

Sex (age at onset of AECP, years)	Time between onset of AECP and cancer	Site and type of cancer	Outcome (months between diagnosis of cancer and death)
M (62)	+ 8 years	Lung/large cell	Deceased (6)
F (85)	- 1 month	Colon/adeno	Alive
M (51)	+ 2 months	Lung/adeno	Deceased (0)
F (70)	- 8 months	Endometrial/adeno	Deceased (13)
M (60)	+ 6 months	Stomach/adeno	Deceased (16)
F (47)	+ 10 months	Stomach/adeno	Deceased (11)
F (76)	+ 14 months	Colon/adeno	Alive
F (59)	+ 12 months	Endometrial/adeno	Deceased (3)
F (39)	+ 11 months	Lung/adeno	Deceased (21)
M (66)	+ 1 month	Stomach/adeno	Deceased (10)

Adeno=adenocarcinoma

Summary data of AECP patients with cancer

observed which gave a RR of 7.7 (95% CI: 3.3–15.2). While 0–39 cancers were expected to occur in the latter cohort during their first year of observation, six cancers were observed which gave a RR of 15.4 (5.7–33.6). IgG antibodies to laminin 5 were not present in the serum of any controls.

Patients with AECP had an RR for cancer that was similar to that for malignancy among adults with dermatomyositis; as with dermatomyositis, the RR for cancer in these patients was particularly high in the first year of disease. Several older reports noted an association between “bullous pemphigoid” and cancer.⁴ Whereas several studies have dismissed this association, controversy persists and centers on seronegative patients with mucosal involvement.⁵ This potential association was suggested at a time when AECP was not distinguished from bullous pemphigoid, and when most AECP patients would have been thought to be seronegative (based on the lower sensitivity of assays previously used to detect autoantibodies). Accordingly, it is possible that the suggested association between “bullous pemphigoid” and cancer was based on cohorts including a disproportionate number of patients with AECP.

We considered several potential sources of bias. Ascertainment bias could have resulted in the preferential inclusion of patients at high risk of cancer for reasons unrelated to the primary risk factor under study (ie AECP). We thought this bias unlikely since all AECP patients were assembled before any suspected association between disease with cancer. Moreover, patients in this series were not watched more closely for cancer. Most cancers developed after patient enrollment and the relative proportion of patients with cancer was consistent throughout the study, (three cancers after enrolment of ten patients, six cancers after enrolment of 21 patients, and ten cancers in the entire cohort of 35). That 80% of patients with AECP who had cancer died within 21 months of cancer diagnosis also made it unlikely that the diagnosis of cancer in this cohort was fortuitous and early. The comparison of cancer incidence among AECP patients at tertiary care medical centres with that in the general population could have been an invalid comparison; however several studies found the incidence of cancer in patients with bullous pemphigoid (or other skin diseases) at tertiary care medical centers to be approximately 10%, well below the 29% incidence that we found.

We also considered the potential bias introduced by forms of treatment. Drugs commonly used in AECP patients (eg, glucocorticosteroids or cytotoxic drugs) can increase cancer risk. However, some patients had relatively mild disease and did not require treatment with such drugs. In those receiving glucocorticosteroids or cytotoxic drugs, the interval between the onset of AECP and cancer was so short that it was unlikely that the drugs caused the cancer. Moreover, cancers identified in AECP patients were solid cancers rather than lymphomas or leukaemias which are more commonly associated with exposure to such drugs.

