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6 months fixed duration multidrug therapy in paucibacillary leprosy: Risk of relapse and disability in Agra PB cohort study

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PB-Figure 1.emf
PB-Figure 2.emf

6 months fixed duration multidrug therapy in paucibacillary leprosy: Risk of relapse and disability in Agra PB cohort study.

by

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Abstract

Background: Low relapses after multidrug therapy in paucibacillary (PB) leprosy led to recommendation of reducing therapy to 6 months. However only a few reports are available on long term outcome of 6 months fixed duration therapy for PB patients. Studies on measuring risk of disability are rare. Present study is to assess the cure; default, relapse and disability in a prospective cohort of PB leprosy during follow up of >4 years after treatment.

Design: Prospective

Setting: Primary in our field area of Agra District

Participants: 920 paucibacillary leprosy patients entering the study, 621 completed treatment, 599 followed finally including 271 males, no ethnic differentiation, patients of all age groups except children below 5 years and old persons above 70 years were not included.

Treatment: 6 months fix duration multidrug therapy (MDT) as recommended by W.H.O.

Primary and Secondary outcomes: Treatment completion, cure, relapse and development of disability based on clinical assessment by well experienced doctors.

Statistical Methods: Data has been analyzed using SPSS software, risk is computed as incidence per 100 person years and test of significance used.

Results: Study reports 91% cure rate. Incidence of relapse was 1.3/100 person years with no significant variation by age, sex, delay in detection, patches, Nerves. Crude incidence of disability was 2.2% and varied significantly by age and nerve thickening but not by sex, number of patches, nerves and delay in treatment. Incidence of disability was 0.50/100 person years in treatment completed and 0.43 among defaulters.

Conclusion: Study concludes that relapses do occur after MDT treatment but at the level of 1-2%, incidence of disability remains low (<1/100 PY) in PB leprosy. Low incidence of relapse and disability suggests that 6 months therapy is quite effective. However further improvement may help to improve its efficacy. Longer follow up may add to efficacy measures.

Introduction

Leprosy is unique in terms of the nature of the causative organism, the chronicity of the disease, its prolonged treatment and the definitions of cure and relapse. The principal mode of assessing the efficacy of therapeutic regimens in leprosy is the relapse rate[1]. The important predisposing factors for relapse include the presence of persister bacilli, monotherapy, inadequate or irregular therapy, presence of multiple skin lesions and/or thickened nerves and lepromin negativity. The conventional methods of confirming activity or relapse in an infectious disease have limited utility in leprosy because of the difficulty in demonstrating bacilli in paucibacillary (PB) cases and absence of a method of *in vitro* cultivation of *M. leprae*. Bacteriological parameters are useful in smear positive multibacillary (MB) leprosy, whereas in PB leprosy, the criteria for relapse depend primarily on clinical features since even histological examination cannot clearly distinguish between reaction and relapse[2].

There are wide variations in estimates of relapse rates in different regions. The risk of relapse from programme based data were reported[2-4] to be low from 0.29% to 1.1% and in closely monitored studies it was estimated as 1% to 6.9% for PB leprosy patients after stopping MDT[5,6]. Although most of these studies provided crude estimates of relapse but a few also estimated using person-years of observation, giving relapse rates of 0.65 to 3.0% for PB leprosy [5,7,8]. One of the reasons for low relapse rate was that follow up was done usually for shorter intervals after therapy. Beside relapses in PB leprosy, there is hardly any study in literature reporting risk of developing disability but one[6] based on pre-MDT era reported that 6.7% developed Grade 1 and another 5.2% Grade 2 disability. However, one recent study based on multidrug treatment had given estimates of risk of developing disability of 2.74/100 person years in multibacillary leprosy[9]. Therefore, more studies on long tern follow up were required to assess the risk of relapse and disability rate in the cohort of patients treated with 6 months fixed duration therapy and thus the present study was undertaken in cohort PB leprosy patients from field surveys in Agra district –namely Agra cohort, with the objectives to assess the risk of relapse and disability rate beside the extent of treatment completion and cure rate.

Design and Methods

Study site, field setting and duration of study

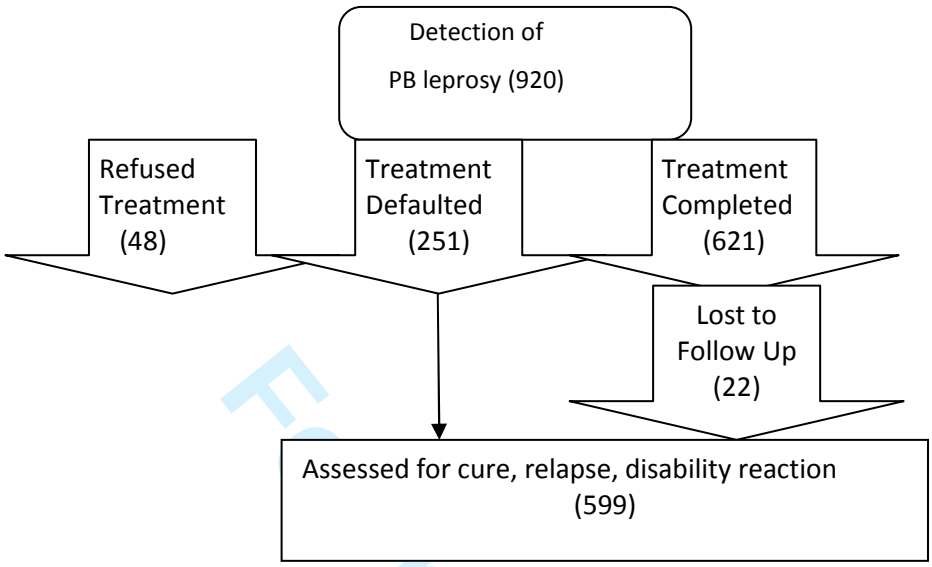
The study was started in our field area in Agra District of Uttar Pradesh on patients detected in field surveys under several studies on prevalence of leprosy during 2001-2006[10-13]. The Agra District is located 200 KM away from Delhi and spread in the radius of 100 KM on either side in length and borders with district Itawa & Firozabad on eastern side, Mathura & Bharatpur on north-west side and Gwalior & Dholpur on south side. Several studies were undertaken since the district was highly endemic for leprosy with prevalence of 16.4/10000 during 2001-03 and 7/10000 during 2004-06. The present study is based on patients detected in such surveys and all patients were followed up till April 2011.

Inclusion/Exclusion criterion of Patients for the study

The study has been conducted in patients detected in the field survey in Agra district during 2001-06. Newly detected leprosy patients diagnosed clinically as paucibacillary (PB) leprosy were taken for the study. This included patients with upto 5 skin lesions, either erythmatous or hypo-pigmented with definite impairment or loss of sensations (tested with ball point pen) and/or 1 thickened nerves. None of the patients had taken leprosy treatment earlier. Children below 5 and adults above 70 were although treated as per norms but not included in the study and so were the pregnant and lactating women.

Cohort size and treatment allocation

During 2001-2006 in Agra district, several field surveys were undertaken to detect leprosy cases. In these surveys, a total of 1050 paucibacillary (PB) leprosy cases were detected. After excluding cases given ROM in the randomized trial, rest was put on W.H.O. MDT as the cases were detected in ongoing surveys. Of the 920 PB cases, 48 did not start the treatment (2 for pregnancy, 2 old aged, 44 simply refused). After this, 872 cases on PB-MDT, 251 (28.8%) discontinued (defaulted) treatments at various durations and reasons. Therefore, a cohort of 599 (96.5%), out of 621 PB patients completed treatment could be followed up for a mean duration of 4.39(SD:1.6) years after completion of MDT treatment. Present study is based on this cohort of 599 cases (see flow chart).



At the time of starting treatment, all the patients were informed about disease, its implications, treatment, possible side effects, remedies and benefits. Although the treatment given was WHO standard regimen as in routine Government leprosy control programme but for reasons of follow up etc patients were asked to consent and then they were put on respective treatment. In case of children, consent of their parents was taken.

Treatment

W.H.O. supplied MDT packs were used for the study and appropriate W.H.O. recommended doses (Available in blister packs) were given to Children aged 5-14 and adults (aged >14). Monthly PB-MDT was given, with supervisory dose under supervision and for rest of days patients were guided to take daily treatment doses of Dapsone.

Follow-up and assessment

Patients were visited every month till the completion of treatment for drug intake, clinical conditions and side effects. However, formal assessment of each available patient was made every 6 months for 5 years and annually thereafter. Lesion activity- erythema, infiltration and size, reaction, any new lesion and / or new nerve thickening or any deformity was recorded in consultation with the medical doctor who was apart of the study. Cure of the disease was defined as complete healing of the lesion or patch becoming

flat hypopigmented with decrease in size of the lesion and/or regain of sensations. Loss to follow was defined when patients could not be assessed for fairly long time.

