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The epidemiology of recurrent bacterial pneumonia in people with AIDS in Europe

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SUMMARY

Data from AIDS surveillance systems in the World Health Organization European region (1993–2001) were analysed to describe the main epidemiological aspects of recurrent bacterial pneumonia (RBP) as AIDS-defining illness (ADI) in Europe. Among the 153 756 AIDS cases analysed, 5796 (3·8%) had RBP. The proportion of RBP was higher (8·3%) in eastern than in western Europe (3·6%), possibly because of a greater propensity of certain countries to diagnose RBP. In western Europe, the proportion of RBP as ADI appeared to increase over time up to 1998 (from 2·5% to 4·5%), and declined thereafter (3·3% in 2001). RBP was strongly associated with intravenous drug use (odds ratio 3·0, 95% CI 2·7–3·3), whereas it did not differ in age groups or geographical areas. The study findings confirm the crucial role of intravenous drug use in the occurrence of RBP and suggest that highly active antiretroviral therapies might have had a postponing impact on the relative frequency of RBP as ADI.

INTRODUCTION

Recurrent bacterial pneumonia (RBP) is a complication of HIV infection included among AIDS-defining illnesses (ADI) in 1993 [1]. Since then, few epidemiological studies have specifically focused on the frequency and determinants of AIDS-associated RBP [2–5]. Moreover, information is scanty and inconsistent as regards the impact of highly active antiretroviral therapies (HAART), employed for the treatment of HIV-infected persons, on the occurrence of RBP as ADI [5–7]. To describe temporal patterns, frequency and main epidemiological characteristics of AIDS-associated RBP, we conducted a statistical analysis of European AIDS surveillance data.

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METHODS

The 30 June 2002 update of the European Non Aggregate AIDS Data Set (ENAADS) was analysed [8]. ENAADS contains anonymous information for each individual case of AIDS fulfilling the 1993 European AIDS-Surveillance Case Definition [1]. AIDS cases were recorded by the national surveillance systems of 37 countries from the World Health Organisation (WHO) European region, which registered at least one case of AIDS since the beginning of the epidemic. Data were collected by EuroHIV (the European Centre for the Epidemiological Monitoring of AIDS, St Maurice, France), according to a standard

core of epidemiological information that included: country of report, gender, age and year at AIDS diagnosis; HIV transmission category; and up to four ADI diagnosed within 4 months from the first AIDS-defining disease [8]. Detailed information on ENAADS has already been provided [9].

In this analysis, the study group consisted of adult and adolescent AIDS cases (i.e. $\geqslant$13 years old), diagnosed between January 1993, when RBP was included among ADI, and December 2001 (AIDS cases diagnosed between January and June 2002 were not included in the present analysis to limit the effect of incomplete notification and reporting delay). A case was considered affected by RBP if this condition was listed in one of the four diagnostic indicators recorded at the time of AIDS diagnosis, and each AIDS case was subsequently classified according to the presence or absence of RBP among ADI. The association between selected characteristics (i.e. country of origin, HIV transmission category, gender, age, and year at AIDS diagnosis) and the presence of RBP at AIDS diagnosis was assessed by means of odds ratios (OR) and 95% confidence intervals (CI). Multiple logistic regression (MLR) equations were fitted [10], including terms for age, gender, HIV transmission category, geographic area of western Europe and year at AIDS diagnosis (1993 and 1994 were grouped together, to limit potential under-reporting of RBP due to the introduction of the revised classification of AIDS). To allow for potential extra-binomial variation due to heterogeneity of data, the standard error of the point estimate was computed by means of the Huber/White/sandwich estimator of variance–covariance matrix [11] using the STATA software package [12].

RESULTS

Between 1993 and 2001, 153 756 adult/adolescents were reported with AIDS in the WHO European region: RBP was one of the ADI in 5796 of these cases (3·8%) (Table 1). The proportion of cases with RBP was markedly higher in eastern (8·3%) than in western Europe (3·6%), (OR 3·4). However, in eastern Europe, the vast majority (69%) of RBP cases was concentrated in a single country, namely Ukraine. When Ukraine was excluded from the analysis, there was no longer evidence of a statistically significant higher frequency of RBP in eastern Europe, compared to northern Europe (OR 1·7, 95% CI 0·6–4·9) (data not shown in tables). Within western countries, RBP as ADI was slightly more common in southern than in northern Europe (OR 1·6, 95% CI 1·04–2·54) (Table 1).