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- 1 Yancey KB, Egan CA. Pemphigoid: clinical, histologic, immunopathologic, and therapeutic considerations. *JAMA* 2000; **284**: 350–56.
- 2 Domloge-Hultsch N, Gammon WR, Briggaman RA, Gil SG, Carter WG, Yancey KB. Epiligrin, the major human keratinocyte integrin ligand, is a target in both an acquired autoimmune and an inherited subepidermal blistering skin disease. *J Clin Invest* 1992; **90**: 1628–33.
- 3 Lazarova Z, Hsu R, Yee C, Yancey KB. Human anti-laminin 5 autoantibodies induce subepidermal blisters in an experimental skin graft model. *J Invest Dermatol* 2000; **114**: 178–84.
- 4 Schroeter AL. Pemphigoid and malignancy. *Clin Dermatol* 1987; **5**: 60–63.
- 5 Hodge L, Marsden RA, Black MM, Bhogal B, Corbett MF. Bullous pemphigoid: the frequency of mucosal involvement and concurrent malignancy related to indirect immunofluorescence findings. *Br J Dermatol* 1981; **105**: 65–69.

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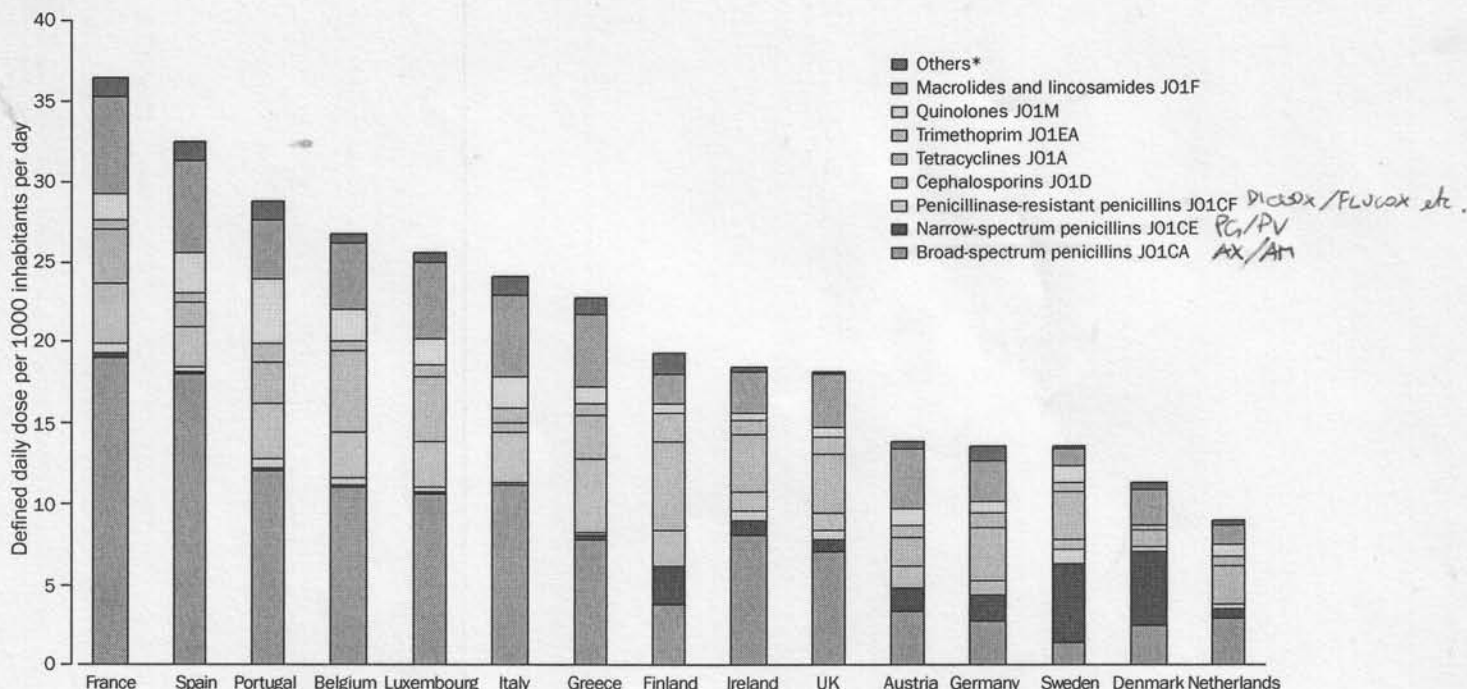
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Variation in antibiotic use in the European Union