Defining Defaulter

A patient who did not complete scheduled 6 months MDT to be able to declare cured. An early defaulter is the one who did not have more than 2 months of MDT and late defaulter is with 3 to 5 months MDT.

Defining Relapse or Reaction

The case of relapse was confirmed by a clinician with >30 years experience in leprosy. Gradual or insidious appearance of new lesion(s) or definite increase in size of the lesion and/or appearance of new nerve thickening were taken as relapse. Any sudden redness, swelling of the lesion with or without new lesion especially during the first 6 to 12 months of follow up, was considered as late reaction. All such patients were first put on corticosteroids[14]. If there was no obvious change in morphology of lesion (inflammation) in 4 weeks, the patients were considered as to have relapsed. If patient responded to 4 weeks corticosteroids, then it was recorded as reaction and not relapse.

Defining disability of Grade 1 and Grade 2

Disability Grade 1 was defined as patient developing anesthesia in palm or sole tested with a ball point pen and Grade 2 as visible deformity in either Hand or Feet or eye (Lagophthalmas). During this time, all cases of clinical relapse, reaction and developing of disability (Grade 1 & Grade 2) were recorded after medical confirmation and necessary medical relief was either provided or referred

Ethical Approval and informed consent

Ethical Approval was taken from Institutional ethical committee who was being informed periodically about the progress of the work. All the patients were informed about the possible side effects, remedies and benefits. Although the treatment given was WHO standard regimen but for reasons of follow up etc, the patients were asked to consent and then they were put on respective treatment. In case of children, consent of their parents was taken.

Statistical methods

The comparison of patients developing disability was done using survival analysis and Log-Rank test to test the significance[15] using SPSS v12 software and Fisher exact test or χ^2 test of significance used to compare proportions[16].

Results

Demographic Characteristics of patients

The patients of all ages were detected in surveys. The mean age was 34.2 years (SEM=0.6). About half of total patients (49.7%) were aged 35 & above and only 12.5% were the child cases (<15 years). Male patients in this study accounted for 45.3% of the total 872 cases put on PB-MDT. At the time of survey, 51.8% patients were those who reported to acquire leprosy during last 12 months, 32.3% in last 12-36 months and rest had disease since over 36 months. A total of 79.1% had upto 2 skin patches, 40.3% with 1 thickened nerve, 84.6% with borderline tuberculoid (BT) disease and only 0.3% (2 cases) were smear positive that too just 1+. Similar distribution is observed among those completed treatment and defaulters (Table 1).

Treatment completion, cure rate and reaction:

Of the total 872 patients who were put on PB-MDT treatment, 621(71.2%) completed their scheduled 6 months treatment and 251 (28.8%) defaulted at various stages of treatment. Among the defaulters, 70.1% defaulted early (within 3 months) and 29.9% during 3-5 months treatment.

Among 621 completed treatments, only 599 could be followed up and 22 were lost to follow up (LFU). About 83% of the patients could be followed up for 3-8 years and some 2.9% for over 8 years. A total of 545(91%) of the 599 were observed to be completely cured, 1.7% either not cured or partially cured and rest were observed to have either relapsed (35), developed reaction (5/599) or developed disability of Grade 1 (5) or Grade 2 (8) (Table 2).

Incidence of Relapse

The overall incidence of relapse was observed to be 1.3 per 100 person years (Figure 1). The incidence of relapse by age, although, did not change much but was observed to be slightly

high in children (<15 years) and among older persons (>54 years). The incidence of relapse by sex, no. of patches, presence of nerve and delay in treatment also did not vary (Table 3).

Incidence of disability among completed treatment vs. defaulters

The crude incidence of disability was observed to be 2.2% in comparison to 2.02% among defaulters. The crude incidence by age varied significantly among completed treatment group (χ^2 = 22.7,p=0.0001) and no significant variation found in defaulters. Although no significant difference in crude incidence of disability was observed by sex, no. of patches and delay in treatment but by nerve status. Patient initially with no nerve developed disability more (χ^2 = 4.1, p=0.043) (Table 4).

Of the 592 patients completed treatment and followed up for over 4 years (Mean = 4.4 years), 13 new cases of disability were observed during follow suggesting incidence of disability as 0.50 per 100 person years (PY) in comparison to 0.43 among defaulters (Table 5, Figure 2). Among the defaulters, incidence of disability was 0.43 in early default and 0.41 in late default.

Discussions and Conclusion

In the present study, 91% of the PB leprosy patients who completed treatment and followed up were completely cured. The reaction rate was observed to be very low (0.8%). The occurrence of events like reaction, relapse and disability measures the efficacy of any treatment regimen. In present cohort of PB leprosy, the relapse rates have been reported in some studies after MDT with a low rate in programme based data and high in closely monitored studies. Some studies had reported relapse rate of <1% to 6.9% in PB leprosy[2-8]. In the present study, overall relapse rate is observed as 1.3/100 persons years in the PB cohort observed during 2001-10 in Agra district. Most relapses (30/35) were observed 1-5 years after releasing from treatment and almost 11.4% (4/35) beyond 5 years of follow up. The relapse rates did not differ significantly by age, sex, delay at detection, clinical status and with nerve involvement.

Although it is difficult to qualify for high and low relapse rates but relapses do occur and can occur anytime after release from treatment[13]. More relapse may be seen if these patients are followed up for further longer period but extent is not easy to project. In many cases, the cause of relapse may be individuals' immunological response to mycobacteria. It would therefore be interesting to investigate the reason of relapses–is it insufficient treatment causing early relapse, persistent dormant mycobacteria leading to late relapse or immunological variations across populations giving mix of above two?

The incidence of disability was noticed 13 patients (5 Grade 1 & 8 Grade 2). Although crude incidence of 2.02% was noticed and significant variation by age (χ^2=22.7, p=0.0001) and nerve involvement (χ^2=4.1, p=0.043) but no significant difference observed by sex,number of patches and duration of delay in treatment. The overall incidence of disability was 0.50 per 100 person years among the group of completing treatment and 0.43 per 100 person years among treatment defaulters (Table 5, Figure 2) with very little difference between early and late defaulters (Log rank test=0.23, p=0.63). This study observed much lower crude incidence of disability than as observed in a pre-MDT time study that reported crude incidence of grade 1 & grade 2 disabilities as 6.7% & 5.2% respectively[6].

The findings of present study once again confirms the findings of another cohort study on MB leprosy[9] that treatment status (complete vs. default) probably does not affect the risk of disability but initiation of treatment may do so. This is beside the fact that at what stage treatment is taken after the disease starts progressing. However, some early cases of grade 1 disability may get altered to normal[6] but many may advance disability to grade 2. This is an important feature of leprosy and may be the result of already set-in pathways for disabilities.

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Contributors: Although all authors were responsible for the conception, design and acquisition of data, drafting, revising and final approval of the article. AK played the lead role in planning,

conducting, supervising field study, analysis and report writing; AG for clinical evaluation and BKG for clinical monitoring and report preparation.

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Conflict of interests: None

Patient Consent: obtained

Ethical Approval was granted by the institutional ethical committee, which was being informed periodically about the progress of the work.

Table 1: PB leprosy patients by Demographic and Clinical status, Agra district (U.P.) India during 2001-06

Charaecterstics		Patients on W.H.O. MDT (872)		
		%Total (872)	Completed Treatment(621)	Defaulted treatment(251)
Age	≤14	12.5	13.8	9.2
	15-34	37.8	36.9	40.2
	35-54	35.6	36.4	33.5
	>54	14.1	12.9	17.1
Mean (SEM)		34.2(0.6)	=	=
Sex	Male	45.3	48.1	38.2
	Female	54.7	51.9	61.8
Delay in detection (months)	≤12	51.8	49.6	57.4
	13-36	32.3	34.0	28.3
	>36	15.8	16.4	14.3
Patches	0-2	79.1	78.1	81.7
	3-5	20.9	21.9	18.3
Nerves	0	59.7	58.3	63.3
	1	40.3	41.7	36.7
Clinical status				
I/TT		12.9	12.7	13.5
BT/BTR		84.6	85.0	83.7
N		2.5	2.3	2.8
Smear	+ve	0.2	0.3	0
	-Ve	18.4	18.8	17.1
	Not done	81.4	80.9	82.9

Table 2: Clinical status of patients at the last visit who completed 6 months multidrug treatment (MDT) for Leprosy