Because of the small number of AIDS notifications and of the wide heterogeneity in the frequency of RBP recorded within eastern European countries, the analysis of potential determinants of RBP as ADI was restricted to the 147 071 AIDS cases from western Europe (Table 2).

By multivariate analysis, the OR of having RBP as ADI was higher among women (MLR-OR 1·3), whereas it did not differ across age groups or geographical areas of western Europe. The mode of HIV infection acquisition turned out to be the most important determinant of RBP. In comparison with heterosexuals, intravenous drug users (IDUs) had a threefold higher risk of RBP (MLR-OR 3·0), whereas the lowest probability of having RBP as ADI (MLR-OR 0·7) was registered in men who have sex with men (MSM) (Table 2). Over time, the frequency of RBP seemed to increase between 1993/1994 (2·5%) and 1998 (4·5%) and to decrease thereafter, but the wide 95% CIs of the MLR-OR estimates did not allow a precise assessment of time trends (Table 2).

To take into account such main effect, risk factors for RBP were also separately analysed in the different HIV transmission categories (data not shown in tables). The lack of association between age, geographic area and the risk of RBP as ADI persisted in all categories apart from recipients of blood or of blood derivatives (where an inverse association with age was found). The excess risk noted among the totality of women was clearly seen among IDUs (MLR-OR 1·4, lower 95% CI 1·2) but it was of borderline statistical significance in heterosexuals (MLR-OR 1·2, lower 95% CI 1·0). On the contrary, it did not emerge in recipients of blood transfusions or of blood derivatives (MLR-OR 0·7, upper 95% CI 1·1). The effect of calendar period was particularly evident among IDUs (MLR-OR for 1998 *vs.* 1993/1994 = 2·3, lower 95% CI 1·4), less marked among MSM (MLR-OR for 1998 *vs.* 1993/1994 = 1·4, lower 95% CI 1·1) and not statistically significant among heterosexuals or recipients of blood transfusions or of blood derivatives (data not shown in tables).

DISCUSSION

This epidemiological evaluation of RBP revealed that, from its inclusion in the AIDS definition in 1993 to the end of 2001, 3·8% of AIDS cases in the WHO European Region had RBP at diagnosis. Intravenous

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Table 1. *Distribution of AIDS cases by country of origin and recurrent bacterial pneumonia at AIDS diagnosis* (*WHO European Region, 1993–2001*)

Country of origin	Number of AIDS cases	AIDS cases with recurrent bacterial pneumonia		
		No.	(%)	OR (95% CI)[a]
Northern Europe				
Denmark	1225	29	(2·4)	
Finland	207	3	(1·4)	
Germany	11 045	386	(3·5)	
Iceland	25	1	(4·0)	
Ireland	344	20	(5·8)	
Netherlands	2823	46	(1·6)	
Norway	423	19	(4·5)	
Sweden	990	16	(1·6)	
United Kingdom	10 444	207	(2·0)	
Total	27 526	727	(2·6)	1[b]
Central Europe				
Austria	1164	83	(7·1)	
Belgium	1509	34	(2·3)	
France	29 451	535	(1·8)	
Luxembourg	98	1	(1·0)	
Switzerland	3592	330	(9·2)	
Total	35 814	983	(2·7)	1·04 (0·46–2·37)
Southern Europe				
Greece	1445	58	(4·0)	
Israel	514		(0·0)	
Italy	32 259	1129	(3·5)	
Portugal	7494	154	(2·1)	
Spain	41 721	2162	(5·2)	
Turkey	298	26	(8·7)	
Total	83 731	3529	(4·2)	1·62 (1·04–2·54)
Eastern Europe				
Albania	15	3	(20·0)	
Azerbaijan	55	8	(14·5)	
Belarus	21	10	(47·6)	
Croatia	128	1	(0·8)	
Czech Republic	123	12	(9·8)	
Estonia	26	2	(7·7)	
Hungary	278	11	(4·0)	
Latvia	109	3	(2·8)	
Lithuania	42	4	(9·5)	
Macedonia	33	6	(18·2)	
Moldova	34	9	(26·5)	
Poland	988	97	(9·8)	
Romania	1303	0	(0·0)	
Slovakia	26	2	(7·7)	
Slovenia	72	3	(4·2)	
Ukraine	2739	382	(13·9)	
Yugoslavia	693	4	(0·6)	
Total	6685	557	(8·3)	3·35 (1·44–7·76)
All countries	**153 756**	**5796**	**(3·8)**	

[a] Odds ratios (OR) and 95% confidence intervals (CI).
[b] Reference category.

