ABSTRACTS of Invited Speakers

IL-1 : Key-Note Address

NEW CHALLENGES AND STRATEGIES IN CHANGING SCENARIO OF LEPROSY

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Elimination of leprosy as a public health problem in India has been one of important success stories of modern times. Achieving more than 95% decline in number of leprosy cases and total control on ug resistance were important landmarks for which Govt of India, state governments, national and international NGOs and WHO deserve all appreciation. However, the progress has been very slow and virtually stagnation is seen during the last ten years.

Pockets of endemicity are still present in several parts of the country.

Alarmingly there is rise in deformities which shows disconnect between access to services and our population. Persistent high child rates show continued transmission. Both of these markers indicate a totally unacceptable situation. It is obvious that post 2005 strategy will not work in the current situation.

While accelerating the case detection and treatment activities by active surveys will be of help temporarily, we need to develop micro-planning for different areas as the reasons are likely to vary in different settings and health systems will have be oriented according to local ground realities. We need area specific data and participation of state health services, NGOs, medical colleges and research institutions in this endeavor.

Further, additional measures like chemo-prophylaxis, immunoprophylaxis (MIP/BCG) or both need to be considered. Modified regimens like U-MDT may have programmatic and logistic value. Currently we have excellent molecular tools to trace the transmission and also to keep a watch on ug resistance situation.

We need to have objectivity of reducing the child transmission in a progressive manner and should target zero deformity as main goal. Data from National sample survey to assess the burden of leprosy (report submitted in 2012) and midterm evaluation of NLEP supported by WHO would be useful to plan afresh.

Information generated from several studies supported by Indian Council of Medical Research during the last 10-12 years would also be relevant for this purpose. We can and should win but we have to be in a hurry to overcome the current situation as fast as possible.

IL-2

Challenges in the Management of Leprosy from a Dermatologists Perspective

Prof. Bhushan Kumar

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With the integration of leprosy control into general health services, dermatologists are more responsible than ever before, in the diagnosis of the incident and remaining leprosy cases scattered widely.

Current issues, which need attention, are: criterias for diagnosis of leprosy based on presence of patches, nerve trunk(s) enlargement associated with sensory loss and lesional anesthesia, classification based on location, distribution of lesions, duration of MDT for MB cases and dosage and duration of steroids for treatment of reactions and training of health care workers.

Following continued movement of populations, the disease is likely to be encountered sporadically all over the country and not merely confined to endemic pockets. The most imperative concern is the availability of the expertise especially for management of reactions, neuritis, deformities, trophic ulcers, relapses, ug resistance, and for preventing, arresting and reversing the process of dehabilitation because of leprosy.

Screening tools need to be developed to detect sub-clinical infection and to decrease the delay between diagnosis and treatment. Predicting lepra reactions, their early detection and adequate management will change the perception about the disease.

There is still difficulty in finding an effective intervention to interrupt transmission. There is no evidence that reaching a predefined prevalence will reduce transmission, incidence, or the annual number of new cases?

We need plans for long term care of patients with nerve damage/ reactions, who will continue to present for many years to come? The dermatologists must take over the responsibility for leprosy again; "the disease returns to the original stakeholders". The dermatologists have contributed for leprosy control in the past, and they will now be expected to continue to do so rather with greater zeal in the post elimination era.

IL 3

The Role of Vaccines in Leprosy

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Leprosy is a non-fatal infectious disease caused by *Mycobacterium leprae* whose clinical manifestations are largely confined to skin, peripheral nervous system, eyes, upper respiratory tract (URT) and testes. Among the infectious diseases, it is the leading cause for physical disability.

Mycobacterium leprae discovered in 1872 by G.A. Hansen, was the first major bacterial pathogen of man identified as a causative agent of leprosy as human disease, but till date, it is one the few human pathogens that could not be cultivated in any acceptable in-vitro medium system.

During the last 30 years, India has also achieved spectacular success in achieving more than 95% reduction in the burden of disease by massive coverage with multi-ug treatment (MDT). India reached the elimination levels more than seven years ago.

During the last century, a sizable number of mycobacterial and non-mycobacterial preparations have been tried as immunomodulators against leprosy. Katoch had reviewed these advances. The different agents which have been tried include Mycobacteria, such as, Bacille Calmette-Guerin (BCG), BCG+ killed *M.leprae, Mycobacterium indicus pranii* (Mw), the ICRC bacillus, *M. habana, M. vaccae, M. gordonae* etc., cell wall fractions of *M. leprae*, acetoacetylated *M. leprae*, purified antigens and number of immunomodulators like transfer factor, interferon-gamma, interleukin-2 and levamisole.