Clinical status	Duration of Follow up (Years)					
	<1	1-3	3-5	5-8	>8	Total(%)
Complete Cure	18	40	357	114	16	545 (91.0)
Partial /Not Cure	5	3	2	0	0	10(1.7)
Relapse	1	11	12	2	0	26(4.3)
Relapse+Reaction	0	0	2	0	0	2 (0.3)
Relapse+Grade 1	0	0	1	1	1	3(0.5)
Relapse+Grade 2	0	2	2	0	0	4(0.7)
Only Grade 1	0	0	1	0	0	1(0.2)
Only Grade 2	0	2	2	0	0	4(0.7)
Not cured+Grade 1	0	0	1	0	0	1(0.2)
Type 1 Reaction	1	2	0	0	0	3(0.5)
Total	25	60	380	117	17	599

%	4.2	10.0	63.4	19.5	2.9	(100.0)

Table 3: Incidence of relapses/100 person years at risk

		Cases	Mean Person Years	Person Years at risk (PYAR)	No. of Relapses	Relapse /100 PYAR
Age	<15	81	4.62	374.4	06	1.6
	15-34	221	4.23	933.8	11	1.2
	35-54	220	4.53	996.7	10	1.0
	>54	77	4.31	331.7	08	2.4
	Total	599	4.39	2636.4	35	1.3
Sex						
	Male	287	4.27	1226.9	16	1.3
	Female	312	4.52	1409.5	19	1.4
Delay in Treatment (Year)						
	Upto 1	301	4.37	1315.2	17	1.3
	1-2	201	4.22	850.8	11	1.3
	>3	97	4.85	470.4	07	1.5
Patches	0-2	466	4.37	2037.7	28	1.4
	3-5	133	4.50	598.7	07	1.2
Nerves	0	344	4.24	1458.7	21	1.4
	1	255	4.62	1177.7	14	1.2

Table 4: Crude incidence of disability among PB Leprosy

Factor		Completed Treatment		Defaulters		X^2 and p-value	
		Cases	%CID	Cases	%CID	Completed Treatment	Defaulters
Age	<15	81	0	20	0	22.7, 0.0001	
	15-34	217	0.46	71	1.41		NS
	35-54	219	2.28	72	2.78		
	>54	75	9.33	35	2.86		
Total		592	2.20	198	2.02		
Sex	Male	280	1.74	66	0	NS	NS
	Female	312	2.56	132	3.01		
Patch	0-2	459	2.18	164	1.83	NS	NS
	3-5	133	2.26	34	2.94		
Nerve	0	344	1.16	127	2.36	4.1, 0.043	NS
	1	248	3.63	71	1.41		
Delay in Treatment							
	<12 Mo	299	1.67	115	2.61	NS	NS

13-36 >36	200 93	3.00 2.15	55 28	0 3.57		

Table 5: Incidence of disability/100 person years at risk

	Cases	Mean Person Years	Person Years at risk (PYAR)	new disability cases	incidence/ 100 PYAR
Completed MDT Treatment	592	4.40	2597.4	13	0.50*
Defaulters of MDT Early (<3 months) Late (3-5 month)	198 142 56	4.72 4.87 4.33	933.7 691.4 242.3	4 3 1	0.43* 0.43 0.41
All	789	4.48	3531.1	17	0.48
*Log rank test= 0.23, p=0.63					

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STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3
Objectives	3	State specific objectives, including any prespecified hypotheses	3
Methods			
Study design	4	Present key elements of study design early in the paper	4-6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	4
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*5-6*
Bias	9	Describe any efforts to address potential sources of bias	none
Study size	10	Explain how the study size was arrived at	4
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	5-6
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	6
		(*b*) Describe any methods used to examine subgroups and interactions	
		(*c*) Explain how missing data were addressed	Not applicable
		(*d*) If applicable, explain how loss to follow-up was addressed	5
		(*e*) Describe any sensitivity analyses	
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	6
		(b) Give reasons for non-participation at each stage	5-6
		(c) Consider use of a flow diagram	5
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	7
		(b) Indicate number of participants with missing data for each variable of interest	5-6
		(c) Summarise follow-up time (eg, average and total amount)	8
Outcome data	15*	Report numbers of outcome events or summary measures over time	7-8
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	7-8
		(*b*) Report category boundaries when continuous variables were categorized	7-8
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	
Discussion			
Key results	18	Summarise key results with reference to study objectives	8-9
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	8-9
Generalisability	21	Discuss the generalisability (external validity) of the study results	8-9
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	10

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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PB-Figure 1.emf PB-Figure 2.emf	

6 months fixed duration multidrug therapy in paucibacillary leprosy: Risk of relapse and disability in Agra PB cohort study.

by

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Abstract

Background: Low relapses after 12 months multidrug therapy in paucibacillary (PB) leprosy led to recommendation of reducing therapy to 6 months. However only a few reports are available on long term outcome of 6 months fixed duration therapy for PB patients. Studies on measuring risk of disability are rare. Present study is to assess the cure; default, relapse and disability in a prospective cohort of PB leprosy during follow up of >4 years after treatment.

Design: Prospective

Setting: Primary in our field area of Agra District

Participants: 920 paucibacillary leprosy patients entering the study, 621 completed treatment, 599 followed finally including 271 males, no ethnic differentiation, patients of all age groups except children below 5 years and old persons above 70 years were not included.

Treatment: 6 months fix duration multidrug therapy (MDT) as recommended by W.H.O.

Primary and Secondary outcomes: Treatment completion, cure, relapse and development of disability based on clinical assessment by well experienced doctors.

Statistical Methods: Data has been analyzed using SPSS software, risk is computed as incidence per 100 person years and test of significance used.

Results: Study reports 91% cure rate. Incidence of relapse was 1.3/100 person years with no significant variation by age, sex, delay in detection, patches, Nerves. Crude incidence of disability was 2.2% and varied significantly by age and nerve thickening but not by sex, number of patches, nerves and delay in treatment. Incidence of disability was 0.50/100 person years in treatment completed and 0.43 among defaulters.

Conclusion: Study concludes that relapses do occur after MDT treatment but at the level of 1-2%, incidence of disability remains low (<1/100 PY) in PB leprosy. Low incidence of relapse and disability suggests that 6 months therapy is quite effective. However further improvement may help to improve its efficacy. Longer follow up may add to efficacy measures.

Introduction

Leprosy is unique in terms of the nature of the causative organism, the chronicity of the disease, its prolonged treatment and the definitions of cure and relapse. The principal mode of assessing the effectiveness of therapeutic regimens in leprosy is the relapse rate[1]. The important predisposing factors for relapse include the presence of persister bacilli, monotherapy, inadequate or irregular therapy, presence of multiple skin lesions and/or thickened nerves and lepromin negativity. The conventional methods of confirming activity or relapse in an infectious disease have limited utility in leprosy because of the difficulty in demonstrating bacilli in paucibacillary (PB) cases and absence of a method of *in vitro* cultivation of *M. leprae*. Bacteriological parameters are useful in smear positive multibacillary (MB) leprosy, whereas in PB leprosy, the criteria for relapse depend primarily on clinical features since even histological examination cannot clearly distinguish between reaction and relapse[2].

There are wide variations in estimates of relapse rates in different regions. The risk of relapse from programme based data were reported[2-4] to be low from 0.29% to 1.1% and in closely monitored studies it was estimated as 1% to 6.9% for PB leprosy patients after stopping MDT[5,6]. Although most of these studies provided crude estimates of relapse but a few also estimated using person-years of observation, giving relapse rates of 0.65 to 3.0 per 100 person years for PB leprosy[5,7,8].

One of the reasons for low relapse rate was that follow up was done usually for shorter intervals after therapy. Beside relapses in PB leprosy, there is hardly any study in literature reporting risk of developing disability but one[6] based on pre-MDT era reported that 6.7% developed Grade 1 and another 5.2% Grade 2 disability. However, one recent study based on multidrug treatment had given estimates of risk of developing disability of 2.74/100 person years in multibacillary leprosy[9]. Therefore, more studies on long tern follow up were required to assess the risk of relapse and disability rate in the cohort of patients treated with 6 months fixed duration therapy and thus the present study was undertaken in cohort PB leprosy patients from field surveys in Agra district –namely Agra cohort, with the objectives to assess the risk of relapse and disability rate beside the extent of treatment completion and cure rate.

Design and Methods

Study site, field setting and duration of study

The study was started in our field area in Agra District of Uttar Pradesh on patients detected in field surveys under several studies on prevalence of leprosy during 2001-2006[10-13]. The Agra District is located 200 KM away from Delhi and spread in the radius of 100 KM on either side in length and borders with district Itawa & Firozabad on eastern side, Mathura & Bharatpur on north-west side and Gwalior & Dholpur on south side. Several studies were undertaken since the district was highly endemic for leprosy with prevalence of 16.4/10000 during 2001-03 and 7/10000 during 2004-06. The present study is based on patients detected in such surveys and all patients were followed up till April 2011.

