Papers

Prospective cohort study of predictors of incident low back pain in nurses

Julia Smedley, Peter Egger, Cyrus Cooper, David Coggon

Abstract

Objective: To assess the impact of handling patients and indicators of individual susceptibility on risk of low back pain in nurses.
Design: Prospective cohort study with follow up by repeated self administered questionnaires every three months over two years.
Setting: NHS university hospitals trust.
Subjects: 961 female nurses who had been free from low back pain for at least one month at the time of completing a baseline questionnaire.
Main outcome measures: Incidence of new low back pain during follow up and of pain leading to absence from work.
Results: Of 838 women who provided data suitable for analysis, 322 (38%) developed low back pain during follow up (mean 18.6 months), including 93 (11%) whose pain led to absence from work. The strongest predictor of new low back pain was earlier history of the symptom, and risk was particularly high if previous pain had lasted for over a month in total and had occurred within the 12 months before entry to the study (incidence during follow up 66%). Frequent low mood at baseline was strongly associated with subsequent absence from work for back pain (odds ratio 3.4; 95% confidence interval 1.4 to 8.2). After adjustment for earlier history of back pain and other potential confounders, risk was higher in nurses who reported frequent manual transfer of patients between bed and chair, manual repositioning of patients on the bed, and lifting patients in or out of the bath with a hoist.
Conclusions: Of the indicators of individual susceptibility that were examined, only history of back trouble was sufficiently predictive to justify selective exclusion of some applicants for nursing posts. The main route to prevention of back disorders among nurses is likely to lie in improved ergonomics.

Introduction

Low back pain is common in the general population, affecting more than 60% of people at some time in their lives and often causing appreciable disability.[1][2] It is particularly common in nurses. In a recent survey 10% of 1616 female nurses employed by a large NHS trust reported having lost more than a month in total from work because of back problems.[3] This high incidence is not only a burden on the many nurses who develop back pain but also a substantial cost to employing hospitals in lost efficiency, lost time, wasted training, and claims for industrial injuries.

The high rate of back disorders in nurses is associated with heavy physical workload,[4] particularly in lifting and moving patients,[5-7] and with adverse postures.[8][9] One approach to prevention, therefore, is through improvements in ergonomics and training, with avoidance or modification of the tasks that carry the highest risks. In addition, exclusion of people who are specially vulnerable to back injury from the most hazardous jobs may be justified. To optimise preventive strategies, however, more information is needed about the levels of risk associated with specific nursing activities and about the influence of individual susceptibility on risk. To examine these questions we carried out a two year longitudinal study of back pain in a cohort of nurses working in hospitals.

Subjects and methods

In 1993 we sent a baseline questionnaire to the 2405 hospital based nurses employed by Southampton University Hospitals Trust. The trust provides inpatient facilities in most clinical specialties other than psychiatry. The questionnaire asked about various non-occupational risk factors for back pain, including age, height, and weight; about activities in the nurse's current job; and about past and recent low back pain and other symptoms. Throughout the study low back pain was defined as pain in an area (illustrated in a diagram) between the 12th ribs and the gluteal folds that lasted for longer than a day and occurred other than in association with pregnancy, menstruation, or febrile illness. The results of a cross sectional analysis of this initial survey have already been published.[3]

Of 1616 women who completed the baseline questionnaire, 1336 (83%) agreed to take part in the longitudinal phase of the study. This paper presents results for the subset of 961 women who had not had any low back pain in the month before they completed the baseline questionnaire. Their ages ranged from 19 to 64 years with a mean of 38 years. Three hundred and forty seven were auxiliary or enrolled nurses, 573 were staff nurses or sisters, and 41 worked in administrative or specialist posts.

Each woman was sent a short follow up questionnaire every three months for two years. This

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Table 1 Completeness of follow up

Last questionnaire returned (months)	No of follow up questionnaires returned									Total
	0	1	2	3	4	5	6	7	8	
Baseline	118									118
3		101								101
6		12	54							66
9			14	32						46
12			4	10	41					55
15				2	10	37				49
18					3	14	33			50
21						2	3	25		30
24						3	13	67	363	446
Total	118	113	72	44	54	56	49	92	363	961

Table 2 Risk of low back pain during follow up according to age, height, and weight. For each outcome all risk estimates are mutually adjusted

		All low back pain		Low back pain leading to absence from work	
	No of women*	No of cases	Odds ratio (95% CI)	No of cases	Odds ratio (95% CI)
Age (years):					
< 30	226	85	1.0	24	1.0
30-39	251	88	0.8 (0.5 to 1.1)	22	0.6 (0.3 to 1.3)
40-49	193	88	1.1 (0.7 to 1.7)	28	1.1 (0.5 to 2.3)
≥ 50	141	51	0.8 (0.5 to 1.3)	14	0.6 (0.3 to 1.5)
Height (cm):					
< 158	183	66	1.0	20	1.0
158-162	214	72	1.0 (0.7 to 1.6)	17	0.7 (0.3 to 1.7)
163-165	134	48	1.0 (0.6 to 1.7)	17	1.2 (0.5 to 3.0)
166-169	172	78	1.7 (1.1 to 2.6)	23	1.5 (0.7 to 3.4)
≥ 170	108	48	1.6 (1.0 to 2.7)	11	1.1 (0.4 to 3.0)
Weight (kg):					
< 55.5	180	58	1.0	16	1.0
55.5-60.7	173	70	1.4 (0.9 to 2.2)	18	1.3 (0.5 to 3.1)
60.8-65.7	160	61	1.0 (0.6 to 1.7)	16	1.0 (0.4 to 2.5)
65.8-73.0	154	67	1.5 (0.9 to 2.4)	18	1.4 (0.6 to 3.6)
≥ 73.1	144	56	1.1 (0.7 to 1.9)	20	1.7 (0.7 to 4.2)

* Data missing on 27 women.

Table 3 Risk of low back pain during follow up according to earlier history of low back pain. All risk estimates are adjusted for age and height (classified as in table 2)

Earlier history of low back pain			All low back pain		Low back pain leading to absence work	
Total duration	Time since last symptoms	No of women*	No of cases	Odds ratio (95% CI)	No of cases	Odds ratio (95% CI)
None	—	460	120	1.0	35	1.0
1-6 Days	> 1 year	57	23	1.9 (1.1 to 3.1)	9	2.7 (1.1 to 6.6)
1-4 Weeks	> 1 year	59	26	2.2 (1.3 to 3.6)	12	3.5 (1.5 to 8.1)
≥ 1 Month	> 1 year	46	25	2.9 (1.7 to 5.0)	4	1.6 (0.5 to 5.1)
1-6 Days	≤ 1 year	45	24	3.4 (2.0 to 5.8)	3	1.2 (0.3 to 4.5)
1-4 Weeks	≤ 1 year	66	36	3.1 (2.0 to 4.9)	8	2.3 (0.9 to 5.6)
≥ 1 Month	≤ 1 year	92	61	6.1 (4.1 to 9.1)	21	7.3 (3.5 to 15.2)

* Data missing on 13 women.

asked about any change in manual handling activities and about the occurrence of any low back pain and resultant loss of time from work since the last contact. Women who did not respond to a questionnaire were sent a single reminder and were also mailed again at the next three monthly follow up. Those who failed to respond to two successive three monthly follow ups were regarded as having dropped out. At the end of the two year study period we checked the personnel records of those who dropped out and to those whose addresses were known we sent a further questionnaire asking about low back pain since the last contact and whether this had led to time off work.

In our analysis we used a discrete-time logistic-normal survival model to explore risk factors for the incidence of new low back pain during follow up.[10][11] This was chosen in preference to a proportional hazards model because symptoms were timed by calendar month, leading to multiple ties in the recorded onset of back pain. We examined the risk of all low back pain and of back pain leading to loss of time from work. The risk factors studied included constitutional and non-occupational attributes measured at baseline and occupational activities at the time back pain began.

Results

Table 1 summarises the response to follow up. Altogether, 843 women (88%) returned at least one follow up questionnaire, and 446 (46%) were still under follow up after 24 months. Addresses were available for 291 of the 397 women who dropped out, and 176 answered the final questionnaire at the end of the study period. Of these, 42 reported low back pain since dropping out, and 10 had had to take time off work because of back pain. Their two year cumulative incidence of symptoms (47%) was similar to that of those who remained under follow up throughout the study (46%). Table 1 also shows the numbers of questionnaires that women returned while under follow up. Further analysis is based on the 838 women who completed at least one follow up questionnaire and who provided usable information about back pain. Of these, 322 (38%) developed low back pain while under follow up (33.1 new episodes per 100 woman years), including 93 (11%) whose pain was bad enough to require time off work. Table 2 shows the risk of incident low back pain according to age, height, and weight. Symptoms were significantly more common in the tallest women, but this excess did not lead to much more absence from work. No clear trends were apparent in relation to age or weight. Neither was there an association with body mass index (data not shown).

All of the women included in the analysis had been free from back pain for at least one month at the time they completed the baseline questionnaire, but almost half had suffered from symptoms earlier. Table 3 summarises the risk of low back pain during follow up according to the duration of previous pain and the time since last symptoms. Risk tended to increase with the total duration of previous pain and was highest in those who had experienced symptoms during the year before entry to the study. Of 92 women who reported pain in the 12 months before answering baseline questionnaire and a history of pain for at least one month in total, 61 (66%) developed further symptoms during follow up (91.0 new episodes per 100 woman years) and 21 (23%) required time off work as a consequence.

Table 4 shows the association of incident low back pain with other complaints reported at baseline. After adjustment for age, height, and earlier history of back pain women with frequent low mood at baseline were significantly more likely to require time off work for back pain during follow up (odds ratio 3.4; 95% confidence interval 1.4 to 8.2).

When we looked at associations of back pain with occupational activities we adjusted for age, height, earlier history of back pain, and reports of other symptoms at baseline. Table 5 presents risk estimates for eight tasks commonly carried out by nurses that entail handling patients. With all low back pain as the outcome, exposure-response trends were observed for manual transfer of patients between bed and chair; transfer of patients between bed and chair with a hoist; manually moving patients around—that is, repositioning them—on the bed; and lifting patients in or out of the bath with a hoist. Associations with back pain leading to absence from work were less clear. Exposures to the various tasks tended to correlate with each other, and when we analysed all of the activities in a single statistical model risk estimates were generally reduced and less significant. The association with frequent transfers between bed and chair with a hoist completely disappeared. Otherwise, however, the pattern was similar.

Discussion

Most previous studies of low back pain have been retrospective or cross sectional. By using a longitudinal design we avoided having to rely on women's distant memory for the ascertainment of symptoms. Moreover, because risk factors were assessed before the onset of symptoms there was less opportunity for bias. In particular, any errors in the reporting of nursing activities would be expected to obscure rather than exaggerate associations with back pain. The incompleteness of follow up was a potential weakness, but we were able to contact almost half of those who dropped out at the end of the study, and their reported incidence of back pain was similar to that of women who remained under follow up.

Handling patients

Our results confirm the high incidence of back disorders among nurses and support a relation with tasks entailing the handling of patients. The need for nurses to carry out lifting and other manual handling tasks is determined by their patients' mobility, and, not surprisingly, many of the handling activities were intercorrelated. This made it more difficult to distinguish their individual contributions to risk, but the most hazardous activities seemed to be manual transfer of patients between bed and chair, manual repositioning of patients on the bed, and lifting patients in and out of the bath with a hoist. These findings accord with those of our earlier cross sectional survey in the same population.[3] Manual transfers and repositioning would be expected to stress the spine, but the association with lifting by hoist is harder to explain. It may reflect confounding by other tasks that are associated with bathing patients.