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Data on antibiotic use are not publicly available in most European Union countries. We obtained data for non-hospital antibiotic sales for 1997 from the 15 member states and analysed these according to the Anatomic Therapeutic Chemical classification system, and expressed them as defined daily doses per 1000 people per day. Sales of antibiotics varied more than four-fold: France (36.5), Spain (32.4), Portugal (28.8), and Belgium (26.7) had the highest sales, whereas the Netherlands (8.9), Denmark (11.3), Sweden (13.5), and Germany (13.6) had the lowest. There was also profound variation in use of different classes of antibiotics. Detailed knowledge of antibiotic use is necessary to implement national strategies for optimum antibiotic use, and to address the threat posed by resistant microorganisms. International efforts are needed to counteract the growing problem of antimicrobial resistance.¹ Although antibiotic use at population level is probably an important risk factor,² data on antibiotic sales have not been publicly available and few international comparisons have been made. We have assessed and compared non-hospital use of antibiotics in the 15 member states of the European Union (EU). The term antibiotics encompasses both semisynthetic derivatives of antibiotics and wholly synthetic compounds used as antibacterial agents—eg, sulphonamides, trimethoprim, and fluoroquinolones.

Data for national sales of antibiotics in 1993 and 1997 were purchased from Institute for Medical Statistics (IMS), Health Global Services, UK, for 13 of the 15 EU countries. This private company gathers data from different sources including manufacturers, wholesalers, pharmacies, prescribing doctors, and hospitals, and calculates national estimates. Data from Sweden and Denmark were obtained from the National Corporation of Swedish Pharmacies and the Danish Medicine Agency, respectively. The National Corporation of Swedish



Outpatient antibiotic sales in 1997 in the European Union

*Includes sulphonamides, penicillinase-resistant penicillins, amphenicols, aminoglycosides, and glycopeptides.

Pharmacies collect, store, and compile data on all drugs dispensed in Swedish pharmacies, all of which belong to this corporation. Data from Denmark were available only for 1997 and included all outpatient sales from community pharmacies. Hospital sales were obtained from nine countries and accounted for 7–15% of total sales in each country. Because hospital data was not available from other countries, only non-hospital sales were used in the final analysis.

Swedish and Danish data were obtained as defined daily dose according to the Anatomic Therapeutic Chemical classification system defined by WHO Collaborating Centre for Drug Statistics Methodology.³ Defined daily dose is a unit based on the average daily dose used for the main indication of the drug. Sales data from Institute for Medical Statistics Health were examined and adjusted according to the Anatomic Therapeutic Chemical classification. Antibiotics for systemic use (Anatomic

Therapeutic Chemical J01) only were included in the subsequent analysis. To make comparison easier, the amount of antibiotic (kg) was converted to defined daily dose (where possible). For antibiotics not given a defined daily dose by WHO, we used the common daily dose in published work. Where such an estimate was not possible (less than 0.01% of total), we excluded data from analysis.

Oral defined daily dose was used for antibiotics with different routes of administration. For antibiotics marketed both alone and in combinations (eg, trimethoprim and sulphonamides), amounts of the individual compounds were accounted for separately. For antibiotics combined with a β lactamase inhibitor, only the amount of the antibiotic was included. We could compare publicly available data⁴ and IMS data on total non-hospital antibiotic use only in Finland. The two sources differed by less than 11%, and showed a similar distribution of antibiotic classes. The number of inhabitants in the EU