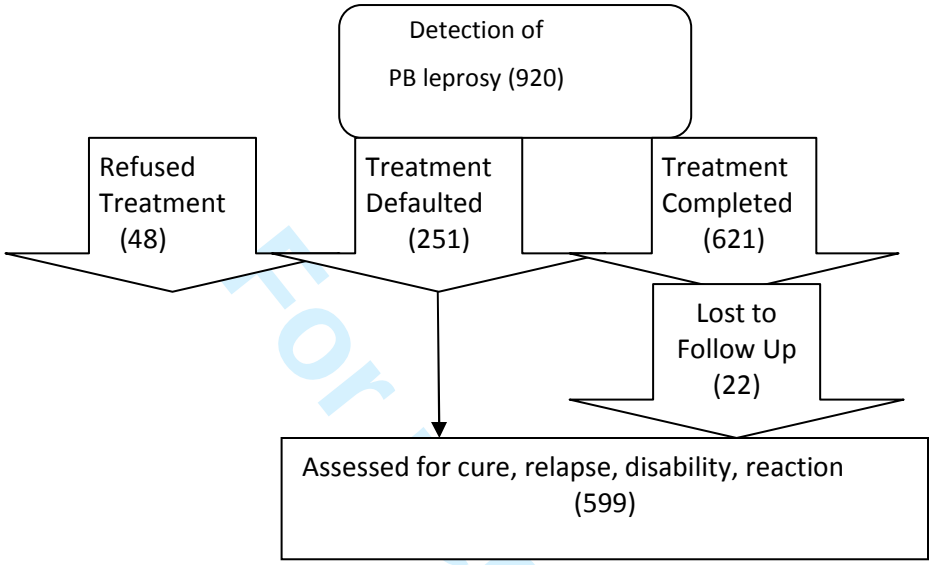
Inclusion/Exclusion criterion of Patients for the study

The study has been conducted in patients detected in the field survey in Agra district during 2001-06. Newly detected leprosy patients diagnosed clinically as paucibacillary (PB) leprosy were taken for the study. This included patients with upto 5 skin lesions, either erythmatous or hypo-pigmented with definite impairment or loss of sensations (tested with ball point pen) and/or 1 thickened nerves. None of the patients had taken leprosy treatment earlier. Children below 5 and adults above 70 were although treated as per norms but not included in the study and so were the pregnant and lactating women.

Cohort size and treatment allocation

During 2001-2006 in Agra district, several field surveys were undertaken to detect leprosy cases. In these surveys, a total of 1050 paucibacillary (PB) leprosy cases were detected. After excluding cases given ROM in the randomized trial, rest was put on W.H.O. MDT as the cases were detected in ongoing surveys. Of the 920 PB cases, 48 did not start the treatment (2 for pregnancy, 2 old aged, 44 simply refused). After this, 872 cases on PB-MDT, 251 (28.8%) discontinued (defaulted) treatments at various durations and reasons. Therefore, a cohort of 599 (96.5%), out of 621 PB patients completed treatment could be

followed up for a mean duration of 4.39(SD:1.6) years after completion of MDT treatment. Present study is based on this cohort of 599 cases (see flow chart).



At the time of starting treatment, all the patients were informed about disease, its implications, treatment, possible side effects, remedies and benefits. Although the treatment given was WHO standard regimen as in routine Government leprosy control programme but for reasons of follow up etc patients were asked to consent and then they were put on respective treatment. In case of children, consent of their parents was taken.

Treatment

W.H.O. supplied MDT packs were used for the study and appropriate W.H.O. recommended doses (Available in blister packs) were given to Children aged 5-14 and adults (aged >14). Monthly PB-MDT was given, with supervisory dose under supervision and for rest of days patients were guided to take daily treatment doses of Dapsone.

Follow-up and assessment

Patients were visited every month till the completion of treatment for drug intake, clinical conditions and side effects. However, formal assessment of each available patient was made every 6 months for 5 years and annually thereafter. Lesion activity- erythema, infiltration and size, reaction, any new lesion and / or new nerve thickening or any deformity was recorded in consultation with the medical doctor who was apart of the

study. Cure of the disease was defined as complete healing of the lesion or patch becoming flat hypopigmented with decrease in size of the lesion and/or regain of sensations. Loss to follow was defined when patients could not be assessed for fairly long time.

Defining Defaulter

A patient who did not complete scheduled 6 months MDT to be able to declare cured. An early defaulter is the one who did not have more than 2 months of MDT and late defaulter is with 3 to 5 months MDT.

Defining Relapse or Reaction

The case of relapse was confirmed by a clinician with >30 years experience in leprosy. Gradual or insidious appearance of new lesion(s) or definite increase in size of the lesion and/or appearance of new nerve thickening were taken as relapse. Any sudden redness, swelling of the lesion with or without new lesion especially during the first 6 to 12 months of follow up, was considered as late reaction. All such patients were first put on corticosteroids[14]. If there was no obvious change in morphology of lesion (inflammation) in 4 weeks, the patients were considered as to have relapsed. If patient responded to 4 weeks corticosteroids, then it was recorded as reaction and not relapse.

Defining disability of Grade 1 and Grade 2

Disability Grade 1 was defined as patient developing anesthesia in palm or sole tested with a ball point pen and Grade 2 as visible deformity in either Hand or Feet or eye (Lagophthalmas). During this time, all cases of clinical relapse, reaction and developing of disability (Grade 1 & Grade 2) were recorded after medical confirmation and necessary medical relief was either provided or referred

Ethical Approval and informed consent

Ethical Approval was taken from Institutional ethical committee who was being informed periodically about the progress of the work. All the patients were informed about the possible side effects, remedies and benefits. Although the treatment given was WHO standard regimen but for reasons of follow up etc, the patients were asked to consent and then they were put on respective treatment. In case of children, consent of their parents was taken.

Statistical methods

The comparison of patients developing disability was done using survival analysis and Log-Rank test to test the significance[15] using SPSS v12 software and Fisher exact test or χ^2 test of significance used to compare proportions[16].

Results

Demographic Characteristics of patients

The patients of all ages were detected in surveys. The mean age was 34.2 years (SEM=0.6). About half of total patients (49.7%) were aged 35 & above and only 12.5% were the child cases (<15 years). Male patients in this study accounted for 45.3% of the total 872 cases put on PB-MDT. At the time of survey, 51.8% patients were those who reported to acquire leprosy during last 12 months, 32.3% in last 12-36 months and rest had disease since over 36 months. A total of 79.1% had upto 2 skin patches, 40.3% with 1 thickened nerve, 84.6% with borderline tuberculoid (BT) disease and only 0.3% (2 cases) were smear positive that too just 1+. Similar distribution is observed among those completed treatment and defaulters (Table 1).

About 40% of the patients had 1 thicken nerve (main trunk or the cutaneous one) as observed in this study. The main nerve involved was ulnar (64.2%), Ulnat cutaneous (4.6%), Lateral popliteal (24%), Radial (0.9%), Radial cutaneous (3.2%), and rest others3.2%). About 2.5% had neuritic leprosy (no skin lesions).

Treatment completion, cure rate and reaction:

Of the total 872 patients who were put on PB-MDT treatment, 621(71.2%) completed their scheduled 6 months treatment and 251 (28.8%) defaulted at various stages of treatment. Among the defaulters, 70.1% defaulted early (within 3 months) and 29.9% during 3-5 months treatment.

Among 621 completed treatments, only 599 could be followed up and 22 were lost to follow up (LFU). About 83% of the patients could be followed up for 3-8 years and some 2.9% for over 8 years. A total of 545(91%) of the 599 were observed to be completely cured, 1.7% either not cured or partially cured and rest were observed to have either

relapsed (35), developed reaction (5/599) or developed disability of Grade 1 (5) or Grade 2 (8) (Table 2).

Incidence of Relapse

The overall incidence of relapse was observed to be 1.3 per 100 person years (Figure 1). The incidence of relapse by age, although, did not change much but was observed to be slightly high in children (<15 years) and among older persons (>54 years). The incidence of relapse by sex, no. of patches, presence of nerve and delay in treatment also did not vary (Table 3).

Incidence of disability among completed treatment vs. defaulters

The crude incidence of disability was observed to be 2.2% in comparison to 2.02% among defaulters. The crude incidence by age varied significantly among completed treatment group (χ^2 = 22.7,p=0.0001) and no significant variation found in defaulters. Although no significant difference in crude incidence of disability was observed by sex, no. of patches and delay in treatment but by nerve status. Patient initially with no nerve developed disability more (χ^2 = 4.1, p=0.043) (Table 4).

Of the 592 patients completed treatment and followed up for over 4 years (Mean = 4.4 years), 13 new cases of disability were observed during follow suggesting incidence of disability as 0.50 per 100 person years (PY) in comparison to 0.43 among defaulters (Table 5, Figure 2). Among the defaulters, incidence of disability was 0.43 in early default and 0.41 in late default.