Other risk factors

Of the other risk factors examined, three—height, earlier history of back symptoms, and low mood—were significant predictors of incident back pain. The association with height was relatively weak and apparent only in the tallest women. This pattern has been observed previously in one study,[23] although not in others.[16 24 25]

Table 4 Risk of low back pain during follow up according to symptoms other than back pain at baseline. For each outcome all risk estimates are mutually adjusted and adjusted also for age, height, and earlier history of low back pain (classified as in tables 2 and 3)

Symptom	No of women*	All low back pain		Low back pain leading to absence from work	
		No of cases	Odds ratio (95% CI)	No of cases	Odds ratio (95% CI)
Headache:					
Never or occasional	676	250	1.0	75	1.0
Frequent	118	54	1.1 (0.7 to 1.5)	14	0.9 (0.5 to 1.8)
Period pain:					
Never or occasional	642	241	1.0	67	1.0
Frequent	152	63	1.2 (0.8 to 1.6)	22	1.6 (0.9 to 2.7)
Fatigue:					
Never or occasional	604	223	1.0	70	1.0
Frequent	187	81	1.2 (0.9 to 1.7)	19	0.9 (0.5 to 1.6)
Low mood:					
Never or occasional	744	275	1.0	78	1.0
Frequent	50	29	1.4 (0.8 to 2.3)	11	3.4 (1.4 to 8.2)
Stress:					
Never or occasional	673	247	1.0	77	1.0
Frequent	121	57	1.1 (0.8 to 1.6)	12	0.6 (0.3 to 1.2)

* Data missing on 47 women for one or more symptoms.

Table 5 Risk of low back pain during follow up according to occupational activities at time of onset. Risks are estimated separately for each outcome with adjustment for age, height, earlier history of low back pain, and symptoms other than back pain at baseline (classified as in tables 2, 3, and 4)

Frequency of activity in average working shift	No of women*	All low back pain		Low back pain leading to absence from work	
		No of cases	Odds ratio (95% CI)	No of cases	Odds ratio (95% CI)
Transfer patient on canvas and poles:					
0	517	201	1.0	63	1.0
1-4	222	82	0.8 (0.6 to 1.1)	21	0.7 (0.4 to 1.3)
≥ 5	44	17	1.4 (0.8 to 2.3)	5	1.5 (0.6 to 3.8)
Manually transfer patient between bed and chair:					
0	265	86	1.0	29	1.0
1-4	254	97	1.3 (0.9 to 1.7)	29	1.0 (0.6 to 1.8)
5-9	112	44	1.6 (1.1 to 2.3)	15	1.9 (1.0 to 3.7)
≥ 10	147	68	1.6 (1.1 to 2.3)	14	1.0 (0.5 to 1.9)
Transfer patient between bed and chair with hoist:					
0	591	214	1.0	68	1.0
1-4	158	69	1.5 (1.0 to 2.0)	18	1.2 (0.7 to 2.2)
≥ 5	26	9	1.6 (0.8 to 3.0)	1	0.7 (0.2 to 3.1)
Manually move patient around on bed:					
0	140	43	1.0	18	1.0
1-4	219	79	1.3 (0.8 to 1.9)	19	0.9 (0.4 to 1.8)
5-9	169	62	1.5 (1.0 to 2.3)	18	1.1 (0.5 to 2.3)
≥ 10	256	115	1.7 (1.1 to 2.5)	32	1.3 (0.7 to 2.5)
Manually lift patient up off floor:					
0	567	209	1.0	62	1.0
≥ 1	201	83	1.1 (0.9 to 1.5)	23	1.2 (0.7 to 1.9)
Lift patient from floor with hoist:					
0	708	267	1.0	78	1.0
≥ 1	63	24	1.3 (0.8 to 2.0)	8	1.5 (0.7 to 3.1)
Manually lift patient in or out of bath:					
0	680	261	1.0	75	1.0
≥ 1	92	30	0.9 (0.6 to 1.4)	11	1.4 (0.7 to 2.6)
Lift patient in or out of bath with hoist:					
0	536	189	1.0	52	1.0
1-4	202	87	1.4 (1.0 to 1.9)	29	2.0 (1.2 to 3.3)
≥ 5	32	15	2.1 (1.2 to 3.6)	4	1.3 (0.5 to 3.8)

* Data were missing on up to 70 women.

Key messages
• A history of back trouble, particularly if recent and prolonged, is highly predictive of new episodes of back pain
• There are grounds for excluding nurses with recent and prolonged back pain from the most physically demanding jobs
• Age, height, and weight are not sufficiently discriminatory for risk of back pain to influence selection and appointment of nurses
• Back pain is more common in nurses who lift and move patients frequently without the use of mechanical aids
• Controlled trials are needed to assess the benefits of ergonomic intervention aimed at prevention of back pain in nurses

Earlier history of back trouble was by far the strongest predictor of new symptoms. This is not surprising given the chronicity and recurrent nature of back disorders, but our data illustrate clearly how risk increases with both the duration and recency of previous symptoms. Other studies have also found that risk of back pain is increased in people with previous back trouble,[12 27-29] although the finding has not been universal.[21] Few have examined the influence of earlier history in more detail, but in Denmark Biering-Sørensen found that the probability of developing further pain within the next year fell from 76% in people with back pain in the past week to 28% in those who last had back pain more than five years earlier.[12]

Several previous studies have linked back complaints with low mood, stress, and job dissatisfaction.[9 13 30-34] Most, however, have been cross sectional, and it is unclear to what extent the psychological complaints were secondary to the back problem rather than antecedent. Our analysis, which was restricted to women who were free from pain at baseline and which adjusted for earlier history of back complaints, indicates that low mood does predict future back problems. It is notable that the association was particularly with back pain leading to loss of time from work. This might reflect an influence particularly on more severe disease or an effect on women's ability to cope when symptoms occurred.

Implications for prevention

Our findings have important implications for the prevention of occupational back pain, especially in nurses. One approach to prevention is through screening before employment and selective recruitment of staff who are at lower risk. Some hospitals have rejected applicants for nursing posts because they were obese, but we found no increase in risk of back disorders with weight or body mass index. Neither were the risks in taller women sufficient to warrant selective exclusion from employment. There may be justification for excluding women with a history of prolonged and recent back pain from the most physically demanding nursing jobs, but this would eliminate only a small proportion of cases.

Thus, the main route to preventing back disorders among nurses is likely to lie in improved ergonomics. In the past three years many NHS trusts have invested substantially in aids for handling patients, such as sliding sheets and hoists, but the outcome has yet to be properly assessed. Our findings point to nursing tasks that might most usefully be eliminated or modified.

There is now an urgent need to evaluate such ergonomic interventions in a controlled trial.

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Association of mutations in mannose binding protein gene with childhood infection in consecutive hospital series

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Abstract

Objective: To determine the extent to which mutations in the mannose binding protein gene predispose to childhood infection.
Design: Clinical details and genotype of mannose binding protein determined in consecutive children attending a paediatric department.
Setting: Inner city hospital paediatric service in London.
Subjects: 617 children attending hospital between October 1993 and August 1995.
Main outcome measure: Infection as the cause for attendance or admission in relation to mutations in the mannose binding protein gene.
Results: The prevalence of mutations in the mannose binding protein gene in children with infection (146/345) was about twice that in children without infection (64/272) (P < 0.0001). Increased susceptibility to infection was found in both heterozygotic and homozygotic children. 13 out of 17 children homozygotic for variant alleles presented with strikingly severe infections, including 6 with septicaemia.
Conclusions: The findings suggest that mutations in the mannose binding protein gene are an important risk factor for infections in children. Screening for such mutations should be included in the investigation of severe or frequent infections.

Introduction

Mannose binding protein is a calcium dependent lectin that plays an important part in innate immunity.[1] A common opsonic defect, associated with low serum concentrations of mannose binding protein,[2] is caused by mutations in codons 54 and 57 of the collagen domain that impair assembly of mannose binding protein homopolymer.[3-5] A third, less common, mutation has been identified in codon 52.[6] Repeated bacterial and fungal infections associated with these mutations have been reported.[3 7 8] Both these mutations and childhood infections are common, but there are no data on the extent to which such mutations predispose to childhood infectious disease. We examined a consecutive series of children attending a hospital paediatric service to determine whether mutations in the genes for mannose binding protein are an important risk factor for infection.

Methods

Patients and methods—Blood samples were obtained from consecutive children attending St Mary's Hospital. All were venesected for clinical reasons and surplus blood was spotted on to blotting paper (Guthrie cards). Samples were collected between October 1993 and August 1995. Diagnoses were confirmed from the notes and the clinical diagnostic codes after discharge. The children were classified, without reference to the mannose binding protein genotyping, as to whether the presenting illness was an infection according to the *International Classification of Diseases*, ninth revision. The study was approved by the ethics committee of Parkside Health Authority. Guthrie cards were autoclaved at 120°C for 7 minutes and stored at room temperature. Genotypes were determined by sequence specific oligonucleotide hybridisation.[9] Homozygosity was confirmed by DNA sequencing.

Statistical analysis—Calculations before the study showed that 150 children per group would enable us to detect a difference of 20% in the infected group with a power of 95% and significance of 5%. Prevalences of the mutations were determined by using the Hardy-Weinberg equation. Differences were evaluated with the χ^2 test, odds ratios, and 95% confidence intervals.

Results

A total of 345 children were admitted with infection; 272 children, who acted as controls, were admitted with various other diagnoses (table 1). Six hundred and ninety blood samples were collected. Data from 617 children (89%) were complete (table 2). Ages ranged from 0 to 18 years, and 58% (357) were male. The expected prevalence of the codon 52 mutation (0.04) was observed. The prevalences of codon 54 (0.1)

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Table 1 Diagnoses in 272 control children without infections

Diagnosis	No of children
Accidental injury	3
Failure to thrive	3
Haematuria	3
Heart disease	3
Rickets	3
Nut allergy	4
Uveitis	4
Headache	5
Joint effusions	5
Malignancy	5
Purpura, allergic	6
Systemic lupus erythematosus	6
Nephrotic syndrome	7
Neonatal jaundice	9
Epilepsy or convulsions	12
Chronic fatigue syndrome	12
Asthma	13
Surgery, various	14
Anaemia, various	17
Congenital abnormality	19
Pains, various sites	19
Prematurity	32
Miscellaneous*	68

*Diagnoses affecting fewer than three children.

Table 2 Details of genotypes for mutations in mannose binding protein gene in children presenting with infections and those without infections

	No of children	No with normal genes	Heterozygotic (codon)				Homozygotic (codon)							Total No with mutations	Gene prevalence (codon)			
			52	54	57	All	52	54	57	52+54	52+57	54+57	All		52	54	57	All
Controls	272	208	11	34	15	60*	0	0	1	1	1	1	4†	64	0.02	0.07	0.04	0.13
Children with infection	345	199	32	71	30	133*	0	3	0	4	4	2	13†	146	0.06	0.12	0.05	0.23
Total	617	407	43	105	45	193	0	3	1	5	5	3	17	210	0.04	0.10	0.05	0.18

*P<0.0001 for children with infection being heterozygotic.
†P=0.048 for children with infection being homozygotic.

Table 3 Infections in 133 children heterozygotic for mutations in mannose binding protein gene

Diagnosis	No of children
Osteomyelitis	3
Otitis media	4
Streptococcal infection	4
Urinary tract infection	4
Gastroenteritis	5
Cellulitis and abscess	8
HIV infection	8
Fever of unknown origin	14
Tonsillitis	14
Meningococcaemia	17
Chest infection	23
Miscellaneous*	29

*Infections affecting fewer than three heterozygotic children.

and codon 57 (0.05) mutations were lower than expected, but when we corrected for the ethnic composition of the sample (African and Caribbean 21%; white, Asian, and Oriental 79%) the expected prevalences for codon 54 in the Eurasian group (0.12) and for codon 57 in Afro-Caribbeans (0.22) were obtained. One child was homozygotic for codon 57 mutation. Three were homozygotic for codon 54 mutation, whereas the Hardy-Weinberg equation predicted that the number would be six. Fourteen were phenotypically homozygotic, having combinations of mutant 52, 54, or 57 alleles. Thus 17 (3%) were homozygotic for mutations in the mannose binding protein gene.

We examined the association of mutant gene alleles for mannose binding protein with infection. Of the 272 children without infections (controls), 64 carried variant alleles and 208 carried normal genes (wild type). In contrast, of the 345 children with infections,

146 carried variant alleles and 199 were wild type (table 2). The increased prevalence of variant alleles in infected children was highly significant (odds ratio 2.4; 95% confidence interval 1.7 to 3.4; P<0.0001). The ethnic composition of the infected and control groups was similar. When the ethnic groups were analysed separately a significant excess of variant alleles in infected children remained (data not shown). Table 3 gives details of the infections in heterozygotic children.