A brief account of these mycobacterial preparations as well as other vaccines will be discussed.

IL 4

Touchstones for Prevention of Disability in Leprosy: Full Circle… A Pragmatic Approach for The Clinician

Robert Jerskey

POD Consultant, USA

- "The full circle is symbolic of equality, where no person is more prominent than any other person." - Native American Indian Wisdom.
- The full circle also signifies re-turning; an opportunity to re-examine all, across one's clinic/field landscape at the present juncture of time - and refine.
- This presentation is crafted for those at entry level and for those with years in the field and - across the range between.
- This presentation touches on select P.O.D. topics in the field of leprosy, inviting the attendee to investigate and cultivate areas and skills that aw their attention.

Highlights include these discussions:

- o The value of a multi-sensory approach in the clinic/field so as to not miss "hidden impairments" that underlie disability. This dovetails with the conference theme of "Be the change you want to see in the world".
- o De-mythologizing the impact of the burgeoning global wound care product industry.
- o Re-examination of the W.H.O. Disability Grading System. Is Grade 0, the largest percentage in most registries, under-scrutinized? Is there a marker that can be employed to measure critical nerve involvement underlying disability? While adessing these questions, the terms "insensate", "anaesthetic" and "loss of protective sensation" are discussed. A suggested solution is proposed.
- o Monofilaments [MF] and the challenge in identifying and monitoring those with impaired sensation and "loss of protective sensation". Possible solutions for optimal use to help mitigate the risk of the patient developing further nerve damage, deformity, disability. Among the solutions discussed: is there a missing link, i.e., from the kit of 20 monofilaments, that can help reconcile the vast gap between the 10 gm and the 300 gm MF in the small kits?

IL 5

Occurrence of relapse in a cohort of 577 leprosy patients released from treatment (RFT) between April 2005 and March 2010 from the public health facilities in parts of Maharastra, India - A 3-year active follow up study

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Background:

Extent of post RFT events including relapse has never been documented under the public health (PHC) set up.

Six PHCs in Panvel, Raigad district providing 620 eligible cases (SA1-rural) and Mumbai G/N, G/S and H municipal wards, providing 542 eligible cases (SA2- urban) were included in this study.

Results:

Total of 104 (18%) cases were detected with 'events' among 577 RFT patients (SA1+SA2 combined), including 350 MB and 227 PB Rx groups, available and consenting.

- Neuritis topped the list (63%) followed by relapse (60%) and reaction (20%).
- 54% of them had multiple problems.
- Considering the MB & PB Rx groups, occurrence of post RFT events (20% & 15%; p=0.08) and 'relapse' (12% and 9% p=0.2) were closely comparable.

Conclusion:

Relapse is seen in 11% patients of which 58% were BT cases receiving 12 mths of MB-MDT, thus it would be incorrect to conclude that in MDT treated cases, risk of relapse is negligible. Secondly, proportion of patients with post RFT events requiring medical attention is sizable (18%). Importance of a good surveillance system cannot be overemphasized.

Acknowledgements:

This is part of ICMR task force, multi-centric study on “ug resistance in relapse cases of leprosy'. We are thankful for the Permission and co-operation rendered by the district and state level medical authorities to carry out this study.

IL 6

Clinicians perspective in changing scenario in Leprosy

Jadhav Vitthal

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Owing to integration of Leprosy programme in general health services, post elimination era of Leprosy is faced with problem of declining expertise and resources. On the other hand new case detection rate of Leprosy is on the rise.

Dermatologists have to play crucial role in this changing scenario. This seems impossible unless young dermatologists commit themselves to the noble cause of early detection and appropriate treatment of the disease and participate in research.

It will be worthwhile to invest in reinforced leprosy training in undergraduate postgraduate and field level, follow UMDT protocol and give a try to Chemoprophylaxis of contacts. One needs realistic and practical thought to use newer ugs for problem of relapse and reactions. WHO recommendations are well thought and time tested and clinician should have faith in it.

IL 7

The Management of Post RFT Reaction, Reactivation & Relapse in Leprosy

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Leprosy is one of the several diseases in the state and National Health Schemes of various States and Union territories of the country. There is no vertical programme for the disease and it has been merged with the General Health Systems of each State and UT. Moreover to simplify the delivery mechanisms, as well as for operational reasons, fixed duration therapy is advocated and both PB & MB patients are treated for 6 months and 12months respectively. After completion of prescribed therapy, patients are RFT. There is no mechanism inbuilt in the system to follow up the treated patients and patients self report, based on their perceptions which several times is not timely.