Discussions and Conclusion

In the present study, 91% of the PB leprosy patients who completed treatment and followed up were completely cured. The reaction rate was observed to be very low (0.8%). The occurrence of events like reaction, relapse and disability measures the effectiveness of any treatment regimen. In present cohort of PB leprosy, the relapse rates have been reported in some studies after MDT with a low rate in programme based data and high in closely monitored studies. Some studies had reported relapse rate of <1% to 6.9% in PB leprosy[2-8]. WHO also reported very low level of relapse[17] but based on country

reports.These reports have information not on all cases being given treatment but only those who report a relapse –resulting in very low repoted relapses.

In the present study, overall relapse rate is observed as 1.3/100 persons years in the PB cohort observed during 2001-10 in Agra district. Most relapses (30/35) were observed 1-5 years after releasing from treatment and almost 11.4% (4/35) beyond 5 years of follow up. The relapse rates did not differ significantly by age, sex, delay at detection, clinical status and with nerve involvement.

Although it is difficult to qualify for high and low relapse rates but relapses do occur and can occur anytime after release from treatment[13]. More relapses may be seen if these patients are followed up for further longer period but extent is not easy to project. In many cases, the cause of relapse may be differential individuals' immunological response to mycobacteria. It would therefore be interesting to investigate the reason of relapses–is it insufficient treatment causing early relapse, persistent dormant mycobacteria leading to late relapse or immunological variations across populations giving mix of above two?

The incidence of disability was noticed 13 patients (5 Grade 1 & 8 Grade 2). Although crude incidence of 2.02% was noticed and significant variation by age (χ^2=22.7, p=0.0001) and nerve involvement (χ^2=4.1, p=0.043) but no significant difference observed by sex,number of patches and duration of delay in treatment. The overall incidence of disability was 0.50 per 100 person years among the group of completing treatment and 0.43 per 100 person years among treatment defaulters (Table 5, Figure 2) with very little difference between early and late defaulters (Log rank test=0.23, p=0.63). This study observed much lower crude incidence of disability than as observed in a pre-MDT time study that reported crude incidence of grade 1 & grade 2 disabilities as 6.7% & 5.2% respectively[6].

The findings of present study once again confirms the findings of another cohort study on MB leprosy[9] that treatment status (complete vs. default) probably does not affect the risk of disability but initiation of treatment may do so. This is beside the fact that at what stage treatment is taken after the disease starts progressing. However, some early cases of grade 1 disability may get altered to normal[6] but many may advance disability to grade 2. This is an important feature of leprosy and may be the result of already set-in pathways for

disabilities. Therefore more studies are required to understand and assess the cause of these pathways to disabilities.

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Contributors: Although all authors were responsible for the conception, design and acquisition of data, drafting, revising and final approval of the article. AK played the lead role in planning, conducting, supervising field study, analysis and report writing; AG for clinical evaluation and BKG for clinical monitoring and report preparation.

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Conflict of interests: None

Patient Consent: obtained

Ethical Approval was granted by the institutional ethical committee, which was being informed periodically about the progress of the work.

Table 1: PB leprosy patients by Demographic and Clinical status, Agra district (U.P.) India during 2001-06			
Charaecterstics	Patients on W.H.O. MDT (872)		
	%Total (872)	Completed Treatment(621)	Defaulted treatment(251)
Age ≤14	12.5	13.8	9.2
15-34	37.8	36.9	40.2
35-54	35.6	36.4	33.5
>54	14.1	12.9	17.1
Mean (SEM)	34.2(0.6)	33.8(0.7)	35.3(1.1)
Sex Male	45.3	48.1	38.2
Female	54.7	51.9	61.8
Delay in detection (months) ≤12	51.8	49.6	57.4
13-36	32.3	34.0	28.3
>36	15.8	16.4	14.3
Patches 0-2	79.1	78.1	81.7
3-5	20.9	21.9	18.3
Nerves 0	59.7	58.3	63.3
1	40.3	41.7	36.7
Clinical status*			
I/TT	12.9	12.7	13.5
BT/BTR	84.6	85.0	83.7
N	2.5	2.3	2.8
Smear +ve	0.2	0.3	0
-Ve	18.4	18.8	17.1
Not done	81.4	80.9	82.9
*I (Indeterminate), TT(Tuberculoid), BT(Borderline Tuberculoid), BTR(BT with initial Type 1 reaction), N(Neurotic without skin lesions)			

Table 2: Clinical status of patients at the last visit who completed 6 months multidrug treatment (MDT) for Leprosy						
Clinical status	Duration of Follow up (Years)					
	<1	1-3	3-5	5-8	>8	Total(%)
Complete Cure	18	40	357	114	16	545 (91.0)
Partial /Not Cure	5	3	2	0	0	10(1.7)
Relapse	1	11	12	2	0	26(4.3)
Relapse+Reaction	0	0	2	0	0	2 (0.3)
Relapse+Grade 1	0	0	1	1	1	3(0.5)
Relapse+Grade 2	0	2	2	0	0	4(0.7)
Only Grade 1	0	0	1	0	0	1(0.2)
Only Grade 2	0	2	2	0	0	4(0.7)
Not cured+Grade 1	0	0	1	0	0	1(0.2)
Type 1 Reaction	1	2	0	0	0	3(0.5)
Total	25	60	380	117	17	599

%	4.2	10.0	63.4	19.5	2.9	(100.0)

Table 3: Incidence of relapses/100 person years at risk

		Cases	Mean Person Years	Person Years at risk (PYAR)	No. of Relapses	Relapse/ 100 PYAR
Age	<15	81	4.62	374.4	06	1.6
	15-34	221	4.23	933.8	11	1.2
	35-54	220	4.53	996.7	10	1.0
	>54	77	4.31	331.7	08	2.4
Total		599	4.39	2636.4	35	1.3
Sex						
	Male	287	4.27	1226.9	16	1.3
	Female	312	4.52	1409.5	19	1.4
Delay in Treatment (Year)						
	Upto 1	301	4.37	1315.2	17	1.3
	1-2	201	4.22	850.8	11	1.3
	>3	97	4.85	470.4	07	1.5
Patches	0-2	466	4.37	2037.7	28	1.4
	3-5	133	4.50	598.7	07	1.2
Nerves	0	344	4.24	1458.7	21	1.4
	1	255	4.62	1177.7	14	1.2

Table 4: Crude incidence of disability among PB Leprosy

Factor		Completed Treatment		Defaulters		X^2 and p-value	
		Cases	%CID	Cases	%CID	Completed Treatment	Defaulters
Age	<15	81	0	20	0	22.7, 0.0001	
	15-34	217	0.46	71	1.41		NS
	35-54	219	2.28	72	2.78		
	>54	75	9.33	35	2.86		
Total		592	2.20	198	2.02		
Sex	Male	280	1.74	66	0	NS	NS
	Female	312	2.56	132	3.01		
Patch	0-2	459	2.18	164	1.83	NS	NS
	3-5	133	2.26	34	2.94		
Nerve	0	344	1.16	127	2.36	4.1, 0.043	NS
	1	248	3.63	71	1.41		
Delay in Treatment							
	<12 Mo	299	1.67	115	2.61	NS	NS
	13-36	200	3.00	55	0		
	>36	93	2.15	28	3.57		

Table 5: Incidence of disability/100 person years at risk					
	Cases	Mean Person Years	Person Years at risk (PYAR)	new disability cases	incidence/ 100 PYAR
Completed MDT Treatment	592	4.40	2597.4	13	0.50*
Defaulters of MDT	198	4.72	933.7	4	0.43*
Early (<3 months)	142	4.87	691.4	3	0.43
Late (3-5 month)	56	4.33	242.3	1	0.41
All	789	4.48	3531.1	17	0.48
*Log rank test= 0.23, p=0.63					

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STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3
Objectives	3	State specific objectives, including any prespecified hypotheses	3
Methods			
Study design	4	Present key elements of study design early in the paper	4-6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	4
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*5-6*
Bias	9	Describe any efforts to address potential sources of bias	none
Study size	10	Explain how the study size was arrived at	4
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	5-6
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	6
		(*b*) Describe any methods used to examine subgroups and interactions	
		(*c*) Explain how missing data were addressed	Not applicable
		(*d*) If applicable, explain how loss to follow-up was addressed	5
		(*e*) Describe any sensitivity analyses	
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	6
		(b) Give reasons for non-participation at each stage	5-6
		(c) Consider use of a flow diagram	5
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	7
		(b) Indicate number of participants with missing data for each variable of interest	5-6
		(c) Summarise follow-up time (eg, average and total amount)	8
Outcome data	15*	Report numbers of outcome events or summary measures over time	7-8
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	7-8
		(*b*) Report category boundaries when continuous variables were categorized	7-8
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	
Discussion			
Key results	18	Summarise key results with reference to study objectives	8-9
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	8-9
Generalisability	21	Discuss the generalisability (external validity) of the study results	8-9
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	10

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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6 months fixed duration multidrug therapy in paucibacillary leprosy: Risk of relapse and disability in Agra PB cohort study

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6 months fixed duration multidrug therapy in paucibacillary leprosy: Risk of relapse and disability in Agra PB cohort study.

by

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Abstract

Background: Many studies focused on multidrug therapy for MB leprosy and rarely on long term outcome of paucibacillary (PB) leprosy having recommendation of therapy for 6 months fixed duration therapy for PB patients. Studies on measuring risk of disability are rare. Present study is to assess the cure; default, relapse and disability in a prospective cohort of PB leprosy during follow up of >4 years after treatment.