We examined whether variant alleles increased susceptibility to infection in both heterozygotic and homozygotic children (table 2): 60 controls were heterozygotic for variant alleles and 208 were wild type, whereas 133 with infection were heterozygotic for variant alleles and 199 were wild type (2.3; 1.6 to 3.4; P<0.0001). An increased prevalence of infection in heterozygotic children was observed when mutation data for codon 52 (3.0; 1.4 to 6.3; P=0.002), codon 54 (2.2; 1.4 to 3.5; P=0.0009), and codon 57 (2.1; 1.1 to 4.2; P=0.04) were analysed separately. The number of homozygotic children was smaller, but a significant difference was observed. Four controls were homozygotic for variant alleles compared with 13 children in the infection group (3.4; 1.0 to 11.4; P=0.048). Children homozygotic for the mutation presented with strikingly severe infections, including six with septicaemia (table 4).

We examined whether the risk of infection conferred by variant alleles was related to age. Variant alleles conferred significant susceptibility to infection in children aged less than 6 months (3.0; 1.0 to 9.0; P=0.05), in those aged 6-18 months (4.0; 1.0 to 17.0; P=0.03), and those aged over 18 months (2.4; 1.5 to 3.7; P=0.0001) (fig 1).

Table 4 Clinical details of children homozygotic for mutations in mannose binding protein gene

| Genotype	Sex	Age (months)	Clinical detail
Codon 52 + 54	M	106	Recurrent cellulitis and boils, surgical drainage; father and maternal uncle had boils
Codon 52 + 54	M	74	Recurrent, serious chest infections, persistent cough, low IgG3 and 4
Codon 52 + 54	F	94	Tetralogy of Fallot, cleft palate and lip, congenital ptosis
Codon 52 + 54	F	136	Transfusion associated HIV infection, pneumocystis, herpes zoster, recurrent chest infections
Codon 54 homozygote	M	10	Meningococcal sepsis
Codon 54 homozygote	F	79	Meningococcal sepsis
Codon 54 homozygote	F	26	Severe meningococcal sepsis
Codon 54 + 57	M	63	Severe meningococcal sepsis, skin grafting, avascular necrosis of hip
Codon 57 homozygote	M	27	Abdominal pain, sickle trait
Codon 54 + 57	M	0	Premature (born at 25 weeks' gestation); died
Codon 52 + 57	M	0	Premature; respiratory distress syndrome
Codon 52 + 57	F	53	*Haemophilus influenzae* septicaemia, recurrent tonsillitis
Codon 52 + 57	M	15	Pneumococcal septicaemia, sickle trait
Codon 52 + 57	M	12	Streptococcal infection, otitis media; born prematurely, growth retarded
Codon 52 + 54	F	28	Recurrent tonsillitis, bilateral chronic mucoid otitis media
Codon 54 + 57	M	81	Recurrent tonsillitis (six times a year for four years), bilateral otitis media, tonsillectomy
Codon 52 + 57	F	150	Recurrent tonsillitis (four times a year), tonsillectomy
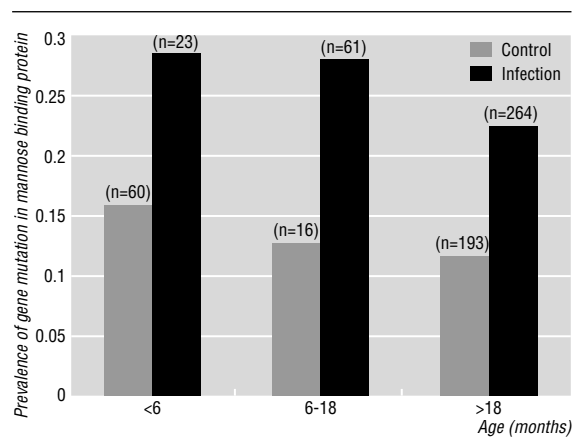
Fig 1 Prevalence of gene mutations in mannose binding protein in infected and control children from different age groups. Prevalence of mutations was significantly greater in infected children under 6 months (P=0.05), between 6 and 18 months (P=0.03), and over 18 months (P=0.0001)

Discussion

Mannose binding protein is an important component of innate or natural immunity.[1] Mutations in the mannose binding protein gene have been associated with recurrent infections.[3 7 8] Both childhood infections and mutations in this gene are common, but there are no data on the roles that the variant alleles have in the susceptibility of children to infection. Our study used concurrent controls and was not referenced to a historically selected adult control group. We obtained 345 samples from children with infections (56%) and 272 samples from non-infected (control) children (44%) from the same population. Most (89%) of the 617 samples were obtained in general paediatric wards and clinics, but many of the 51 (11%) with meningococcaemia or the 16 with HIV infection or AIDS reflected referrals to St Mary's as a centre for paediatric infectious disease.

The data show a striking and highly significant association of infection with mutant mannose binding protein genotypes (table 2). Mutant mannose binding protein alleles were present in about twice as many children with infections as in control children. This was not due to differences in the ethnic composition of the two groups as the association was observed when we analysed ethnic groups separately. This increased risk of infection is similar to that observed in an earlier study of children with an opsonic defect,[10] which is the functional consequence of mannose binding protein mutations.[3 4] In contrast, another study did not find that children who were heterozygotic for mutant mannose binding protein gene alleles were at increased risk of infection.[8] This discrepancy may be due to the use of an adult control group in that study rather than concurrent controls matched for age.

The prevalence of homozygotic alleles for mutant mannose binding protein gene in children was 3%, and most (13/17) had combinations of mutant 52, 54, or 57 alleles. Only three were homozygotic for codon 54 (0.005%), whereas the Hardy-Weinberg equation predicted that six should be. Our sample was not large enough to determine whether the difference was significant, but the data are consistent with other reports that populations are depleted of people

homozygotic for codon 54.[4 6 10] The reasons for this are obscure. It may be relevant that 13 of the 17 children homozygotic for variant alleles presented with serious infections, including six with septicaemia (table 4). Four of the homozygotic children had meningococcaemia, and this association is under further investigation. The association of severe tonsillitis and otitis media with homozygosity for mutant mannose binding protein alleles has been noted elsewhere.[8]

Low concentrations of mannose binding protein may be a particular risk factor between the ages of 6 and 18 months.[11] The data from our study, however, indicate that mannose binding protein mutations confer a significantly increased risk of infection at all ages in childhood (fig 1). It seems reasonable to conclude from this and other reports[7 8] that mannose binding protein gene mutations confer a lifelong risk of infection.

In conclusion, these data show that in a hospital population, children, whether heterozygotic or homozygotic for mannose binding protein gene mutations, are at increased risk of infection. The infections in the homozygotic children were particularly serious, suggesting that screening for these mutations should be included in the investigation of severe or frequent infections. Prospective controlled studies in the community are now needed to define the risk that mannose binding protein gene mutations confer.

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Is the clinical course of HIV-1 changing? Cohort study

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Abstract

Objective: To assess whether the clinical course of HIV infection has changed from 1985 to 1995.
Design: Cohort study.
Setting: Infectious diseases clinic.
Subjects: 285 patients recruited from September 1985 to January 1995 with ≤12 months between the dates of their last seronegative and first seropositive test result and with first follow up visit in the six months after seroconversion and at least 12 months' follow up. Patients were grouped according to the date of seroconversion.
Main outcome measures: Time to CD4 cell count of < 500, 400, and 200×10^6 cells/l and clinical outcome defining AIDS; variation in cell count per day between consecutive visits, and ratio between this variation and time from estimated date of seroconversion at each visit.
Results: The groups were similar in age, number with acute primary HIV infection, CD4 cell count at intake, and cell count at the beginning of antiretroviral treatment; they differed in sex ratio, risk factors for HIV, probability of CD4 cell decline to < 500, 400, and 200×10^6 cells/l, and risk of developing AIDS. Acute infection, seroconversion after December 1989, and serum β2 microglobulin > 296 nmol/l were independent predictors of poor clinical course. The speed of CD4 cell decline, expressed as cell variation divided by the number of days between consecutive visits, increased with more recent seroconversion $(P = 0.02)$. Ratio between the speed of CD4 cell decline and time from estimated date of seroconversion at each visit was also higher in the patients who seroconverted after December 1989.
Conclusions: The faster disease progression and the higher speed of CD4 cell decline at early stages in the patients with recently acquired HIV infection suggest changes in the clinical course of HIV infection.

Introduction

Increasing interest has recently focused on possible secular changes in the course of HIV infection.[1-7] In particular, researchers are interested in whether the calendar year of HIV seroconversion is associated with a specific pattern of CD4 cell trends and clinical evolution.

Some authors have found no change.[4 5] Findings in military staff with HIV infection have shown a rapid fall in CD4 cell count soon after seroconversion but no clear trend for changes in cell count by fixed time after seroconversion.[2 3] Similarly, a study of patients who seroconverted between 1984 and 1991 showed neither change in the course of infection nor an association between calendar year of seroconversion and time to CD4 cell count of $< 500 \times 10^6$ cells/l.[4]

There are, however, several limitations in these studies. Firstly, the study period was limited and included only the early 1990s. Consequently, recent changes in the course of HIV disease were not examined. Secondly, the study population usually comprised homosexual or bisexual men, with little or no information on other risk groups; analysis restricted to only one transmission category could lead to biased conclusions. Thirdly, most investigations have been based on CD4 cell counts determined in different laboratories. Hence, despite the improvements obtained by adjustment, interlaboratory variations might be responsible for measurement bias. Finally, little is known about CD4 cell counts before seroconversion and CD4 counts at the start of antiretroviral treatment. Several factors may complicate the estimate of the impact of the treatment interventions in patients infected with HIV (for instance, use of different drugs and regimens, use of associated treatments, dissimilar duration of treatment), but analytical approaches that do not consider the CD4 cell count relative to the initiation of antiretroviral treatment might lead to biased results concerning the progression of HIV disease.

Because changes in the course of HIV infection could affect clinical management of newly infected patients, as well as having repercussions on the global epidemiology of HIV infection and on healthcare resources, we examined whether the course of HIV disease has changed in recent years. We divided our 10 year cohort of 285 patients positive for HIV antibody with known date of seroconversion into four groups according to the calendar date of their seroconversion, and we then compared the probabilities of CD4 lymphocyte count of < 500, 400, and 200×10^6 cells/l, progression to AIDS, and the speed of decline of CD4 cell count.

Patients and methods

Recruitment and inclusion criteria

From September 1985 to January 1996, 4134 patients at risk for hepatitis, sexually transmitted diseases, and HIV infection were tested for antibody to HIV at the

clinic of infectious diseases, University of Turin. Those with positive test results who had had negative results at some time in the previous 12 months were enrolled in a prospective study to evaluate the course of HIV infection. Additional criteria for inclusion were a first CD4 cell count within six months of the first positive test results and a follow up of at least 12 months after entry. The 285 cohort members were divided into four groups according to their date of seroconversion: 75 subjects seroconverted between September 1985 and December 1987, 60 between January 1988 and December 1989, 69 between January 1990 and December 1991, and 81 between January 1992 and January 1995.

Definitions and study outcomes

In patients who had no symptoms at conversion we assumed the date of entry (estimated date of seroconversion) to be the midpoint between the dates of the last negative and the first confirmed positive test results. In the patients with acute primary HIV infection the entry was considered as the date of the beginning of the symptoms.

The end points were the dates of the first confirmed CD4 count of <500, 400, and 200×10^6 cells/l and the date of the first clinical outcome defining AIDS. Confirmed decline of CD4 cell count was defined as a decrease to below the relevant cell count determined in three consecutive samples. AIDS patients recorded in this report fulfilled the revised AIDS case definition.[8] To implement the analysis and to limit time lag effects we performed a cross check with the national AIDS registry.