	Broad-spectrum penicillins J01CA	Narrow-spectrum penicillins J01CE	Penicillinase resistant penicillins J01CF	Cephalosporins J01D	Tetracyclines J01A	Trimetho- prim J01EA	Quinolones J01M	Macrolides and lincos- amides J01F	Others*	Total
Austria	3.23	1.53	0.01‡	1.30	1.81	0.69	1.16	3.65	0.42	13.80
Belgium	10.96	0.21	0.36	2.85	5.09†	0.59	1.95	4.06	0.65	26.72
Denmark	2.39	4.57	0.34	0.02‡	0.98	0.30‡	0.22‡	1.97	0.56	11.35
Finland	3.78	2.30	0.07	2.11	5.50	1.87†	0.52	1.86	1.33†	19.34
France	18.97†	0.31	0.58	3.75	3.38	0.55	1.72	5.98†	1.27	36.51†
Germany	2.67	1.59	0.02	0.89	3.26	0.93	0.75	2.54	0.93	13.58
Greece	7.74	0.37	0.02	4.68†	2.69	0.64	1.04	4.50	1.01	22.69
Ireland	8.03	0.87	0.63	1.23	3.50	0.92	0.38	2.50	0.28	18.34
Italy	11.20	0.02‡	0.02	3.21	0.56‡	0.87	1.93	5.07	1.11	23.99
Luxembourg	10.58	0.17	0.23	2.86	4.01	0.70	1.61	4.71	0.71	25.58
Portugal	12.08	0.06	0.71	3.28	2.63	1.10	4.04†	3.69	1.24	28.83
Spain	18.01	0.08	0.39	2.48	1.42	0.59	2.48	5.87	1.12	32.44
Sweden	1.36‡	4.85†	0.99†	0.59	2.97	0.57	1.01	0.97‡	0.20	13.51
The Netherlands	2.90	0.61	0.16	0.12	2.35	0.57	0.70	1.24	0.31	8.96‡
UK	6.93	0.78	0.68	0.98	3.66	1.12	0.54	3.22	0.13‡	18.04

Numbers are defined daily dose per 1000 inhabitants per day. *Includes sulphonamides, amphenicols, aminoglycosides, and glycopeptides. †Highest defined daily dose. ‡Lowest defined daily dose.

Outpatient antibiotic sales in 1997 in the European Union

was obtained from Eurostat,⁵ enabling us to convert sales data to defined daily dose per 1000 inhabitants per day.

Seven countries showed an increase in antibiotic use of less than 4% between 1993 and 1997. Large increases were noted in Italy (34%) and Luxembourg (12%). A reduction in antibiotic use was seen in five countries: Sweden had the largest (21%) and Greece the smallest (4%). In 1997, there was a more than four-fold variation between countries in non-hospital use of antibiotics. France had the highest use, and the Netherlands, the lowest (figure, table).

In 11 of the 15 countries, the most commonly used antibiotic was broad-spectrum penicillin, which varied between 56% (Spain) and 20% (Germany) of total sales. In Finland the most common drug was a tetracycline (28%), in Austria a macrolide (26%) and in Denmark and Sweden narrow-spectrum penicillins (40% and 36%, respectively). Total defined daily dose per 1000 inhabitants of all β lactam antibiotics (penicillins and cephalosporins) was six times higher in France (23.0) than in Netherlands (3.6). Cephalosporins were used most in Greece (4.7) and least in the Netherlands (0.12). The highest use of tetracyclines was in Finland (5.5). Quinolones were most widely used in Portugal (4.0) (table).

The most important finding in this analysis was the great variation in outpatient antibiotic use. The large variation is unlikely to be caused by differences in frequency of bacterial infections. The pronounced differences between Belgium and the Netherlands are noteworthy because of the close proximity of the countries and their common language. In addition to physicians' and patients' attitudes to antibiotics, historical backgrounds, cultural and social factors, and disparities in health-care systems might also be important factors in determining prescribing patterns. We did not have sufficient data to describe between-country variability of dose regimens, length of treatment, or availability of antibiotics without prescription.

These results strengthen the view that antibiotics could be used more effectively in many countries. Further analyses of antibiotic use by age-group, setting, and indication are required. The threat posed by resistant microorganisms could be reduced if all countries gathered data on antibiotic prescriptions. We therefore encourage EU member states to challenge the IMS data presented in this study and to do comparable epidemiological studies on antibiotic prescribing and resistance.