Design: Prospective

Setting: Primary in our field area of Agra District

Participants: 920 paucibacillary leprosy patients entering the study, 621 completed treatment, 599 followed finally including 271 males, no ethnic differentiation, patients of all age groups except children below 5 years and old persons above 70 years were not included.

Treatment: 6 months fix duration multidrug therapy (MDT) as recommended by W.H.O.

Primary and Secondary outcomes: Treatment completion, cure, relapse and development of disability based on clinical assessment by well experienced doctors.

Statistical Methods: Data has been analyzed using SPSS software, risk is computed as incidence per 100 person years and test of significance used.

Results: Study reports 91% cure rate. Incidence of relapse was 1.3/100 person years with no significant variation by age, sex, delay in detection, patches, Nerves. Crude incidence of disability was 2.2% and varied significantly by age and nerve thickening but not by sex, number of patches, nerves and delay in treatment. Incidence of disability was 0.50/100 person years in treatment completed and 0.43 among defaulters.

Conclusion: Study concludes that relapses do occur after MDT treatment but at the level of 1-2%, incidence of disability remains low (<1/100 PY) in PB leprosy. Low incidence of relapse and disability suggests that 6 months therapy is quite effective. However further improvement may help to improve its efficacy. Longer follow up may add to efficacy measures.

Introduction

Leprosy is unique in terms of the nature of the causative organism, the chronicity of the disease, its prolonged treatment and the definitions of cure and relapse. The principal mode of assessing the effectiveness of therapeutic regimens in leprosy is the relapse rate[1]. The important predisposing factors for relapse include the presence of persister bacilli, monotherapy, inadequate or irregular therapy, presence of multiple skin lesions and/or thickened nerves and lepromin negativity. The conventional methods of confirming activity or relapse in an infectious disease have limited utility in leprosy because of the difficulty in demonstrating bacilli in paucibacillary (PB) cases and absence of a method of *in vitro* cultivation of *M. leprae*. Bacteriological parameters are useful in smear positive multibacillary (MB) leprosy, whereas in PB leprosy, the criteria for relapse depend primarily on clinical features since even histological examination cannot clearly distinguish between reaction and relapse[2].

There are wide variations in estimates of relapse rates in different regions. The risk of relapse from programme based data were reported[2-4] to be low from 0.29% to 1.1% and in closely monitored studies it was estimated as 1% to 6.9% for PB leprosy patients after stopping MDT[5,6]. Although most of these studies provided crude estimates of relapse but a few also estimated using person-years of observation, giving relapse rates of 0.65 to 3.0 per 100 person years for PB leprosy[5,7,8].

One of the reasons for low relapse rate was that follow up was done usually for shorter intervals after therapy. Beside relapses in PB leprosy, there is hardly any study in literature reporting risk of developing disability but one[6] based on pre-MDT era reported that 6.7% developed Grade 1 and another 5.2% Grade 2 disability. However, one recent study based on multidrug treatment had given estimates of risk of developing disability of 2.74/100 person years in multibacillary leprosy[9]. Therefore, more studies on long tern follow up were required to assess the risk of relapse and disability rate in the cohort of patients treated with 6 months fixed duration therapy and thus the present study was undertaken in cohort PB leprosy patients from field surveys in Agra district –namely Agra cohort, with the objectives to assess the risk of relapse and disability rate beside the extent of treatment completion and cure rate.

Design and Methods

Study site, field setting and duration of study

The study was started in our field area in Agra District of Uttar Pradesh on patients detected in field surveys under several studies on prevalence of leprosy during 2001-2006[10-13]. The Agra District is located 200 KM away from Delhi and spread in the radius of 100 KM on either side in length and borders with district Itawa & Firozabad on eastern side, Mathura & Bharatpur on north-west side and Gwalior & Dholpur on south side. Several studies were undertaken since the district was highly endemic for leprosy with prevalence of 16.4/10000 during 2001-03 and 7/10000 during 2004-06. The present study is based on patients detected in such surveys and all patients were followed up till April 2011.

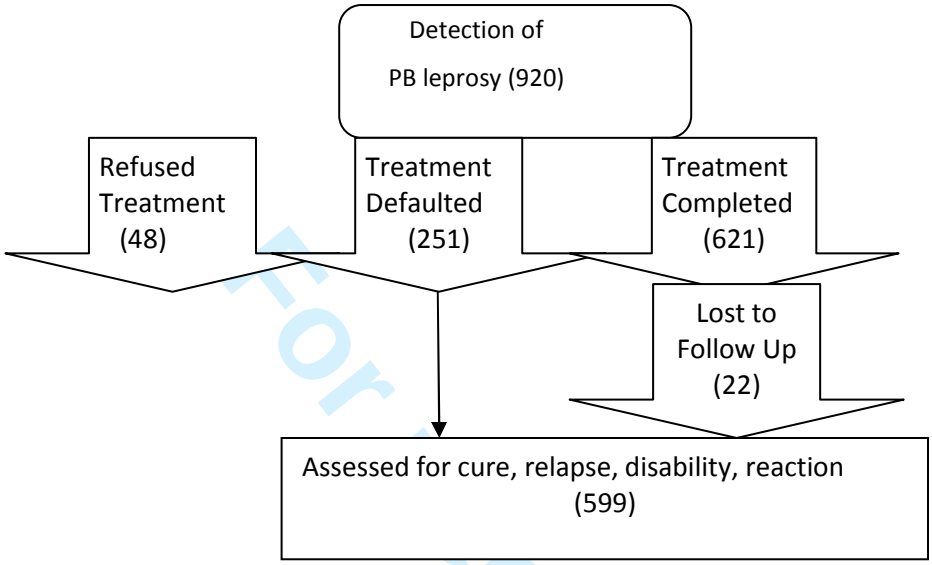
Inclusion/Exclusion criterion of Patients for the study

The study has been conducted in patients detected in the field survey in Agra district during 2001-06. Newly detected leprosy patients diagnosed clinically as paucibacillary (PB) leprosy were taken for the study. This included patients with upto 5 skin lesions, either erythmatous or hypo-pigmented with definite impairment or loss of sensations (tested with ball point pen) and/or 1 thickened nerves. None of the patients had taken leprosy treatment earlier. Children below 5 and adults above 70 were although treated as per norms but not included in the study and so were the pregnant and lactating women.

Cohort size and treatment allocation

During 2001-2006 in Agra district, several field surveys were undertaken to detect leprosy cases. In these surveys, a total of 1050 paucibacillary (PB) leprosy cases were detected. After excluding cases given ROM in the randomized trial, rest was put on W.H.O. MDT as the cases were detected in ongoing surveys. Of the 920 PB cases, 48 did not start the treatment (2 for pregnancy, 2 old aged, 44 simply refused). After this, 872 cases on PB-MDT, 251 (28.8%) discontinued (defaulted) treatments at various durations and reasons. Therefore, a cohort of 599 (96.5%), out of 621 PB patients completed treatment could be

followed up for a mean duration of 4.39(SD:1.6) years after completion of MDT treatment. Present study is based on this cohort of 599 cases (see flow chart).



At the time of starting treatment, all the patients were informed about disease, its implications, treatment, possible side effects, remedies and benefits. Although the treatment given was WHO standard regimen as in routine Government leprosy control programme but for reasons of follow up etc patients were asked to consent and then they were put on respective treatment. In case of children, consent of their parents was taken.

Treatment

W.H.O. supplied standard PB/MDT packs were used for the study and appropriate W.H.O. recommended doses (Available in blister packs) were given to Children aged 5-14 and adults (aged >14). Monthly PB-MDT was given, with supervisory dose under supervision and for rest of days patients were guided to take daily treatment doses of Dapsone.