Laboratory analysis

Antibody to HIV was assessed by enzyme immunoassay, with confirmation by western blot. HIV antigen (p24) was detected by commercially available enzyme immunoassay. CD4 lymphocyte subsets were measured by flow cytometry in a laboratory that used identical analytic procedures.

Statistical analysis

To assess differences between the four groups positive for HIV we used Kruskal-Wallis one way analysis of variance for the continuous variables and χ^2 tests for the categorical variables. Results for continuous variables are expressed as median (range). To estimate the progression rates we used the Kaplan-Meier survival method, and comparison between progression curves was tested for significance with log rank test for two sample comparison and with Gehan's test or Bres-

low's test for multiple sample comparison.[9] A multivariate analysis was carried out to identify the independent cofactors of disease progression by using Cox's proportional hazards model to calculate the hazard ratio of reaching the end points. The variables included in the hazards analysis were sex, age, education, occupation, transmission category, smoking status, drinking status, life style, annual income, use of minor tranquillisers, duration of injecting drug use, history of sexually transmitted diseases, history of primary acute HIV infection, calendar time of seroconversion to HIV, baseline laboratory measurements (CD4 and CD8 cell count, serum IgA, $\beta2$ microglobulin and 5'-neopterin concentrations, and HIV p24 concentration). A backward stepwise selection of the covariates was used in constructing the model. The statistical criterion used to select the best model was the partial likelihood ratio test. The variable "calendar time of seroconversion" was divided into four dummy variables representing the four study periods of seroconversion. As a preliminary step, only the resulting four groups were included in the Cox's proportional hazards analysis, and we tested three groups against the reference group. Afterwards we included all the study variables in the analysis, using the September 1985 to December 1987 group as the reference group. Data were processed with STATISTICA version 5.0[10] and SPSS version 6.0.[11]

Table 1 Baseline characteristics of the four groups of patients with HIV infection according to different time of seroconversion. Values are numbers (percentages) of patients unless stated otherwise

	Sept 1985-Dec 1987	Jan 1988-Dec 1989	Jan 1990-Dec 1991	Jan 1992-Jan 1995
No who seroconverted	75 (26.3)	60 (21.0)	69 (24.2)	81 (28.4)
Sex ratio (men:women)	5.8	1.6	2.6	2.4
Median (range) age at entry (years)	27 (18-58)	26.5 (19-58)	27 (19-52)	27 (17-61)
Injecting drug users	45 (60.0)	30 (50.0)	52 (75.4)	36 (44.4)
Homosexual contacts	23 (30.7)	10 (16.7)	11 (15.9)	20 (24.7)
Heterosexual contacts	6 (8.0)	19 (31.7)	6 (8.7)	25 (30.9)
Other risk	1 (1.3)	1 (1.7)	0	0
Acute primary HIV infection	12 (16.0)	9 (15.0)	12 (17.4)	18 (22.2)
Median (range) time between negative and positive results (days)	217 (28-337)	214 (26-327)	184 (31-321)	192 (21-329)
Median (range) CD4 count ($\times 10^6$ cells/l)	639 (117-1317)	548 (134-1715)	663 (123-1696)	530 (109-1325)
Patients with p24 antigenaemia > 10 ng/l	16 (21.3)	10 (16.7)	16 (23.2)	12 (14.8)
Median (range) CD4 count ($\times 10^6$ cells/l) at start of treatment	286 (167-377)	289 (149-368)	247 (234-346)	257 (168-349)

Table 2 Cumulative estimates of decline in CD4 cell count and progression to AIDS in four groups of patients with HIV infection according to time of seroconversion.* Values are percentages of patients

Time since conversion (years)	$<500 \times 10^6$ cells/l				$<400 \times 10^6$ cells/l				$<200 \times 10^6$ cells/l				AIDS			
	Group 1	Group 2	Group 3	Group 4	Group 1	Group 2	Group 3	Group 4	Group 1	Group 2	Group 3	Group 4	Group 1	Group 2	Group 3	Group 4
1	12.2	17.1	13.8	49.4	12.3	15.5	4.7	39.9	4.1	—	1.6	3.1	—	—	—	2.0
2	19.2	29.6	36.9	66.9	15.0	26.1	19.4	55.7	5.5	3.6	4.9	24.4	2.8	1.9	1.7	6.0
3	22.0	44.4	50.5	—	19.3	40.9	37.8	—	8.4	11.0	8.4	33.4	4.2	7.4	5.1	10.5
4	34.8	61.0	68.1	—	29.3	48.3	56.6	—	14.2	16.7	28.0	—	9.9	9.3	12.6	—
5	49.0	64.8	—	—	40.5	54.6	68.2	—	21.5	24.8	46.6	—	15.6	11.4	27.2	—
6	66.5	71.4	—	—	52.1	57.2	—	—	27.5	30.2	—	—	23.0	22.6	—	—

*Group 1, September 1985-December 1987; group 2, January 1988-December 1989; group 3, January 1990-December 1991; group 4, January 1992-January 1995.

Table 3 Matrix of P values in log rank test and Cox's proportional hazards analysis with hazards ratios (95% confidence intervals)* for group by group comparison of probability of decline to CD4 cell count <400 × 10^6/l (top right) and <500 × 10^6/l (bottom left)

	Sep 1985-Dec 1987	Jan 1988-Dec 1989	Jan 1990-Dec 1991	Jan 1992-Jan 1995
Sep 1985-Dec 1987		0.10	0.0067	0.0006
	—	0.10	0.0040	< 0.0001
		1.43 (0.93 to 2.19)	1.96 (1.24 to 3.09)	4.42 (2.64 to 7.41)
Jan 1988-Dec 1989	0.089		0.16	0.0058
	0.129	—	0.18	< 0.0001
	1.35 (0.92 to 2.0)		1.37 (0.86 to 2.18)	3.10 (1.84 to 5.20)
Jan 1990-Dec 1991	0.0014	0.14		0.0007
	0.0007	0.055	—	0.0011
	2.06 (1.36 to 3.13)	1.52 (0.99 to 2.35)		2.26 (1.39 to 3.68)
Jan 1992-Jan 1995	<0.0001	0.0001	0.0002	
	< 0.0001	< 0.0001	< 0.0001	—
	5.63 (3.55 to 8.92)	4.16 (2.61 to 6.65)	2.73 (1.76 to 4.23)	

*Refer only to comparisons between later and earlier calendar time of seroconversion as baseline group.

Results

From September 1985 to January 1995, 285 patients were included in the study. The median age at seroconversion was 27 (range 17-61) years; 208 (73%) were men. According to the risk factors 163 (57%) were injecting drug users, 64 (22%) male homosexuals, 56 (20%) heterosexuals, and 2 (1%) had other risk factors. Fifty one patients (18%) had acute primary HIV infection. The median time in days was 182 (range 21-337) between the last negative and the first positive test result; 1710 (363-3672) for length of follow up; 91 (1-168) between the first positive test result and first follow up visit; and 83 (36-182) for the interval between visits, which was similar in the different risk groups.

Table 1 shows the baseline characteristics of the four groups of patients divided according to their date of seroconversion date. When we compared the baseline characteristics of the four groups we found differences in sex and in transmission by injecting drug use and by heterosexual contacts (P = 0.019, P = 0.0010, and P = 0.00003 respectively). HIV infection through drug addiction and heterosexual sex were symmetrically distributed throughout the study period. In the mid-1980s most of those who seroconverted were men, but the number of subjects infected heterosexually and the number of women, particularly those infected heterosexually, increased progressively. At the first visit, 54 patients (19%) had circulating HIV p24 antigen > 10 ng/l. The groups did not differ in the intervals between the last negative and the first positive test result or in the temporary loss to follow up or in socioeconomic, lifestyle, and laboratory measurements. Overall, 110 (60%) patients began a course of antiretroviral treatment at some time during follow up. The four groups did not differ in CD4 cell count at the start of antiretroviral treatment, and all subjects used nebulised pentamidine as prophylaxis against *Pneumocystis carinii* pneumonia when the CD4 count fell to < 200 × 10^6 cells/l. CD4 cell counts from before seroconversion were available in 53 patients (19%), and the groups did not differ in the CD4 cell count before seroconversion. Thirty patients (46%) who seroconverted between September 1985 and December 1987, 14 (22%) between January 1988 and December 1989, 17 (26%) between January 1990 and December 1991, and 4 (6%) between January 1992 and January 1995 developed AIDS.

When we compared the probability curves of CD4 lymphocyte count falling to < 500, 400, and 200 × 10^6 cells/l and AIDS progression, patients who seroconverted after December 1989 showed earlier declines and faster progression than did those who seroconverted before (P < 0.0001, P = 0.0001, P = 0.0037, and P = 0.19, respectively). Figure 1 shows the probability curves of CD4 lymphocyte count falling to < 500, 400, and 200 × 10^6 cells/l and AIDS progression in the four groups. Table 2 shows the cumulative estimates of the cell count falling to the end points and the progression to AIDS by time intervals from the seroconversion in the four groups. Tables 3 and 4 show the log rank test

Table 4 Matrix of P values in log rank test and Cox's proportional hazards analysis with hazards ratios (95% confidence intervals)* for group by group comparison of probability of decline to CD4 cell count <200 × 10^6/l (top right) and progression to AIDS (bottom left)

	Sep 1985-Dec 1987	Jan 1988-Dec 1989	Jan 1990-Dec 1991	Jan 1992-Jan 1995
Sep 1985-Dec 1987		0.37	0.0063	0.031
	—	0.72	0.0023	0.00010
		1.11 (0.61 to 2.04)	2.55 (1.39 to 4.65)	5.62 (2.53 to 12.50)
Jan 1988-Dec 1989	0.42		0.0083	0.014
	0.78	—	0.010	0.0001
	1.10 (0.55 to 2.19)		2.28 (1.22 to 4.30)	5.05 (2.23 to 11.43)
Jan 1990-Dec 1991	0.031	0.0068		0.037
	0.0083	0.022	—	0.034
	2.61 (1.28 to 5.34)	2.37 (1.13 to 5.0)		2.21 (1.06 to 4.61)
Jan 1992-Jan 1995	0.25	0.20	0.18	
	0.019	0.031	0.39	—
	4.38 (1.27 to 15.15)	3.98 (1.13 to 14.0)	1.67 (0.51 to 5.49)	

*Refer only to comparisons between later and earlier calendar time of seroconversion as baseline group.
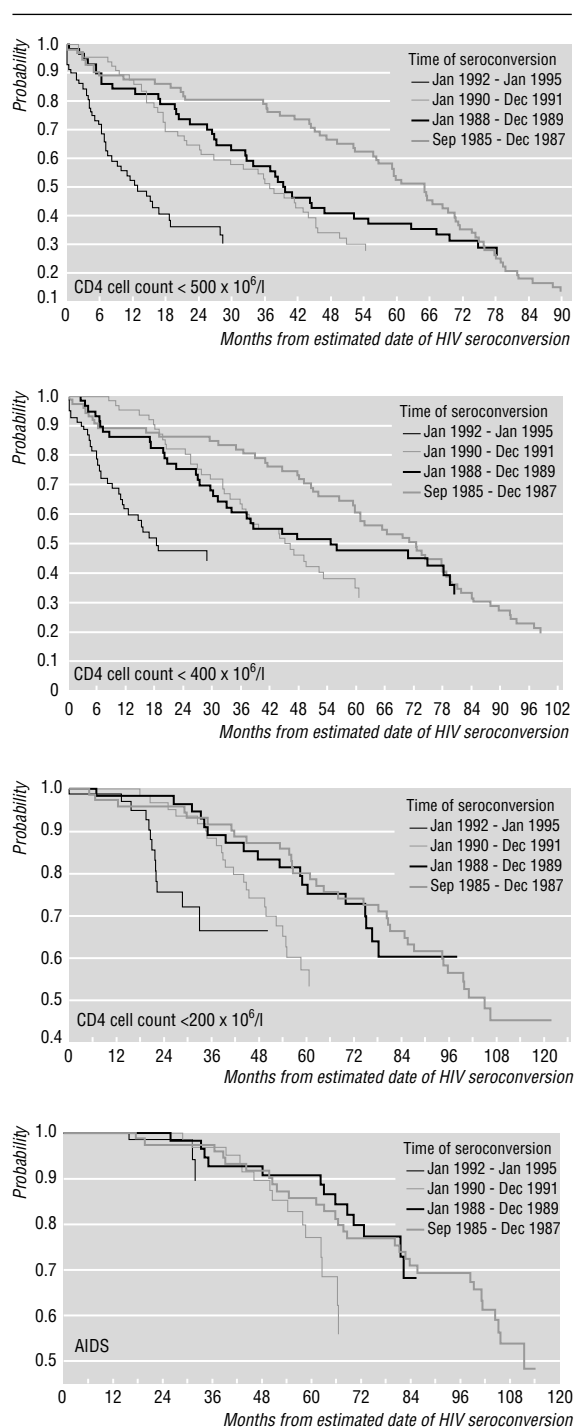
Fig 1 Survival curves for subjects according to period since estimated time of seroconversion to HIV expressed as probability of not having condition

P value and Cox's model P value relative to the group by group comparison of the probability of CD4 cell decline and progression to AIDS.