Reactions, relapses, deformities are being

reported after RFT. There are laid down guidelines for treatment of these but several times the results are not optimum. Quite often these also lead to deformities and resulting lifelong morbidity. There is a need to deliberate on them and devise methods for early detection and treatment of these and prevention of deformities which is a common unwanted sequel to these. Also, these conditions are several times precipitated or manifested due to intercurrent illnesses, co-infections and even due to stress of physiological endocrinal changes. These need to be discussed and will be deliberated on.

Moreover some and important advances have been made in the recent years like demonstration of presence of live *M leprae* in reactional lesions, role of immunomodulator MIP in controlling of these, addition of CLF to PB regimen to reduce them are completely take care of them. These will be discussed in detail at the CME. Also "silent neuritis", its presentation and complications resulting there off will be discussed.

IL 8

The challenge to understand nerve damage in leprosy

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Leprosy is a feared disease as a consequence of the always present nerve damage, nerve damage that may go unnoticed and which involves chemical, immunological and pathophysiological mechanisms.

The nerve damage may occur with pain or without pain, the latter relatively unnoticed as silent nerve damage. There, however, may be neuropathic pain without further noticeable damage.

Already Antia and Shetty showed in the early seventies that ultrastructural there is always some damage even when not detected by physiological methods.

The bacilli seem to enter the nerve via adhesion molecules on the endothelial cells, either for the bacillus itself or for the carrying cell. This usually happens in areas prone to traumata. Later, they enter the Schwann cells by binding to the cell membrane. This may give raise directly to demyelinisaton or complement activation resulting in further nerve damage, in particular mediated through LAM (innate immunity).

The adaptive immune system is involved too, directed against *M.leprae* antigenic determinants either on host cells or on remnants of the bacilli itself. Nerves may be damaged directly or via a bystander effect to compression, enzymes or cyto- and chemokines. Here, the complement system may be involved as well, particularly during a type II reaction (ENL).

The accompanying inflammation results in neural oedema and entrapment, which may give rise to demyelinisation and/or a conduction block. The intraneural flow may stop and the blood flow diminishes leading to neural cell death. Even if the immunological inflammation subsides the pressure and entrapment inside the nerve may continue.

At the end only a fibrotic scarred nerve will remain, with occasionally neuropathic pains.

IL 9

Epidemiology of leprosy - new challenges

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It is widely remarked that the global number of

new cases of leprosy declined quite steeply year by year until about 2005, after which there has been flattening of the curve, with very little further decline in case numbers.

Together with the continuing presence of new cases in chilen, most observers conclude that leprosy is still being transmitted in many communities, despite our best efforts to control the disease. The focus of attention is therefore now on the details of transmission and how it may be reduced, ultimately to zero. There are new concerns about possible environmental reservoirs as sources for continued transmission.

In considering the transmission of leprosy from person to person, it is suggested that the very long incubation period is often forgotten as a good explanation for the epidemiological patterns that we observe.

This long incubation period should also influence our thinking about leprosy control, focusing more on long-term sustainable interventions such as contact examination, and less on short-term special efforts, such as one-off surveys.

The example of Myanmar shows how new case numbers are continuing to decline, possibly because of the excellent contact examination procedures that have been in place for decades; they examine contacts annually for 5 years after the index case is diagnosed.

IL 10

Chemotherapy of Leprosy - Key Challenges

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Introduction:

Chemotherapy of leprosy has undergone a sea change over the past three decades. Elimination of leprosy using chemotherapy based on WHO standard Multidrug Therapy (MDT) regimen has been achieved at National level in majority of leprosy endemic countries though elimination needs to be achieved at sub national level remaining a major challenge in the integrated scenario.

After the completion of MDT – relapses, persistence of skin lesions, late reversal reaction (including neuritis) and fresh nerve damage and disabilities are not uncommon. In large programmes such residual problems are likely to be missed due to poor surveillance and lack of education of patients for self reporting before they are released from treatment. Pauci bacillary leprosy patients with multiple lesions may be left with residual hypopigmented lesions at the end of MDT posing clinical problems during surveillance. These problems pose key challenges and more so with shorter duration of treatment. What such patients need is proper counseling at the end of treatment and during surveillance. Therefore health personnel need orientation in managing such clinical events.