Follow-up and assessment

Patients were visited every month till the completion of treatment for drug intake, clinical conditions and side effects. However, formal assessment of each available patient was made every 6 months for 5 years and annually thereafter. Lesion activity- erythema, infiltration and size, reaction, any new lesion and / or new nerve thickening or any deformity was recorded in consultation with the medical doctor who was apart of the

study. Cure of the disease was defined as complete healing of the lesion or patch becoming flat hypopigmented with decrease in size of the lesion and/or regain of sensations. Loss to follow was defined when patients could not be assessed for fairly long time.

Defining Defaulter

A patient who did not complete scheduled 6 months MDT to be able to declare cured. An early defaulter is the one who did not have more than 2 months of MDT and late defaulter is with 3 to 5 months MDT.

Defining Relapse or Reaction

The case of relapse was confirmed by a clinician with >30 years experience in leprosy. Gradual or insidious appearance of new lesion(s) or definite increase in size of the lesion and/or appearance of new nerve thickening were taken as relapse. Any sudden redness, swelling of the lesion with or without new lesion especially during the first 6 to 12 months of follow up, was considered as late reaction. All such patients were first put on corticosteroids[14]. If there was no obvious change in morphology of lesion (inflammation) in 4 weeks, the patients were considered as to have relapsed. If patient responded to 4 weeks corticosteroids, then it was recorded as reaction and not relapse.

Defining disability of Grade 1 and Grade 2

Disability Grade 1 was defined as patient developing anesthesia in palm or sole tested with a ball point pen and Grade 2 as visible deformity in either Hand or Feet or eye (Lagophthalmas). During this time, all cases of clinical relapse, reaction and developing of disability (Grade 1 & Grade 2) were recorded after medical confirmation and necessary medical relief was either provided or referred

Ethical Approval and informed consent

Ethical Approval was taken from Institutional ethical committee who was being informed periodically about the progress of the work. All the patients were informed about the possible side effects, remedies and benefits. Although the treatment given was WHO standard regimen but for reasons of follow up etc, the patients were asked to consent and then they were put on respective treatment. In case of children, consent of their parents was taken.

Statistical methods

The comparison of patients developing disability was done using survival analysis and Log-Rank test to test the significance[15] using SPSS v12 software and Fisher exact test or χ^2 test of significance used to compare proportions[16].

Results

Demographic Characteristics of patients

The patients of all ages were detected in surveys. The mean age was 34.2 years (SEM=0.6). About half of total patients (49.7%) were aged 35 & above and only 12.5% were the child cases (<15 years). Male patients in this study accounted for 45.3% of the total 872 cases put on PB-MDT. At the time of survey, 51.8% patients were those who reported to acquire leprosy during last 12 months, 32.3% in last 12-36 months and rest had disease since over 36 months. A total of 79.1% had upto 2 skin patches, 40.3% with 1 thickened nerve, 84.6% with borderline tuberculoid (BT) disease and only 0.3% (2 cases) were smear positive that too just 1+. Similar distribution is observed among those completed treatment and defaulters (Table 1).

About 40% of the patients had 1 thicken nerve (main trunk or the cutaneous one) as observed in this study. The main nerve involved was Ulnar (64.2%), ulnar cutaneous (4.6%), Lateral popliteal (24%), Radial (0.9%), Radial cutaneous (3.2%), and rest others3.2%). About 2.5% had neuritic leprosy (no skin lesions).

Treatment completion, cure rate and reaction:

Of the total 872 patients who were put on PB-MDT treatment, 621(71.2%) completed their standard 6 months treatment and 251 (28.8%) defaulted at various stages of treatment. Among the defaulters, 70.1% defaulted early (within 3 months) and 29.9% during 3-5 months treatment.

Among 621 completed treatments, only 599 could be followed up and 22 were lost to follow up (LFU). About 83% of the patients could be followed up for 3-8 years and some 2.9% for over 8 years. A total of 545(91%) of the 599 were observed to be completely cured, 1.7% either not cured or partially cured and rest were observed to have either

relapsed (35), developed reaction (5/599) or developed disability of Grade 1 (5) or Grade 2 (8) (Table 2).

Incidence of Relapse

The overall incidence of relapse was observed to be 1.3 per 100 person years (Figure 1). The incidence of relapse by age, although, did not change much but was observed to be slightly high in children (<15 years) and among older persons (>54 years). The incidence of relapse by sex, no. of patches, presence of nerve and delay in treatment also did not vary (Table 3).

Incidence of disability among completed treatment vs. defaulters

The crude incidence of disability was observed to be 2.2% in comparison to 2.02% among defaulters. The crude incidence by age varied significantly among completed treatment group (χ^2 = 22.7,p=0.0001) and no significant variation found in defaulters. Although no significant difference in crude incidence of disability was observed by sex, no. of patches and delay in treatment but by nerve status. Patient initially with no nerve developed disability more (χ^2 = 4.1, p=0.043) (Table 4).

Of the 592 patients completed treatment and followed up for over 4 years (Mean = 4.4 years), 13 new cases of disability were observed during follow suggesting incidence of disability as 0.50 per 100 person years (PY) in comparison to 0.43 among defaulters (Table 5, Figure 2). Among the defaulters, incidence of disability was 0.43 in early default and 0.41 in late default.

Discussions and Conclusion

In the present study, 91% of the PB leprosy patients who completed treatment and followed up were completely cured. The reaction rate was observed to be very low (0.8%). The occurrence of events like reaction, relapse and disability measures the effectiveness of any treatment regimen. In present cohort of PB leprosy, the relapse rates have been reported in some studies after MDT with a low rate in programme based data and high in closely monitored studies. Some studies had reported relapse rate of <1% to 6.9% in PB leprosy[2-8]. WHO also reported very low level of relapse[17] but based on country reports.

These reports have information not on all cases being given treatment but only those who report a relapse –resulting in very low reported relapses.

In the present study, overall relapse rate is observed as 1.3/100 persons years in the PB cohort observed during 2001-10 in Agra district. Most relapses (30/35) were observed 1-5 years after releasing from treatment and almost 11.4% (4/35) beyond 5 years of follow up. The relapse rates did not differ significantly by age, sex, delay at detection, clinical status and with nerve involvement.

Although it is difficult to qualify for high and low relapse rates but relapses do occur and can occur anytime after release from treatment[13]. More relapses may be seen if these patients are followed up for further longer period but extent is not easy to project. In many cases, the cause of relapse may be differential individuals' immunological response to mycobacteria. It would therefore be interesting to investigate the reason of relapses–is it insufficient treatment causing early relapse, persistent dormant mycobacteria leading to late relapse or immunological variations across populations giving mix of above two?

The incidence of disability was noticed 13 patients (5 Grade 1 & 8 Grade 2). Although crude incidence of 2.02% was noticed and significant variation by age (χ^2=22.7, p=0.0001) and nerve involvement (χ^2=4.1, p=0.043) but no significant difference observed by sex, number of patches and duration of delay in treatment. The overall incidence of disability was 0.50 per 100 person years among the group of completing treatment and 0.43 per 100 person years among treatment defaulters (Table 5, Figure 2) with very little difference between early and late defaulters (Log rank test=0.23, p=0.63). This study observed much lower crude incidence of disability than as observed in a pre-MDT time study that reported crude incidence of grade 1 & grade 2 disabilities as 6.7% & 5.2% respectively[6].

The findings of present study once again confirms the findings of another cohort study on MB leprosy[9] that treatment status (complete vs. default) probably does not affect the risk of disability but initiation of treatment may do so. This is beside the fact that at what stage treatment is taken after the disease starts progressing. However, some early cases of grade 1 disability may get altered to normal[6] but many may advance disability to grade 2. This is an important feature of leprosy and may be the result of already set-in pathways for

disabilities. Therefore more studies are required to understand and assess the cause of these pathways to disabilities.

Limitation of the study: One of the limitations of the study design is that not all patients could be submitted to skin smear due to their non-cooperation and histopathology was not planned and thus only clinical classification based on long experience of Leprologists in the study was used.

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Contributors: Although all authors were responsible for the conception, design and acquisition of data, drafting, revising and final approval of the article. AK played the lead role in planning, conducting, supervising field study, analysis and report writing; AG for clinical evaluation and BKG for clinical monitoring and report preparation.

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Conflict of interests: None

Patient Consent: obtained

Ethical Approval was granted by the institutional ethical committee, which was being informed periodically about the progress of the work.