Cox's proportional hazards models confirmed seroconversion to HIV after December 1989, seroconversion associated with acute primary HIV infection, and serum β2 microglobulin >296 nmol/l at entry to be the most significant independent predictors of poor evolution (table 5).[5] Patients who seroconverted through intravenous drug use and those who acquired HIV sexually did not differ in the CD4 cell decline and progression to AIDS, and this finding was confirmed in the multivariate model.

The rate of CD4 cell decline, expressed as a ratio of CD4 cell variation to the time between visits in days was different in the four groups, with higher values in those who seroconverted after December 1989 (hazard ratio 0.48 (95% confidence interval 0.0065 to 9.21) v 0.50 (0.0025 to 6.71) v 0.65 (0.0068 to 28.9) v 0.53 (0.13 to 22.15); P = 0.020). Likewise, the ratio between the rate of CD4 cell decline and time from estimated date of seroconversion at each visit differed in the four groups (1.52×10^{-3} v 1.145×10^{-3} v 3.317×10^{-3} v 4.97×10^{-3}, P = 0.000042). When we compared patients who seroconverted more recently with those who seroconverted before December 1989, the recently infected subjects showed higher rates of CD4 cell decline at the shortest intervals from the date of estimated date of seroconversion.

The initial CD4 cell loss was different in the four groups (fig 2). In particular, the difference between groups in the rate of daily decline of CD4 cell count at 180 days after estimated date of seroconversion was different, being higher in the patients who seroconverted after December 1989 (1.33 (0.45 to 5.19) cells/day v 2.25 (0.74 to 3.86) v 3.19 (0.20 to 9.19) v 4.52 (0.10 to 22.15); P = 0.025). The rate of daily CD4 cell decline at 360 days after estimated date of seroconversion also differed, being higher in the patients who seroconverted between January 1990 and December 1991 (1.04 (0.09 to 5.52) cells/day v 0.64 (0.05 to 1.99) v 2.0 (0.36 to 28.9) v 0.94 (0.01 to −3.7); P = 0.0034).

Discussion

To study the possible influence of the calendar time of seroconversion on the course of HIV infection we assessed whether the subjects who seroconverted in different time periods between September 1985 and January 1995 had distinct patterns of disease progression. Although all patients had similar immunological characteristics at entry, CD4 cell counts started differing at early stages of the infection, and this finding was solely associated with the higher speed of decline of CD4 cell counts in those who seroconverted after December 1989. Consistent with previous reports, our data show that the first 12 months after seroconversion are extremely critical for the future course of HIV disease and that a higher rate of daily depletion of CD4 cells within the first year of the infec-
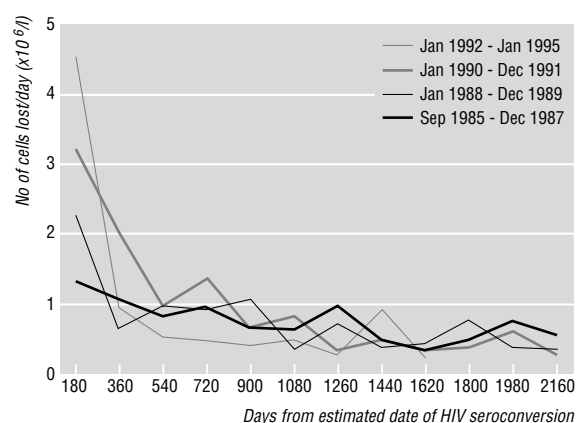

Fig 2 Rate of daily loss of CD4 cells according to estimated time since seroconversion

Table 5 Cox's proportional hazards analysis of factors associated with different biological and clinical end points at entry among 285 patients who seroconverted between September 1985 and January 1995. Values are hazard ratios (95% confidence intervals)

Variable	CD4 count <500	CD4 count <400	CD4 count <200	AIDS
Seroconversion:				
Jan 1988-Dec 1989	1.40 (0.94 to 2.1)	1.56 (0.99 to 2.44)	1.13 (0.61 to 2.12)	0.96 (0.46 to 1.99)
	P > 0.05	P = 0.052	P > 0.05	P > 0.05
Jan 1990-Dec 1991	2.13 (1.39 to 3.26)	1.91 (1.19 to 3.06)	2.51 (1.34 to 4.68)	2.66 (1.28 to 5.55)
	P = 0.0005	P = 0.07	P = 0.0039	P = 0.0091
Jan 1992-Dec 1994	5.67 (3.55 to 9.04)	4.70 (2.76 to 7.95)	5.45 (2.38 to 12.5)	4.03 (1.14 to 14.22)
	P < 0.00001	P < 0.0001	P = 0.0001	P = 0.030
Age	1.01 (0.99 to 1.03)	1.02 (0.99 to 1.04)	1.02 (0.99 to 1.05)	1.01 (0.98 to 1.04)
	P > 0.05	P > 0.05	P > 0.05	P > 0.05
Male sex	1.22 (0.98 to 2.06)	1.13 (0.99 to 1.49)	1.21 (0.97 to 2.04)	1.27 (0.98 to 1.42)
	P > 0.05	P > 0.05	P > 0.05	P > 0.05
$\beta2$ Microglobulin > 296 nmol/l	1.49 (0.98 to 2.25)	1.62 (1.05 to 2.51)	1.90 (1.1 to 3.3)	2.42 (1.30 to 4.51)
	P = 0.06	P = 0.03	P = 0.022	P = 0.0055
Acute HIV infection	2.25 (1.49 to 3.39)	2.23 (1.44 to 3.46)	2.57 (1.47 to 4.48)	2.54 (1.32 to 4.89)
	P = 0.0001	P = 0.00030	P = 0.00090	P = 0.0053
Sex transmission of HIV	1.03 (0.72 to 1.48)	0.95 (0.64 to 1.42)	0.98 (0.57 to 1.70)	1.28 (0.66 to 2.46)
	P > 0.05	P > 0.05	P > 0.05	P > 0.05

P value of each model is < 0.0001.

tion distinguishes those who seroconverted after December 1989.[7]

Reducing bias

To reduce potential sources of bias in the evaluation of the course of HIV disease, we accurately controlled the baseline characteristics of the patients with different calendar times of seroconversion. Similarly, to avoid selection bias we controlled the composition of the population referred to our unit in the study period. The patients who comprised the cohort did not differ in sociodemographic and behavioural factors from the other patients who were found to be positive for HIV in the same period.

The four groups shared similar characteristics at entry but differed in sex ratio and risk factors to HIV. This intergroup discrepancy was consistent with the epidemiological changes of the HIV epidemic in Italy throughout the study period, butt these differences at intake did not seem to affect the final analysis. As shown in the multivariate analysis, male sex was a nonsignificant predictor of poor evolution. Although there was a higher proportion of men in those who seroconverted before January 1988, this covariate did not influence the progression of this group, and seroconversion after December 1989 remained the most important independent factor associated with faster progression of HIV disease. Likewise, sexual transmission was unrelated to the evolution of the disease in our cohort. Moreover, when we considered December 1989 as a cut off date of seroconversion, the resulting two groups of positive subjects, similar also in sex ratio and category of exposure, showed different rates of CD4 cell decline and progression to AIDS. Seroconversion after December 1989 was consistent with a more severe disease course.

The heterogeneous composition of the sample with respect to the risk factors, the adequate size of the four groups, and the satisfactory length of the follow up support the validity of the results. Further, the unchanged site and method of determination of CD4 cell count, the partial availability of cell counts from before seroconversion, the knowledge of cell counts relative to the start of antiretroviral treatment, and the regular monitoring of cell counts from the initial period after seroconversion to very late HIV disease argue for reliability of the data. Finally, the exclusion from the study of the patients with >12 months between the last negative and the first positive test result for HIV infection contributed to the prevention of any error in calculation of progression rates.

Possible limitations

Notwithstanding these attempts to contain potential biases, some limitations should be acknowledged. First and foremost, few virological data—apart from p24 antigenaemia, a rough marker of HIV attributes—were known for our patients. In addition, the value of the presence of circulating HIV antigen at entry as an early predictor of rapid progression was confounded by the association of p24 antigenaemia at entry with the history of acute primary HIV infection in our sample.

The characteristics of HIV play an important part in the course of the disease. Studies suggest that HIV isolates vary in their cellular host range, tropism, and pathogenic potential.[12-16] Furthermore, viral changes often occur throughout the course of HIV infection.[17 18] Recent research supported the association between more rapid disease progression and certain viral phenotypes, such as syncytium inducing strains as opposed to non-syncytium strains.[19 20] Moreover, it is well known that the selective pressure of antiretroviral treatment encourages the appearance of resistant variations, sometimes soon after start of treatment, interfering with immune responses and coinciding with failure of treatment.[21] Accordingly, there is the possibility of primary acquisition of viruses resistant to the antiretroviral treatments in newly infected patients.[22-25] Finally, accumulating evidence indicates that diverse HIV subtypes are spreading to regions of previously restricted genetic diversity.[26] Although data were not available, some mechanisms of those previously reported, alone or together, may account for the increased rates of immunological impairment and progression to AIDS in patients who had recently seroconverted.

With the exclusion of drugs used in antiretroviral treatment, no drugs known to have an appreciable

impact on CD4 cells were extensively used in the study population, but we do not know whether methadone treatment affects HIV disease.[27 28] This potential bias could be important for the final analysis because of the large proportion of injecting drug users in our cohort; however, it would have been minimised by the fact that those who seroconverted had the same access to methadone treatment as those who did not.

Thirdly, another confounder could be laboratory drift of the CD4 cell determinations over time.[29-31] Within the laboratory, however, CD4 measurements at six month intervals in a healthy control group showed no variations, and CD4 cell counts remained unchanged among subjects acting as controls.

In the multivariate model, seroconversion after December 1989 and acute primary HIV infection were confirmed as the most important independent factors of disease progression.[32] In the Italian seroconversion study, older age at seroconversion was associated with a faster progression to AIDS.[33] This discrepancy with our data could be explained by the different composition of our cohort.

Conclusions

The emergence of more virulent strains due to multiple biological mechanisms may be responsible for more aggressive course of HIV disease in patients who have recently seroconverted. Our findings suggest possible changes in the course of HIV epidemic in the 1990s and raise intriguing issues on the course of HIV infection. If our data are confirmed, therapeutic approaches to the infection will need to be reviewed. In particular, if HIV disease has become more aggressive, more frequent screening would be essential to identify patients who have just seroconverted and could benefit from early antiretroviral treatment.