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Table 2. *Distribution of AIDS cases according to selected characteristics and recurrent bacterial pneumonia at AIDS diagnosis (WHO European Region, Western Europe, 1993–2001)*

	No. of AIDS cases	AIDS cases with recurrent bacterial pneumonia		
		No.	(%)	MLR-OR[a] (95% CI)
Age (years)				
⩾40	44 812	1152	(2·6)	1[b]
35–39	32 005	1265	(4·0)	1·01 (0·95–1·07)
30–34	41 668	1706	(4·1)	1·01 (0·94–1·07)
25–29	22 787	836	(3·7)	0·93 (0·83–1·04)
13–24	5799	280	(4·8)	1·23 (0·89–1·69)
Gender[c]				
Male	117 025	3829	(3·3)	1[b]
Female	30 044	1410	(4·7)	1·34 (1·15–1·56)
HIV transmission category				
Heterosexuals	33 557	790	(2·4)	1[b]
MSM[d]	40 728	582	(1·4)	0·71 (0·57–0·89)
IDUs[e]	60 273	3525	(5·8)	2·99 (2·41–3·70)
MSM and IDUs	1587	69	(4·3)	2·34 (1·87–2·94)
Recipients of blood or of blood derivatives	2594	96	(3·7)	1·81 (1·45–2·25)
Others	8332	177	(2·1)	0·95 (0·76–1·18)
Area of origin				
Northern Europe	27 526	727	(2·6)	1[b]
Central Europe	35 814	983	(2·7)	0·84 (0·39–1·83)
Southern Europe	83 731	3529	(4·2)	0·82 (0·57–1·20)
Year at AIDS diagnosis				
1993–1994	47 797	1203	(2·5)	1[b]
1995	24 630	949	(3·9)	1·54 (1·09–2·18)
1996	21 462	921	(4·3)	1·71 (1·19–2·44)
1997	14 710	616	(4·2)	1·69 (1·11–2·57)
1998	11 447	514	(4·5)	1·90 (1·24–2·91)
1999	10 179	428	(4·2)	1·81 (1·08–3·02)
2000	9196	352	(3·8)	1·70 (1·03–2·80)
2001	7650	256	(3·3)	1·49 (0·89–2·49)
Total	147 071	5239	(3·6)	

[a] Multiple logistic regression odds ratios (MLR-OR) and 95% confidence intervals (CI), adjusted for all the variables listed in table.
[b] Reference category.
[c] The sum does not add up to the total because of missing values.
[d] Men who have sex with men.
[e] Intravenous drug users.

drug use was identified as the main determinant of AIDS-associated RBP, while the use of HAART seemed to have had a postponing impact on the relative frequency of RBP as ADI.

Although, in this analysis, the interpretation of time trends was limited by overlapping 95% CI, the relative frequency of AIDS cases with RBP appeared to increase up to 1998, a calendar year in which, in industrialized countries, the downward trend in opportunistic infections (OIs) became evident among persons with HIV infection [13, 14]. Consistent with this finding, longitudinal data from a London clinic collected early after the introduction of HAART showed that the incidence of bacterial pneumonia in HIV-infected patients declined at a lower rate, as compared to other OIs [6]. One possible explanation

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for this contrasting pattern may reside in the fact that RBP, unlike *Pneumocystis carinii* pneumoniae (PCP) or toxoplasmosis, although more frequent in individuals with less than 200 CD4 cells/mm, can occur in patients with higher CD4+ cell counts [3]. In fact, the dramatic change observed since 1996 in the natural history of HIV disease is, at least in part, secondary to a rise in the CD4+ cell count observed in many patients who received adequate therapy. Moreover, the introduction of HAART could be associated with a reduction in the use of preventive drugs (such as trimethoprim–sulphamethoxazole and macrolides), which are active against many of the microorganisms responsible for bacterial pneumonia.