Relapse is ultimate factor that will judge clinical efficacy of any regimen. Biological factors determining relapse following any form of chemotherapy may be quite different from those influencing the decline in BI and attainment of negativity.

MDT is very effective in the prevention and treatment of drug resistance in leprosy but has not been possible to reduce the length of treatment substantially. To overcome this issue several potent ugs that can be administered in combination with Rifampicin to achieve a quicker cure are under study. Again the sterilizing capacity of the drugs given alone or in combination is not complete and responsible for persisters which are not without significance and therefore the strong need to explore new drugs in the management of leprosy.

Conclusion

So the post elimination issues arising out of immunological and neurological components of the disease (including post MDT residual skin lesions) should not be considered as a yardstick and therefore these remain key challenges to the programme in terms of identification and assessment of the magnitude of such problems and a comprehensive strategy to manage such morbidities arising out of the disease.

IL 11

MDT efficacy in multibacillary leprosy: A clinicians' perspective & controversies

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Ever since its inception multiug therapy (MDT) has been the backbone of our leprosy elimination campaign. From the time of the original MDT recommendations, modifications to MDT designed to provide ease, simplification and a reduction in the operational requirements for leprosy chemotherapy have evolved. These include the redefinition of a leprosy case and methods for leprosy classification, shortened duration of multibacillary (MB) treatment, integration, U-MDT and A-MDT.

All these modifications have been implemented not only to improve operational factors in leprosy control program in the field but also, to some extent, if not predominately, to achieve elimination target. Over the last decade we have seen significant research in the form of *M leprae* genome being deciphered, new immunological pathways, various biomarkers, cytokines, genetic polymorphisms involved in leprosy patho-mechanisms being studied but there have not been any significant breakthroughs on the treatment front like new ugs, vaccines, immuno-modulators.

As clinicians involved in leprosy care sometimes we have to look beyond the targets and goals; our priority becomes to treat/ cure leprosy patients early and effectively with minimal side effects and with no relapses. All of us agree that leprosy can be cured by MDT and is not an incurable disease that needs lifelong chemotherapy. Yet after MDT completion there is a substantial subset of MB patients with a high bacterial burden at risk for relapse.

Another phenomenon that is being observed is “non responsiveness” to MDT; over the last five years we have observed a subset of patients who have shown “clinical resistance” and these patients did not show any signs of clinical, bacteriological or microbiological improvement despite MDT and immunotherapy. Even after completing WHO MDT MBR all these patients had a positive morphological index and some even demonstrated increase in BI and MI.

These patients can be potential reservoirs and could play an important role in resurgence of leprosy if we do not find a solution soon. We should be watchful and the simple techniques like SSS, biopsy and follow up of patients after treatment should be started again so that we can monitor these patients and intervene appropriately. In such cases we have seen good results with second line ugs like minocycline, ofloxacin; which should also be made available for this subset of patients under strict authorized utilization.

We have successfully eliminated leprosy and National Programs are stepping up efforts and vigil to eradicate it, at this juncture we must critically analyse our treatment guidelines and adess such treatment response riddles if we do not want to witness the resurgence of leprosy.

IL 12

Childhood leprosy: evolving scenario & implications

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Leprosy in children (under 15 years old) is still common in countries where leprosy continues to be endemic. At the end of the reporting year (March 2014), globally 180 618 leprosy patients were on record for treatment. The prevalence rate was estimated as 0.32 per 10 000 population. The proportion of children among new cases in the countries reporting more than 100 cases in South East Asia ranged from 11.9% in Indonesia to 4.1% in Nepal. Among the all new cases, 13 289 had grade 2 disabilities, which reflects low awareness in the community about leprosy and sub-optimal capacity of health systems to detect the disease early; 9.2% of the new cases were in children indicating active transmission of disease and delay in diagnosis.

In post elimination era, the percentage of childhood cases among the newly detected leprosy patients per year in India remained nearly unchanged (range 9.42–10.14%). It implies an existing undercurrent of disease transmission in the country which may erupt any time as many new cases. The number of child cases has decreased in line with a general reduction in case detection, but there is not necessarily a reduction in the proportion of child cases amongst new cases. The time has come to change the standard indicator (proportion of child cases amongst new cases and in future to express the burden of child cases as an age-speci?c rate – the number of cases per 100,000 children under 15 years.