Key messages

- Interest in possible changes in the course of HIV infection has recently increased

- Previous research has shown no clear trend for changes in CD4 cell count by interval after HIV seroconversion

- Results from a large and heterogeneous cohort of patients who seroconverted between September 1985 and January 1995 showed that the patients who seroconverted after December 1989 had a higher probability of decline in CD4 cell count and progression to AIDS than did patients who had seroconverted before this date

- The overall rate of decline in CD4 cell count was higher in patients who seroconverted after December 1989; 180 days after seroconversion the rate was highest in those who seroconverted after December 1989, and 360 days after seroconversion it was highest in those who seroconverted after December 1989 and before January 1991

- Repeated monitoring within the first months after HIV seroconversion is needed to identify those patients who could benefit from early antiretroviral treatment

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Meta-analysis of prophylactic or empirical antifungal treatment versus placebo or no treatment in patients with cancer complicated by neutropenia

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Abstract

Objective: To determine whether antifungal agents given prophylactically or empirically decrease morbidity and mortality in patients with cancer complicated by neutropenia.
Design: Meta-analysis of randomised trials of amphotericin B, various lipid soluble formulations of amphotericin B (for example, AmBisome), fluconazole, ketoconazole, miconazole, or itraconazole compared with placebo or no treatment.
Setting: Trials conducted anywhere in the world.
Subjects: Patients with cancer complicated by neutropenia.
Main outcome measures: Mortality, invasive fungal infection (defined as positive blood culture, oesophageal candidiasis, or lung or deep tissue infection), and colonisation.
Results: 24 trials with 2758 randomised patients were reviewed; the total number of deaths was 434. Prophylactic or empirical treatment with antifungals as a group had no effect on mortality (odds ratio 0.92; 95% confidence interval 0.74 to 1.14). Amphotericin B decreased mortality significantly (0.58; 0.37 to 0.93) but the studies were small and the difference in number of deaths was only 15. Antifungal treatment decreased the incidence of invasive fungal infection (0.47; 0.35 to 0.64) and fungal colonisation (0.45; 0.30 to 0.69). For every 73 patients treated (95% confidence interval 48 to 158) one case of fungal invasion was prevented in surviving patients.
Conclusions: There seems to be no survival benefit of antifungal agents given prophylactically or empirically to patients with cancer complicated by neutropenia. These agents should be restricted to patients with proved infection and those in randomised trials. A large, definitive placebo controlled trial of amphotericin B is needed.

Introduction

Bacterial infections are a major cause of death in patients with cancer,[1] particularly when they have neutropenia.[2] Disseminated fungal infection, most often caused by *Candida* and *Aspergillus* species,[3] is also considered to be an important cause of morbidity and mortality.[4 5] The death rate in patients with candida sepsis or deep tissue infection is around 75%,[4 5] and a positive blood culture or histological evidence of invasion was found before death in 37% of patients in one series.[2]

Antifungal agents are often given prophylactically in conjunction with chemotherapy or bone marrow transplantation or empirically to patients without documented fungal infection but with persistent fever despite antibiotics. The rationale is to start treatment before it is too late—that is, before death is inevit-

able—as it is difficult to diagnose an invasive fungal infection with certainty.[4 6] Studies with historical controls have shown a positive effect of antifungal agents on mortality,[3 7] but such non-randomised comparisons substantially overestimate the effect of cancer treatments.[8] Randomised studies have yielded varying results, and the power of most of them has been very low. We conducted a meta-analysis of trials in which a commonly used antifungal agent was compared with non-treatment in a control group.

Methods

The primary aim was to determine whether commonly used antifungal agents decrease mortality. Secondary variables were the effect on invasive fungal infection and colonisation.

Search strategy

All randomised trials, irrespective of language, of amphotericin B, various lipid soluble formulations of amphotericin B (for example, AmBisome), fluconazole, ketoconazole, miconazole, or itraconazole compared with placebo or no treatment in patients with cancer complicated by neutropenia were eligible. We excluded studies which solely concerned treatment or prevention of oral candidiasis. A Medline search from 1966 on SilverPlatter was developed iteratively. The final strategy could retrieve all relevant trials from whatever source if they were registered in Medline. The search was most recently updated in February 1996.

One or more of *random*, control*, blind*, clinical-trial in pt, clinical-trials/all subheadings, placebo*,* and *tg=comparative-study* were combined with one or more of *amphotericin, AmBisome, fluconazol*, itraconazol*, ketoconazol*,* and *miconazol** and with one or more of *bone?marrow*, transplant*, cancer*, fungemia, h?ematologic*, malignanc*, neoplas*, neutropeni*, granulocytopeni*, leuk?emi*, lymphom*, sepsis, septic*, intensive-care/all subheadings, intensive care,* and *immunodeficiency.* Information about trials not registered in Medline, including unpublished trials, were located by contacting the pharmaceutical industry and the authors and by scanning reference lists of articles and reviews. We also scanned selected conference proceedings—namely, the interscience conference of antimicrobial agents and chemotherapy, 1990-5; the general meeting of the American Society for Microbiology, 1990-5; and the seventh European congress of clinical microbiology and infectious diseases, 1995.

Data extraction

Decisions on which trials to include and which variables to use when more options were available for the same outcome were based on the methods sections of the trials only. Details on diagnosis, drug, dose, rules

for use of additional (rescue) antifungal agents, average length of treatment with placebo, length of follow up, randomisation[9] and blinding methods, number of randomised patients, number of patients excluded from analysis, deaths, invasive fungal infections, colonisation, and use of rescue drugs were extracted by each of us independently. Disagreements were resolved by discussion.

We defined invasive fungal infection as a positive blood culture, oesophageal candidiasis, lung infection, or microscopically confirmed deep tissue infection. We excluded cases of oropharyngeal and vulvovaginal candidiasis, skin infections, *Candida* in the urine, and vaguely described infections. To check the robustness of our findings we also analysed fungal infection according to the authors' own definitions.

Authors were asked to confirm the extracted information and answer additional questions. For six trials[27 30 31 35 36 39] we obtained additional outcome data. Numbers in the tables therefore differ from those in the published articles. To increase the response rate we used Medline to obtain authors' most recent addresses. In an attempt to increase the power of the meta-analysis and avoid reporting bias we specifically asked authors for three months' mortality data for all randomised patients, including those subjected to secondary exclusion. We also sought details on the randomisation process, especially whether randomisation was concealed and irreversible so that an allocation could not be known beforehand or changed later. This question, however, seemed not always to have been well understood. We considered randomisation to have been concealed when central randomisation, sealed envelopes, or a code provided by a pharmacy or a company was described. On one occasion what seemed to have been sound randomisation provided by a pharmacy proved on further questioning to be medicine packages labelled A and B, which we would not have expected in a trial published in 1993.[39] With such a procedure, should the code be broken for just one patient it would be possible to predict all future allocations.

Statistics

Outcomes were weighted by inverse variance. As the studies were expected to be heterogeneous because of the various designs, diagnoses, drugs, doses, routes of administration, and criteria for fungal invasion, colonisation, and use of rescue drugs a random effects model was used.[10] When the P value for heterogeneity exceeded 0.10, however, a fixed effects analysis was preferred.[11] We used the Meta-analyst 0.975 program.[12] Odds ratios were calculated with 95% confidence intervals.

Table 1 Details of studies reviewed

Year published and first author	Drug, dose/24 h, and route	Disease	Design	Concealment of randomisation	Blinding of study
1980, Suda[14]	Amphotericin B 600 mg orally	Acute leukaemia	Prophylactic	NA	No
1992, Perfect[15]	Amphotericin B 0.1 mg/kg intravenously	Bone marrow transplantation	Prophylactic	Yes	Yes
1994, Riley[16]	Amphotericin B 0.1 mg/kg intravenously	Bone marrow transplantation	Prophylactic	Yes	Yes
1982, Pizzo[17]	Amphotericin B 0.5 mg/kg intravenously	Acute leukaemia	Empirical	Yes	No
1989, EORTC[18]	Amphotericin B 0.6 mg/kg intravenously	Acute leukaemia	Empirical	NA	No
1993, Tollemar[19-21]	Liposomal amphotericin B 1 mg/kg intravenously	Bone marrow transplantation	Prophylactic	Yes	Yes
1994, Goldstone[22]	Liposomal amphotericin B 2 mg/kg intravenously	Bone marrow transplantation	Empirical	NA	No
1992, Goodman[23]	Fluconazole 400 mg orally	Bone marrow transplantation	Prophylactic	Yes	Yes
1993, Winston[24]	Fluconazole 400 mg orally	Acute leukaemia	Prophylactic	Yes	Yes
1995, Yamac[25]	Fluconazole 400 mg orally	Acute leukaemia	Prophylactic	NA	No
1995, Slavin[26]	Fluconazole 400 mg orally	Bone marrow transplantation	Prophylactic	NA	Yes
1994, Fukuda[27]	Fluconazole 400 mg intravenously	Acute leukaemia	Prophylactic	Yes	No
1981, Acuna[28]	Ketoconazole 200 mg orally	Bone marrow transplantation	Prophylactic	NA	Yes
1982, Siegel[29]	Ketoconazole 200 mg orally	Bone marrow transplantation	Prophylactic	NA	NA
1992, Palmblad[30]	Ketoconazole 200 mg orally	Acute leukaemia	Prophylactic	Yes	NA
1983, Brincker[31]	Ketoconazole 400 mg orally	Acute leukaemia	Prophylactic	Yes	Yes
1983, Hughes[32]	Ketoconazole 400 mg orally	Acute leukaemia	Prophylactic	NA	Yes
1984, Estey[33]	Ketoconazole 400 mg orally	Acute leukaemia	Prophylactic	NA	NA
1987, Hansen[34]	Ketoconazole 400 mg orally	Acute leukaemia	Prophylactic	NA	NA
1991, Benhamou[35]	Ketoconazole 600 mg orally	Bone marrow transplantation	Prophylactic	NA	Yes
1978, Brincker[36]	Miconazole 2 g orally	Acute leukaemia	Prophylactic	Yes	Yes
1987, Wingard[37]	Miconazole 15 mg/kg orally	Bone marrow transplantation	Prophylactic	Yes	Yes
1993, Vreugdenhil[39]	Itraconazole 400 mg orally	Acute leukaemia	Prophylactic	Yes	Yes
1990, Caselli[40]	Three arms orally: itraconazole 2 mg/kg, ketoconazole 5 mg/kg, amphotericin B 50 mg/kg	Acute leukaemia	Prophylactic	NA	NA

NA=Data not available.

Table 2 Numbers of randomised patients and exclusions, numbers of patients who received rescue antifungal treatment, durations of follow up, and durations of treatment in controls

First author	No of randomised patients				No given rescue drug		Follow up period (days)	Days on placebo
	Total	Exclusions	T	C	T	C		
Suda	70	0	39	31	0	0	NA	NA
Perfect	188	6†	91	91	72	77	42	10
Riley	35	0	17	18	5	8	30	15
Pizzo	34	0	18	16	NA	NA	50	10
EORTC	157	25	80	77	NA	NA	30	NA
Tollemar	84	8	42	42	1	7	NA	19
Goldstone	137	4†	64	69	17	28	NA	NA
Goodman	356	1	179	177	101	116	90	20
Winston	257	2‡	124	133	79	98	90	14
Yamac	70	NA	41	29	NA	NA	NA	NA
Slavin	301	1†	152	148	58	81	89	55
Fukuda	63	0	37	26	0	0	NA	7
Acuna	52	NA	28	24	11	5	NA	NA
Siegel	25	NA	12	13	5	6	NA	NA
Palmblad	116	9	55	61	12	32	59	56
Brincker	38	0	19	19	2	2	28	28
Hughes	64	8	42	22	NA	NA	NA	14
Estey	150	3	77	73	NA	NA	56	39
Hansen	60	4†	27	29	6	5	NA	NA
Benhamou	125	0	63	62	52	51	36	30
Brincker	30	0	15	15	1	2	90	23
Wingard	208	15	97	111	64	62	NA	9
Vreugdenhil	98	6	49	49	9	15	80	80
Caselli	40	0	30	10	NA	NA	NA	NA

T=Treated group. C=Control group. NA=Data not available.†Not reported per treatment group.‡Survival status unknown.