- 1 Wise R, Hart T, Cars O, et al. Antimicrobial resistance is a major threat to public health. *BMJ* 1998; 317: 609-10.
- 2 Melander E, Ekdahl K, Jönsson G, Mölstad S. The frequency of penicillin-resistant pneumococci in children is correlated to the community-level utilisation of antibiotics. *Pediatr Infect Dis J* 2000; 19: 1172-77.
- 3 ATC Index with DDDs. Oslo: WHO Collaborating Centre for Drug Statistics Methodology, 1999.
- 4 Nordic Statistics on Medicines. Uppsala: Nordic Council on Medicines, 1997.
- 5 Demographic statistics. Brussels: Eurostat, 1997. (ISBN 92-828-0737-1)

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Western and eastern European trends in testicular cancer mortality

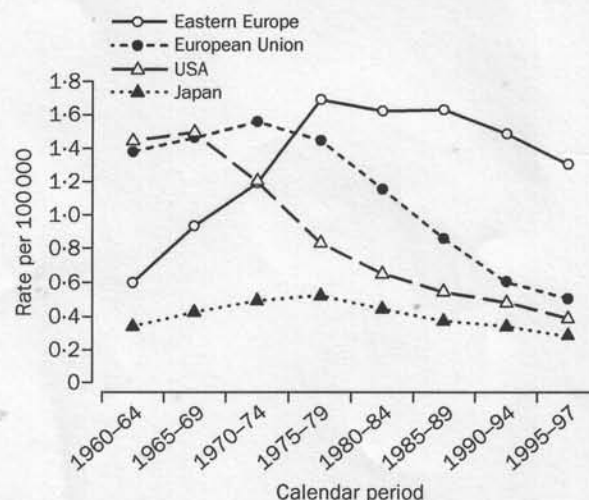
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Testicular cancer is curable if treated appropriately. We used national mortality data to compare specific death rates from the disorder in western and eastern Europe, the USA, and Japan. Testicular cancer mortality rates have fallen by about 70% in the USA and western Europe since the 1970s. In eastern Europe, however, death rates from testicular cancer have been declining only since the late 1980s, and at a much slower rate than that recorded elsewhere (about 20%). Consequently, many avoidable deaths, mainly in young adults, are still occurring in eastern Europe. Available effective treatment strategies for testicular cancer must be implemented in these countries.

Testicular cancer is generally curable if appropriate treatment is given. Despite a rise in the number of patients with testicular cancer since the 1970s, mortality rates have fallen in North America¹ and western Europe.² In men aged 45 years and younger, mortality rates fell by about a third in the late 1980s by comparison with rates registered in the 1970s—ie, 500 deaths per year in Europe are now prevented.²

Mortality rates began to decline in the 1980s in Poland, Czechoslovakia, and East Germany, but at a slower rate than that recorded in USA and western Europe.³ Trends in testicular cancer rates should, therefore, be monitored especially carefully in eastern Europe, to identify whether they continue to drop and at what pace. Cancer of the testis is a good indicator of progress in adult cancer treatment worldwide. Our aim was to do a systematic analysis of trends in testicular cancer mortality in Europe, the USA, and Japan.² We derived official death certification numbers from the WHO Database, and recoded them according to the Ninth Revision of the International Classification of Diseases. We obtained estimates of the resident population from the same WHO database. Age-standardised rates were based on the world standard population.^{1,2}

The figure shows trends in certified mortality from testicular cancer at age 20-44 years in four broad geographic areas. In the European Union (EU) and in six countries of central and eastern Europe, peak mortality rates (1.6/100 000 and 1.7/100 000, respectively) were reached in the 1970s. Since that date, mortality rates have fallen in this age group by 67% in the European Union. However, in eastern European countries, after a peak in the late 1970s, the decline in mortality has been



Trends in age-adjusted (world population) death certification rates from testicular cancers in men aged 20-44 years

Eastern European countries represented are Bulgaria, Czech Republic, Hungary, Poland, Romania, and Slovakia.