Leprosy control programmes need to monitor the number of children (and their ages) being detected and to consider in each case the likely source of infection; ensuring household contact surveys (or, preferably 'extended contact surveys' which include near neighbours) are carefully conducted. The clinician's response to a new child case should include not only prescribing MDT at appropriate doses, but also a careful assessment for existing nerve function impairment and risk of future impairment, and an assessment of the child's and the family's ability to respond to the diagnosis in a way that minimises the psychological impact and maximises successful self-care. The feasibility of routine provision of prophylaxis (chemo- or immune- or both) for healthy children in households of each newly diagnosed adult leprosy case needs further research.

The children are more likely to present with paucibacillary (PB) leprosy than are adults. There are major diagnostic challenges when assessing a child with suggestive signs of leprosy, and if there is any doubt it is generally safer to keep the child under observation (maybe 2–3 months), then re-examine in the most favourable circumstances possible. Compliance with ug therapy in children requires a level of understanding and involvement of the career. Delay in diagnosis may contribute to the occurrence of disability and the reasons for this delay may differ in children compared with adults. The occurrence of reactions or neuritis is reported from 20-30% of child cases and is commonly the reason for initial presentation, but little has been published on the frequency, management or results of treatment of reaction or neuritis in children.

IL 13

Emergence of Rifampicin Resistance identified by rpoB Gene Mutations in *Mycobacterium leprae* from Relapsed Leprosy Patients

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Background

Rifampicin (RIF) is an important first-line antibiotic for the treatment of mycobacterial infections including leprosy. It is a bactericidal antibiotic that inhibits the bacterial RNA polymerase. Rifampicin resistance is therefore a valuable surrogate marker for drug resistance in leprosy. Clinical and laboratory studies of RIF initially targeted a broad spectrum of susceptible bacteria, and resistance was reported in laboratory studies and from patients who received RIF monotherapy. Resistance rates to rifamycins, determined in the laboratory, have ranged from 1010 to 107, depending on the organism and the methodology used.

Objective

Molecular determination of rifampicin resistance in *M. leprae* in clinically relapse leprosy patient.

Material and Methods

In the present study, we analyzed the DNA sequences of particular regions of *M. leprae* folP1, rpoB, and gyrA, which are responsible for resistance to dapsone, rifampin, and fluoroquinolones, respectively. Several *M. leprae* isolates showed point mutations in the genes. These results suggest the emergence of ug resistant *M. leprae*.

Results

Among the 215 cases, we detected polymorphisms in rpoB gene at codons 410 (Glu-Val), 411 (Ala-Val), 424 (Val-Gly), 427 (Ile-Phe), 433 (Thr-lle), 438 (Gln-Val), 439 (Phe-Leu), 441 (Asp-Tyr) and 442 (Gln-His). This is a major concern during the era of elimination of leprosy.

Conclusion

Results from this study reports resistance to rifampicin in relapsed cases after completion of MDT. Rise in number of the cases with resistance to rifampicin is likely that resistant strains are actively circulating in India suggesting an urgent need for ug-resistant monitoring policy and a careful post-treatment follow-up of cured patients in order to detect relapse earlier and rapidly identify resistant strains. This further indicates an urgent need for identification and inclusion of new ugs in the regimen for treating such cases.

IL 14

The challenge of neuropathic pain in leprosy

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Pain in leprosy is often nociceptive and associated with inflammation and can be present before, during and aft)er treatment and is caused by Leprosy reactions, (Type 1, Erythema Nodosum Leprosum and Neuritis) which are all associated with pain in skin and nerves.

Pain can also be neuropathic (NP) when there is spontaneous pain in absence of a noxious stimuli and in areas of sensory loss). Allodynia - which is pain in response to stimulus which does not normally provoke pain is also part of NP.

Pain can be identified as neuropathic by using the DN4 questionnaire which asks screening questions, pain severity and impact should also be assessed by using the brief pain inventory (BPI). Two previous studies have been done on

neuropathic pain in leprosy, one in Mumbai found that 22% of patients attending a referral clinic for follow up had NP (1) , in a cohort study in Ethiopia 17% of patients who had completed MDT in the last 18 months had NP.(2) We have also completed a study in leprosy pain which we have used detailed sensory testing on patients using the protocol developed by the German neuropathic pain network. Using this protocol was challenging in the resource limited setting in Mumbai. We found that leprosy patients with neuropathy had a unique loss of sensation to temperature but we did not identify a modality associated with presence of pain.

Leprosy patients should be asked about neuropathic pain and the impact that it has on their lives measured. Trials are needed of interventions for treating neuropathic pain.