Results

We identified 31 trials,[13-42] of which 29 were reported in English and two in Japanese. Seven trials were excluded: one was not truly randomised[41]; in another only 14 of 146 patients had neutropenia and only data on oropharyngeal candidiasis were provided[42]; a third trial was concerned only with a subgroup of 72 of 298 randomised patients who came to necropsy[13]; and four trials were unpublished[29 35 38] (H Brincker, personal communication). Of the 24 trials reviewed, two were published only as abstracts[28 29] and one was published as an interim analysis.[22]

An antifungal agent was given prophylactically in 21 trials and empirically in three (table 1). Acute leukaemia was the most common indication in 14 trials and bone marrow transplantation in 10. The total number of randomised patients was 2758 (table 2). Duration of follow up was given in only 13 trials (54%; median 56 days). Probably it varied for different patients within the same study, as several authors stated explicitly that the trial drugs had been given till the neutropenia had resolved.[15-21 24 25 30 35 37 39] The average number of days on placebo was reported in 16 trials (67%), in which the median was 20 days. Use of rescue antifungal treatment was more common in the untreated groups (odds ratio 0.68; 95% confidence interval 0.52 to 0.90).

A total of 434 deaths were reported, corresponding to a mortality of 18% when studies without mortality figures were excluded. Prophylactic or empirical treatment with antifungals had no effect on mortality (table 3); 210 patients given antifungal treatment died compared with 224 controls (odds ratio 0.92; 95% confidence interval 0.74 to 1.14 (P = 0.44)). There was no

heterogeneity between the trials (P = 0.60) and no tendency for newer drugs or regimens to be more effective than older ones. The odds of dying were lowest with the oldest drug, amphotericin B, which had a significant effect on mortality (odds ratio 0.58; 0.37 to 0.93) (table 3). As expected, studies with a concealed randomisation method gave a more conservative estimate of the treatment effect than other studies[9] (odds ratio 1.01 (0.78 to 1.31) v 0.75 (0.51 to 1.09)). The odds ratios were similar for patients with acute leukaemia and those who had bone marrow transplantation (0.91 (0.67 to 1.24) v 0.93 (0.69 to 1.25)). Odds ratios were also independent of sample size and the design of the study—that is, the odds ratio was 0.67 (0.33 to 1.38) for studies based on empirical treatment, but the number of deaths (15 v 20) was too small for meaningful comparison with the studies of prophylactic treatment.

Antifungal treatment decreased the incidence of invasive fungal infection significantly (P < 0.00001), both by our definition (odds ratio 0.47; 95% confidence interval 0.35 to 0.64) and by the wider definitions used by the primary authors (0.43; 0.32 to 0.56). There was no heterogeneity between the trials (P = 0.16). However, the use of ketoconazole was associated with an increase rather than a decrease in the incidence of infections (1.36; 0.67 to 2.78) (table 3).

Authors' definitions of fungal colonisation and their methods varied widely and there was considerable heterogeneity between the trials for the effect of the drugs (P < 0.00001). However, the overall effect of treatment on fungal colonisation was very similar to the effect on invasive infection (odds ratio 0.45; 0.30 to 0.69 (P = 0.0002)) (table 3).

Discussion

This meta-analysis failed to show an effect of prophylactic or empirical treatment with azoles on mortality, though there was a significant effect with amphotericin. The difference between treatment with amphotericin and no treatment was only 15 deaths, however, of which 12 occurred in two studies using low dose amphotericin (0.1 mg/kg intravenously/24 h).[15 16] Further, unreported interim analysis was used in one study (see below),[16] and small studies often exaggerate the treatment effect.[8] Unfortunately, the largest study of amphotericin has not been reported apart from the subset of patients who came to necropsy.[13] It is therefore difficult to judge whether the effect seen with amphotericin was real or a result of bias.

It may be very difficult to define the cause of death in patients severely ill with cancer. Therefore, we did not use death attributed to fungal infection as an outcome measure, as this information may be unreliable and prone to bias. Two studies reported only infection related deaths,[30 33] but we succeeded in obtaining data on total mortality for one of them.[30] The advantage of using total mortality as the outcome measure is not only that it is unbiased; it may also be the most relevant, as the drugs could have important adverse effects leading to drug related mortality. Ketoconazole, for example, is immunosuppressive, and in all three trials in which bacterial infections were reported these were more common with ketoconazole than with placebo (37 v 21,[30] 33 v 24,[33] and 20% v 15%

Table 3 Numbers of deaths and numbers of patients with invasive fungal infections and colonisation

First author	Deaths T	Deaths C	Odds ratio (95% confidence interval)	Infections T	Infections C	Odds ratio (95% confidence interval)	Colonisation T	Colonisation C	Odds ratio (95% confidence interval)
Suda	13	13	0.70 (0.26 to 1.83)	6	5	0.95 (0.26 to 3.43)	NA	NA	NA
Perfect	3	11	0.29 (0.10 to 0.87)	2	5	0.41 (0.09 to 1.86)	8	13	0.58 (0.23 to 1.47)
Riley	0	4	0.12 (0.02 to 0.92)	0	3	0.13 (0.01 to 1.31)	2	7	0.21 (0.04 to 1.21)
Pizzo	3	5	0.46 (0.10 to 2.18)	1	5	0.18 (0.03 to 1.02)	NA	NA	NA
EORTC	11	14	0.72 (0.31 to 1.69)	1	4	0.28 (0.05 to 1.66)	NA	NA	NA
Tollemar	5	3	1.73 (0.41 to 7.35)	1	3	0.35 (0.05 to 2.61)	NA	NA	NA
Goldstone	1	1	1.08 (0.07 to 17.47)	NA	NA	NA	NA	NA	NA
Total amphotericin			0.58 (0.37 to 0.93)			0.38 (0.19 to 0.76)			0.46 (0.20 to 1.06)
Goodman	55	46	1.26 (0.80 to 2.00)	5	27	0.22 (0.11 to 0.45)	53	119	0.21 (0.13 to 0.32)
Winston	26	24	1.20 (0.65 to 2.23)	5	10	0.53 (0.19 to 1.51)	34	83	0.23 (0.13 to 0.39)
Yamac	NA	NA	NA	4	9	0.25 (0.07 to 0.84)	NA	NA	NA
Slavin	21	28	0.69 (0.37 to 1.27)	8	17	0.44 (0.20 to 1.01)	117	128	0.52 (0.29 to 0.96)
Fukuda	2	1	1.40 (0.14 to 14.51)	2	2	0.68 (0.09 to 5.27)	6	2	2.32 (0.43 to 12.55)
Total fluconazole			1.07 (0.78 to 1.46)			0.34 (0.22 to 0.52)			0.36 (0.18 to 0.70)
Acuna	NA	NA	NA	3	0	6.91 (0.68 to 70.01)	21	16	1.50 (0.45 to 5.01)
Siegel	NA	NA	NA	0	0	1.08 (0.02 to 54.42)	7	10	0.42 (0.07 to 2.36)
Palmblad	15	16	1.05 (0.46 to 2.39)	3	0	8.55 (0.87 to 84.15)	15	32	0.34 (0.16 to 0.74)
Brincker	2	2	1.00 (0.13 to 7.73)	2	1	2.02 (0.20 to 20.73)	10	12	0.65 (0.18 to 2.37)
Hughes	NA	NA	NA	NA	NA	NA	24	19	0.21 (0.05 to 0.82)
Estey	11	12	0.85 (0.35 to 2.06)	5	6	0.78 (0.23 to 2.64)	8	18	0.35 (0.14 to 0.88)
Hansen	NA	NA	NA	2	0	8.27 (0.50 to 135.86)	3	8	0.33 (0.08 to 1.40)
Benhamou	4	4	0.98 (0.24 to 4.10)	3	6	0.48 (0.12 to 1.86)	19	37	0.29 (0.14 to 0.61)
Total ketoconazole			0.96 (0.56 to 1.64)			1.36 (0.67 to 2.78)			0.39 (0.27 to 0.56)
Brincker	6	5	1.31 (0.31 to 5.68)	1	2	0.49 (0.05 to 5.10)	8	14	0.08 (0.01 to 0.79)
Wingard	20	20	1.18 (0.59 to 2.35)	5	11	0.51 (0.19 to 1.42)	54	44	1.91 (1.10 to 3.32)
Total miconazole			1.21 (0.65 to 2.25)			0.51 (0.20 to 1.30)			0.48 (0.02 to 10.35)
Vreugdenhil	12	15	0.74 (0.31 to 1.78)	5	9	0.52 (0.17 to 1.59)	15	16	0.91 (0.39 to 2.13)
Caselli	NA	NA	NA	0	0	NA	12	7	0.29 (0.06 to 1.33)
Total all trials			0.92 (0.74 to 1.14)			0.47 (0.35 to 0.63)			0.45 (0.30 to 0.69)

T=Treated group. C=Control group. NA=Data not available.

of neutropenic courses[34]). Fluconazole was associated with an excess of graft versus host disease or organ failure, or both, in the two large studies of bone marrow transplant recipients—namely, 29 v 16 deaths[23] (or 44 v 24 from later correspondence[43]) and 102 v 85 cases of graft versus host disease.[26]

A positive effect on mortality may be overlooked if the trial drug is given for too short a period to allow the granulocyte count to rise, as the effect might be less during granulocytopenia. However, the odds ratio was 0.86 (95% confidence interval 0.63 to 1.17) in trials in which treatment was continued till the neutrophil count recovered, which was similar to the effect seen in other trials.

It may also be difficult to show an effect if rescue antifungal treatment is instituted too quickly in controls. Three large studies of fluconazole 400 mg daily in which roughly half of all deaths in the meta-analysis were recorded illustrate this possibility. In two studies the trial drugs were continued until the neutrophil count had increased to more than $1.0 \times 10^9/l$ and had remained at that level for seven days or until systemic fungal infection was suspected or proved.[23] [24] In the third study trial drugs were given for 75 days or until systemic fungal infection was proved[26]; if fungal infection was only suspected amphotericin B was added empirically to the trial drugs. This difference in design led to placebo being given for an average of only 20 and 14 days, respectively, in the first two studies whereas it was given for 55 days in the third study (table 2).

Only the third study found a significant difference in mortality (31 v 52 deaths after 110 days). However, a biased decision on length of follow up may have been taken. In a conference abstract describing all 301 patients and the same mean time on the study drug as in the final paper only 14 versus 25 deaths were mentioned.[44] The abstract notes a follow up period of 75 days (maximum length of treatment) plus an additional two weeks. The final paper gave no explanation why the follow up period was extended to 110 days. We used the data after 89 days (21 v 28 deaths), which came closest to the three month follow up that we aimed at in the meta-analysis and which we assume were also those stipulated in the trial protocol for the study. The primary author did not respond to our request for further information.

Stopping rules and ethics

Another bias which may have occurred relates to informal interim analyses. Concern has been raised about bias in cancer trials caused by loose stopping rules,[45] and a recent survey showed that most cancer cooperative groups perform annual interim analyses of their trials without formal stopping rules at all.[46] One author informed us that one of his studies was stopped prematurely after 30 patients when an interim analysis showed a significant effect, but the trial report did not mention this or that the study was planned to include 50 patients.[36] The final report of another study did not mention any interim analysis,[16] though an interim analysis was reported in a conference abstract.[47] A third study described interim analyses but gave no rules,[33] and a fourth study was published only as an interim analysis.[22]

Loose stopping rules are an important source of bias only in small meta-analyses[48][49]—for example, the subgroup analysis of mortality with amphotericin mentioned above. The possibility of publication bias,[50] which is also a well documented phenomenon in cancer trials,[8][51] is of greater concern. As an example, a study of fluconazole was stopped by the manufacturer of the drug in 1990 when 32 patients had been entered; the investigator never learnt the reason or the results (H Brincker, personal communication). Our contacts with the pharmaceutical companies were not successful. Pfizer and Janssen-Cilag refused access to unpublished reports or even just to list them so that we could approach the investigators. This behaviour, which was recently repeated when other meta-analysts approached Janssen,[52] must be changed.[53] Clinical trial data can be assembled only through patients' willingness to contribute to science for the benefit of future patients. These data should therefore be regarded as public property to be used for the public good. Pharmaceutical companies must therefore not obstruct researchers in their attempts to contact each other or try to prevent the medical community, patient organisations, or society from obtaining as unbiased information as possible on the effectiveness of treatments.