Table 1: PB leprosy patients by Demographic and Clinical status, Agra district (U.P.) India during 2001-06			
Charaecterstics	Patients on W.H.O. MDT (872)		
	%Total (872)	Completed Treatment(621)	Defaulted treatment(251)
Age ≤14	12.5	13.8	9.2
15-34	37.8	36.9	40.2
35-54	35.6	36.4	33.5
>54	14.1	12.9	17.1
Mean (SEM)	34.2(0.6)	33.8(0.7)	35.3(1.1)
Sex Male	45.3	48.1	38.2
Female	54.7	51.9	61.8
Delay in detection (months) ≤12	51.8	49.6	57.4
13-36	32.3	34.0	28.3
>36	15.8	16.4	14.3
Patches 0-2	79.1	78.1	81.7
3-5	20.9	21.9	18.3
Nerves 0	59.7	58.3	63.3
1	40.3	41.7	36.7
Clinical status*			
I/TT	12.9	12.7	13.5
BT/BTR	84.6	85.0	83.7
N	2.5	2.3	2.8
Smear +ve	0.2	0.3	0
-Ve	18.4	18.8	17.1
Not done	81.4	80.9	82.9
*I (Indeterminate), TT(Tuberculoid), BT(Borderline Tuberculoid), BTR(BT with initial Type 1 reaction), N(Neurotic without skin lesions)			

Table 2: Clinical status of patients at the last visit who completed 6 months multidrug treatment (MDT) for Leprosy

Clinical status	Duration of Follow up (Years)					
	<1	1-3	3-5	5-8	>8	Total(%)
Complete Cure	18	40	357	114	16	545 (91.0)
Partial /Not Cure	5	3	2	0	0	10(1.7)
Relapse	1	11	12	2	0	26(4.3)
Relapse+Reaction	0	0	2	0	0	2 (0.3)
Relapse+Grade 1	0	0	1	1	1	3(0.5)
Relapse+Grade 2	0	2	2	0	0	4(0.7)
Only Grade 1	0	0	1	0	0	1(0.2)
Only Grade 2	0	2	2	0	0	4(0.7)
Not cured+Grade 1	0	0	1	0	0	1(0.2)
Type 1 Reaction	1	2	0	0	0	3(0.5)
Total	25	60	380	117	17	599 (100.0)
%	4.2	10.0	63.4	19.5	2.9	

Table 3: Incidence of relapses/100 person years at risk

	Cases	Mean Person Years	Person Years at risk (PYAR)	No. of Relapses	Relapse/ 100 PYAR
Age <15	81	4.62	374.4	06	1.6
15-34	221	4.23	933.8	11	1.2
35-54	220	4.53	996.7	10	1.0
>54	77	4.31	331.7	08	2.4
Total	599	4.39	2636.4	35	1.3
Sex					
Male	287	4.27	1226.9	16	1.3
Female	312	4.52	1409.5	19	1.4
Delay in Treatment (Year)					
Upto 1	301	4.37	1315.2	17	1.3
1-2	201	4.22	850.8	11	1.3
>3	97	4.85	470.4	07	1.5
Patches 0-2	466	4.37	2037.7	28	1.4
3-5	133	4.50	598.7	07	1.2
Nerves 0	344	4.24	1458.7	21	1.4
1	255	4.62	1177.7	14	1.2

Table 4: Crude incidence of disability among PB Leprosy						
Factor		Completed Treatment		Defaulters		X^2 and p-value	
		Cases	%CID	Cases	%CID	Completed Treatment	Defaulters
Age	<15	81	0	20	0	22.7, 0.0001	
	15-34	217	0.46	71	1.41		NS
	35-54	219	2.28	72	2.78		
	>54	75	9.33	35	2.86		
Total		592	2.20	198	2.02		
Sex	Male	280	1.74	66	0	NS	NS
	Female	312	2.56	132	3.01		
Patch	0-2	459	2.18	164	1.83	NS	NS
	3-5	133	2.26	34	2.94		
Nerve	0	344	1.16	127	2.36	4.1, 0.043	NS
	1	248	3.63	71	1.41		
Delay in Treatment							
	<12 Mo	299	1.67	115	2.61	NS	NS
	13-36	200	3.00	55	0		
	>36	93	2.15	28	3.57		

Table 5: Incidence of disability/100 person years at risk					
	Cases	Mean Person Years	Person Years at risk (PYAR)	new disability cases	incidence/ 100 PYAR
Completed MDT Treatment	592	4.40	2597.4	13	0.50*
Defaulters of MDT	198	4.72	933.7	4	0.43*
Early (<3 months)	142	4.87	691.4	3	0.43
Late (3-5 month)	56	4.33	242.3	1	0.41
All	789	4.48	3531.1	17	0.48
*Log rank test= 0.23, p=0.63					

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Figure 1: Incidence of relapse in PB leptosy after MDT

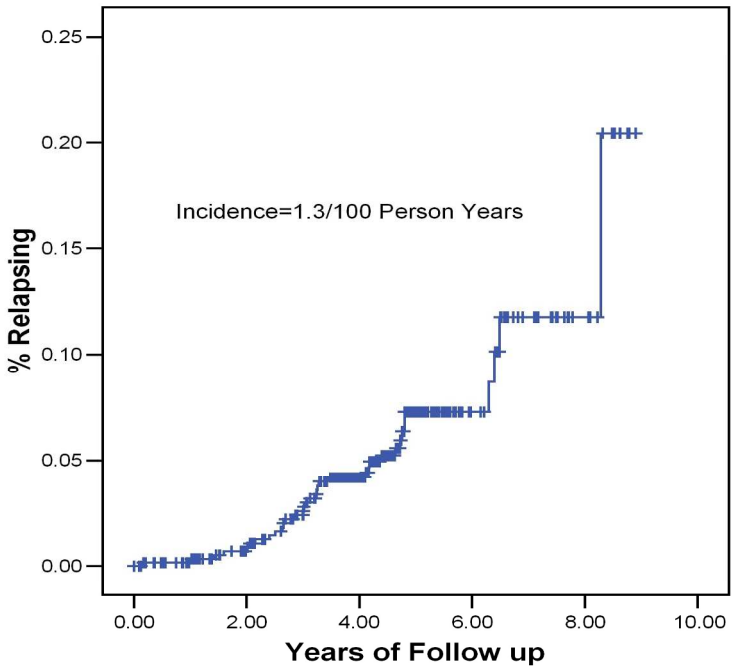

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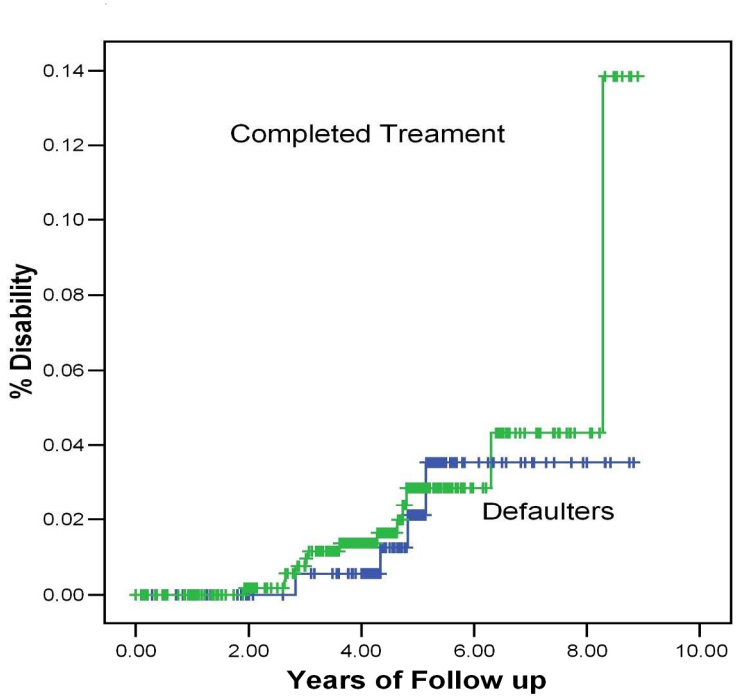
Figure 2: Incidence of disability in PB Leprosy by Treatment status



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STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3
Objectives	3	State specific objectives, including any prespecified hypotheses	3
Methods			
Study design	4	Present key elements of study design early in the paper	4-6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	4
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*5-6*
Bias	9	Describe any efforts to address potential sources of bias	none
Study size	10	Explain how the study size was arrived at	4
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	5-6
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	6
		(*b*) Describe any methods used to examine subgroups and interactions	
		(*c*) Explain how missing data were addressed	Not applicable
		(*d*) If applicable, explain how loss to follow-up was addressed	5
		(*e*) Describe any sensitivity analyses	
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	6
		(b) Give reasons for non-participation at each stage	5-6
		(c) Consider use of a flow diagram	5
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	7
		(b) Indicate number of participants with missing data for each variable of interest	5-6
		(c) Summarise follow-up time (eg, average and total amount)	8
Outcome data	15*	Report numbers of outcome events or summary measures over time	7-8
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	7-8
		(*b*) Report category boundaries when continuous variables were categorized	7-8
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	
Discussion			
Key results	18	Summarise key results with reference to study objectives	8-9
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	8-9
Generalisability	21	Discuss the generalisability (external validity) of the study results	8-9
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	10

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.