The present analysis suggested that, in recent years (i.e. 1999–2001), the proportion of RBP cases declined towards the level observed in the pre-HAART era. Theoretically, this finding could have been, at least partially, influenced by time trends of community-acquired bacterial pneumonia in the general population of these western European countries. However, we are not aware of comparable data required to assess the potential impact of such trends on the frequency of AIDS-associated RBP. Another likely explanation for the RBP time pattern observed among AIDS cases in western Europe is represented by the increasing proportion of persons unaware of having HIV infection who are diagnosed with AIDS [15, 16] and who cannot benefit from HAART and prophylaxis against OIs [5, 17]. Our findings, thus, reinforce the need for a wider offer of HIV voluntary testing and counselling in order to reach the significant number of persons unaware of their HIV status, particularly patients requiring care for illnesses often associated with HIV infection, like bacterial pneumonia [18]. Moreover, OIs occur more frequently in HIV-infected patients who are non-responders to HAART, and several findings in the last few years are suggesting an increasing number of AIDS cases attributable to HIV treatment failures [17].

The strong relationship between AIDS-associated RBP and use of intravenous drugs observed in this study has been already established [2–4]. Since it was not feasible to identify potential effect modifiers among the evaluated risk factors for RBP, we tried to highlight the role of each of them separately in IDUs and in the other HIV transmission categories. We are aware that this approach substantially reduces the statistical power of tests of association, and that it increases the false-negative error rate. Bearing in mind such methodological drawbacks, our analysis confirmed a lack of association between age, broad geographic areas of western Europe and the presence of RBP as ADI, while the above-mentioned time trends were particularly marked among IDUs.

Moreover, the apparent increased frequency of RBP in southern Europe, compared to northern Europe, probably reflects the predominance of cases attributable to the use of intravenous drugs in such countries [8]. Although data from eastern European countries were excluded from the analysis of determinants of AIDS-associated RBP, in eastern Europe the frequency of RBP among IDUs (15·2%) was significantly higher ($P<0{\cdot}001$, χ^2 test) than among non-IDU AIDS cases (4·9%) (data not shown in tables). Overall, these results further stressed the strong association between use of intravenous drugs and RBP.

Others have already observed that women with HIV infection and AIDS are more likely to be diagnosed [19] or to die [20] with RBP than men. In this study, we confirmed such higher risk and we observed that the excess risk was concentrated in IDU women, who had a 40% higher risk of RBP than IDU men. This indication (i.e. that the use of intravenous drugs is a strong determinant of RBP, particularly in women) is in accordance with longitudinal data from an Italian study conducted among HIV-positive and HIV-negative IDUs showing that women IDUs had a 1·4-fold higher risk of community-acquired pneumonia than men irrespective of HIV antibody status (Boschini A, et al., personal communication). We have no plausible explanation for this association, but its consistency across different data sources and study designs warrants further investigation.

At univariate analysis, AIDS cases diagnosed in eastern Europe showed a significantly higher proportion of RBP than those diagnosed in western Europe, with a marked heterogeneity within eastern European countries. We are not aware of previous studies of AIDS-associated RBP in eastern Europe, and the interpretation of such a pattern remains uncertain. The most likely explanation for this is that certain eastern European countries had a greater propensity to diagnose RBP, e.g. Ukraine, where 14% of cases had RBP as ADI and these RBP represented 69% of all RBP diagnosed in eastern European countries. In fact, after the exclusion of Ukraine from the analysis, there was no statistically significant difference in the frequency of RBP between eastern Europe and western Europe.

In addition to limitations specific for RBP, such as the one mentioned above, AIDS surveillance data

have methodological drawbacks that should be taken into account. For instance, different degrees of completeness of the national AIDS surveillance system across European countries are well known and have been discussed in previously [9, 21], although it is unlikely that they have differentially affected the association between RBP as ADI and the variables under investigation.

In conclusion, this statistical analysis of European AIDS surveillance data showed that RBP constitute a common ADI, and it confirmed that use of intravenous drugs is, by far, the most important determinant of its occurrence. The unchanged importance of RBP as ADI over time underscores the need to identify HIV-infected persons, particularly IDUs, as early as possible, to provide them with comprehensive care, and to concentrate efforts to improve adherence to antiretroviral therapies as a means to reduce the occurrence of RBP. Finally, literature data still provides conflicting results in support of the administration of pneumococcal vaccine in HIV-positive patients [22]. The possible role of available or of newly developed vaccines against pneumococcal diseases in reducing the incidence of RBP in HIV-infected persons needs further studies.

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