Rodeño P, Cercenado E, Vicente T, Bouza E. Pneumococcal pneumonia in adult hospitalized patients infected with the human immunodeficiency virus. *Arch Intern Med* 1992;152:1808-12.
- 17 Rubin RH, Tolkoff-Rubin NE, Cotran RS. Urinary tract infection, pyelonephritis and reflux nephropathy. In: Brenner BM, Rector FCJr. (eds.) *The Kidney*. Philadelphia, W.B. Saunders Company, 4th ed., 1991; p.1369-429.
- 18 Barnes RC, Daifuku R, Roddy RE, Stamm WE. Urinary tract infection in sexually active homosexual men. *Lancet* 1986;1:171-3.

- 19 Wilson AP, Tovey SJ, Adler MW, Grüneberg RN. Prevalence of urinary tract infection in homosexual and heterosexual men. *Genitourin Med* 1986;62:189-90.
- 20 Svanborg-Edén C, Svennerholm AM. Secretory IgA and IgG antibodies prevent adhesion of *E coli* to human urinary tract epithelial cells. *Infect Immun* 1978;22:790-7.
- 21 Rosenberg ZF, Fauci AS. Immunopathogenesis of HIV infection. In: De Vita VT, Hellmans S, Rosenberg SA. (eds) *AIDS. Etiology, Diagnosis, Treatment and Prevention*. Philadelphia, J.P. Lippincott Company, 3rd ed., 1992; p. 89-98.
- 22 Lane HC, Masur H, Edgar LC, Whalen G, Rook AH, Fauci AS. Abnormalities of B-cell activation and immunoregulation in patients with the acquired immune deficiency syndrome. *N Engl J Med* 1983;309:453-8.
- 23 Katz R, Krown SE, Safai B, Oettgen HF, Hoffman MK. Antigen specific and polyclonal B-cell responses in patients with acquired immunodeficiency syndrome. *Clin Immunol Immunopathol* 1986;39:359-67.
- 24 Ballet JJ, Sulcebe G, Couderc LJ, et al. Impaired anti-pneumococcal antibody response in patients with AIDS related persistent generalized lymphadenopathy. *Clin Exp Immunol* 1987;68:479-87.
- 25 Chirmule N, Oyaizu N, Kalyanaraman VS, Pahwa S. Inhibition of normal B-cell function by Human Immunodeficiency Virus envelope glycoprotein, gp 120. *Blood* 1992;79:1245-54.