Rationale

Amphotericin and fluconazole had a clear effect on invasive fungal infection. It is of concern, however, that the diagnosis of systemic infection is difficult and somewhat arbitrary and therefore open to bias. The blinding of some studies may have been less than desired because of the effect of the drugs on oral candidiasis or their side effects or because the final evaluation of the infections might have taken place after the code was broken. Only two reports mentioned that possible end points were evaluated without knowledge of the treatment assignment.[24][37] However, the effect was so large and consistent that it would be unreasonable to ascribe it to bias alone.

We were not surprised that the use of rescue antifungal agents was more common in controls, as this may not only reflect a difference in the incidence of systemic fungal infection. The decision to use another drug may also have been influenced by the presence of oral candidiasis or access to culture data showing superficial colonisation. As we could not detect an unequivocal effect of prophylactic or empirical antifungal treatment on survival, we dismiss the common rationale for the widespread use of these drugs in neutropenic patients—namely, the fear that the patient might die if treatment is instituted too late.

Another rationale for prophylaxis might be to prevent invasive mycosis in sites which are difficult to treat. The number of patients who would need to be treated to prevent one case of fungal invasion may be calculated as the inverse of the risk difference.[54] The overall risk difference was 0.034 (95% confidence interval 0.016 to 0.053). The number of patients who would need to be treated to prevent one case of fungal invasion is therefore 29 (19 to 63). A more interesting figure, however, is the number who would need to be treated to prevent one case among surviving patients. In those studies in which the fate of patients with fungal invasion was reported 60% of the patients died. Thus to prevent one case of fungal invasion in a surviving patient we should need to treat 73 patients (48 to 158). However, many infections described in the reports were fungaemias or oesophageal candidiasis. Therefore, the number of patients who would need to be treated to prevent one difficult to treat fungal invasion must be even higher. To elucidate this further we looked at a subset of seven trials in which both the fungal diagnosis and the ultimate fate of the affected patients were reported.[17-21][23][31][36][37] These trials, which included 907 patients, were representative of the whole sample of trials. The odds ratio for fungal invasion by our criteria was 0.32 (0.19 to 0.52).

Table 4 shows the numbers of invasive fungal infections in patients after the exclusion of those who died. Clinically we could argue that, as fungal infection reflects the poor general condition of patients, the most seriously affected patients might be expected to die irrespective of any antifungal treatment whereas many less seriously affected patients might be expected to combat the fungus with their own immune system once the immune depression caused by cytotoxic drugs was abolished. Accordingly, in the study by Goodman *et al* 11 of 13 patients with tissue infection died whereas all 17 whom we defined as "invasive" cases because of a positive blood culture alone survived.[23]

Among the remaining 17 trials, in which the fate of individual patients was not reported, three cases of cerebral mucormycosis were mentioned, in two of which the patients were receiving placebo; no mortality data were given for these patients.[26][33] Thus it seems difficult to identify any type of difficult to treat patients among the 2758 randomised patients in these studies who would benefit definitively from antifungal prophylaxis. For example, oesophageal candidiasis is usually avoided by treating the clinical symptoms of oral candidiasis with fluconazole, and candidaemias may be treated when they occur. A final concern is that widespread use of antifungal agents could lead to resistance or to infection with inherently resistant species of fungi—for example, *C krusei* and *glabrata,* which may be a problem when fluconazole is used.[55]

Some patients have a particularly high risk of invasive infection—for example, because of prolonged neutropenia, heavy colonisation or colonisation with *Aspergillus,* previous invasion, concomitant bacteraemia, treatment with steroids, and graft versus host disease.[56-58] These patients, however, were also represented in the trials we reviewed, and it has not been

Table 4 Invasive fungal infections in surviving patients in trials in which diagnosis and fate of affected patients were reported

First author	Blood		Tissue		Oesophagus		Lungs		Urine		Skin and mucosa	
	T	C	T	C	T	C	T	C	T	C	T	C
Pizzo	0	0	0	0	0	1	0	1	0	0	0	1
EORTC	1	0	0	0	0	0	0	0	0	0	0	2
Tollemar	0	0	0	0	0	0	0	0	0	0	0	0
Goodman	4	13	0	2	0	2	0	0	0	1	0	0
Brincker, 1983	0	0	0	0	0	1	0	0	0	0	0	0
Brincker, 1978	0	0	0	0	0	0	0	0	0	0	0	0
Wingard	3	6	0	0	0	0	0	0	0	0	0	0

T=Treated group. C=Control group.

Key messages

- Prophylactic or empirical treatment with antifungal agents is often recommended for patients with cancer complicated by neutropenia for fear that they might die if treatment is delayed

- A meta-analysis has failed to show a convincing survival benefit of antifungal agents in patients with cancer complicated by neutropenia

- Amphotericin B and fluconazole decrease the incidence of invasive fungal infections

- Seventy three patients need to be treated to prevent one case of fungal invasion in surviving patients

- The use of antifungal agents should be restricted to patients with proved infections

shown that it would be worthwhile to treat this subgroup prophylactically or empirically.

We therefore question the current widespread practice of routinely giving either prophylactic or empirical treatment with antifungal agents to patients with cancer complicated by neutropenia. We suggest that these drugs should be restricted to patients with proved infections and to patients participating in randomised trials. As a beneficial effect of amphotericin on mortality was suggested by the meta-analysis a large, definitive placebo controlled trial of this drug should be performed. Further, the effect of empirical treatment, for which the data were very sparse, could be addressed in future studies. The studies should include data on length of hospital stay and similar measures which will allow cost-benefit analyses to be performed. Our review will be published in the Cochrane Database of Systematic Reviews, where it will be updated when new trials appear.[59]

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Impact of a dedicated service for male mentally disordered remand prisoners in north west London: retrospective study

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Government policy has encouraged speedy transfer of mentally ill prisoners to NHS care,[1 2] but arrangements have often proved slow and ineffective.[3 4] The Bentham Unit was set up in February 1994 to provide rapid assessment and (where appropriate) transfer for male mentally disordered remand prisoners in the former North West Thames Regional Health Authority. The unit provides regular outreach assessment sessions at Wormwood Scrubs and other prisons and is based in a 14 bed locked ward to which patients may be admitted before court disposal and determination of final placement.

Subjects, methods, and results

We retrospectively identified all prisoners referred for NHS psychiatric assessment who had been remanded to prisons within the area covered by North West Thames Regional Health Authority (Wormwood Scrubs, Brixton, Pentonville, Wandsworth, and Feltham) between 1 April and 31 August 1994 and determined those who were assessed and admitted by the Bentham Unit. We measured the intervals between remand, assessment, and transfer and compared these measures between subgroups subject to different placements. Similar comparisons were made with those referred from Wormwood Scrubs during the same months in 1993 (before the unit opened).

During the 1994 study period, 158 remand prisoners in North West Thames region were referred. The Bentham Unit assessed 62 (39%) of these. For 71 patients subsequently admitted to NHS inpatient care, the median interval between remand and final transfer to NHS hospital was 36 days (table 1). Admission to a remand bed at the Bentham Unit or the similar local Riverside Forensic Service[5] was associated with a shorter length of stay in prison but a significantly longer total interval between remand and final transfer (median 85 days v 55 days, P = 0.015).

Of the 158 referrals, 58 were prisoners remanded to Wormwood Scrubs. Comparison with referrals from Wormwood Scrubs during the same months in 1993 showed a significant increase in the proportion of the remand population referred (4% v 8%) and a doubling in the proportion finally admitted to NHS hospital (14 (2%) in 1993 v 29 (4%) in 1994). During the 1994 period 21 of 29 patients were temporarily admitted to the Bentham Unit.

For all Wormwood Scrubs patients subsequently transferred to NHS inpatient care, there were large and significant reductions between the 1993 and 1994 study periods in the median intervals between remand and first assessment by a NHS psychiatrist (median 27

Table 1 Intervals between remand and first transfer out of prison and between remand and final transfer to NHS psychiatric care of prisoners in the care of North West Thames Regional Health Authority, 1 April to 31 August 1994, and similar comparisons of prisoners remanded to Wormwood Scrubs in 1993 and 1994 and transferred to NHS care

Male prisoners assessed and transferred	1993	1994			
		All transfers	Transfers to Bentham Unit	Transfers to Riverside Forensic Service	Transfers to other hospitals
Remanded to all London prisons 1 April to 31 August 1994					
No transferred to NHS inpatient care	—	71	27	14	30
Median (range) No of days in remand prison	—	36 (2-286)	35 (6-143)	35 (5-199)	55 (2-286)
Median (range) No of days in NHS remand bed	—	—	69 (10-179)	54 (1-128)	—
Median (range) No of days between remand and final relocation	—	86 (2-312)	137 (51-210)**	74 (31-312)*	55 (2-286)**
Remanded to Wormwood Scrubs 1 April to 31 August 1994					
No (%) remanded and referred for NHS psychiatric assessment	30/683 (4.4)	58/731 (7.9)†			
Median (range) No of days between remand and first NHS psychiatric assessment	49 (5-194)**	9 (1-186)**			
No relocated to NHS psychiatric beds (% of remand population)	14 (2)	29 (4)			
Median (range) No of days in remand prison	122 (32-478)**	54 (10-274)**			
Median (range) No of days between remand and final relocation	122 (32-478)	144 (51-274)			

*P< 0.05, **P< 0.005, Mann-Whitney U test.
†P< 0.01, χ^2 test, df=1.

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days v 11 days, P<0.05), and between remand and transfer from prison (median 122 days v 46 days, P<0.05). Although the median interval between remand and final placement increased marginally between 1993 and 1994, patients were transferred from prison more quickly, and those who were admitted to the Bentham Unit also had a median 69 days of NHS psychiatric care before final placement.

Comment

Combining outreach services with a 14 bed secure ward, the Bentham Unit transfers mentally ill remand prisoners faster than do catchment services. Although the comparison of transfers from Wormwoods Scrubs does not allow differences between the periods before and after the unit operated to be reliably attributed to the service, intervention by the unit has coincided with a significant decrease in the time that male mentally disordered remand prisoners spend in prison and a doubling of the number of patients referred for assessment and the number transferred to NHS care. This suggests that a previously unmet need has been identified.

As a regional service, the Bentham Unit seems to reverse the principle of local care promoted by Reed.[2]

However, given the failure of local arrangements,[3 4] the role of similar units with special skills in forensic psychiatry should be further assessed. Early transfer out of prison will deliver more timely treatment and enable local providers to engage with patients before they are finally relocated. Research must assess the full clinical, social, and economic impacts of specialist units to generate an evidence base for the development of future forensic services.

1 NHS Management Executive. Services for mentally disordered offenders and patients with similar needs. London: NHSE, 1992. (Circular EL(92)6.)
2 Department of Health, Home Office. *Review of health and social services for mentally disordered offenders and others requiring similar services. Final summary report.* London: HMSO, 1992.
3 Coid J. Mentally abnormal offenders on remand. I. Rejected or accepted by the NHS. *BMJ* 1988;296:1779-84.
4 Dell S, Grounds A, James K, Robertson G. *Mentally disordered remand prisoners: summary report to the Home Office.* Cambridge: Institute of Criminology, University of Cambridge, 1991.
5 Cripps J, Duffield G, James DV. Bridging the gap in secure provision. *J Forensic Psychiatry* 1995;6:77-91.

One hundred years ago
The General Medical Council election

The fight for the vacant seat on the General Medical Council is nearly over, but the interest in it taken by all who are not what Americans call "Mugwumps" in the matter of medical politics, so far from abating, seems actually to grow in intensity as the end approaches. We would again impress upon our readers the importance of the whole profession in England and Wales availing itself of the suffrage at this critical time. On former occasions the number of voters has been so small relatively to the strength of the electorate as to make the cause of direct representation appear weak, indeed almost ridiculous. We learn with satisfaction that in the present election the profession is showing itself less indifferent; already we understand the poll is heavier up to the hour of writing than it was at a corresponding period in the last election. But the votes so far recorded do not even now, we believe, exceed 10,000, which means that more than half of the number of those having the right to vote have taken no part in the election of a man to represent them on the General Medical Council. We therefore appeal with all the emphasis in our power to those who have not yet voted to do so without an hour's delay. (*BMJ* 1897;ii:1011.)