IADVL

IADVL SIG Neglected Tropical Diseases (NTD)

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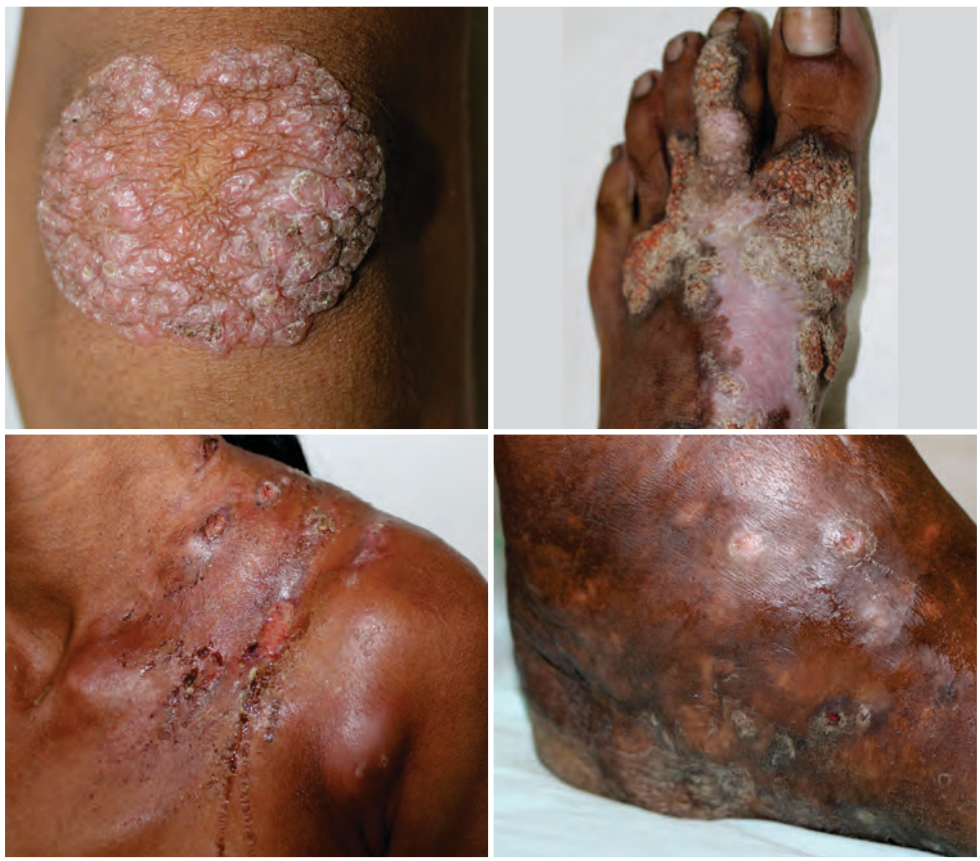
Dr V Ramesh MD
Co-ordinator SIG NTD , Professor & Head,
Dermatology & STD
ESI Medical College, NIT, Faridabad, Delhi NCR
Ex HOD, Safdarjung hospital, Delhi, India

Dr Archana Singal MD, FAMS
Convenor SIG NTD, Director Professor,
Dermatology & STDUniversity college of
Medical Sciences & GTB Hospital
HOD Dermatology, Faculty of Medical Sciences,
University of Delhi

Dr Parul Verma
Editor
Associate Professor, Dermatology Venereology & Leprosy
KGMU, Lucknow (U.P.)



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Welcome Note !

Dr. V Ramesh MD
Co-ordinator SIG NTD

Dr. Archana Singal MD, FAMS
Convenor SIG NTD

Dear IADVL Members

SIG-NTD welcomes you to first edition of its Newsletter.

The very concept of Neglected Tropical Diseases (NTD) categorizes those conditions which fan across many specialities. Almost all are infections caused by diverse organisms affecting the poorer segments of the society. A common thread running through these disorders is insufficient clinical data, continuing morbidity and poor treatment options. All these indicate that they have been relatively neglected by both the research workers and practicing clinicians. About 20 such diseases have been enumerated by the WHO, 12 of which pertain to India. What should also alert us is that most of these diseases are in our arena, so much so that one of these diseases is a SIG by itself, i.e. leprosy. Similarly, leishmaniasis also probably deserves to be a separate one and maybe mycetoma along with the other deep mycoses. However more work and institutional multicentric studies are necessary to glean more information on these conditions. Most of these are also majorly limited to certain geographic areas, e.g. lymphatic filariasis in Kerala and PKDL in Bihar. Other ectoparasitic conditions like scabies and pediculosis are rampant in the populations. I do agree that they are related to socio-economic conditions but still they do present in a vast array of clinical forms that remain to be documented. Some conditions form a bridge between two specialities, e.g. dengue and chikungunya fever. The rash that occurs in these disorders and the hyperpigmentation that occurs after recovery often present to us. Parasitic conditions like cutaneous cysticercosis and other rare parasites that affect the skin form an interesting component of NTD. Keeping these in mind this newsletter is circulated to share information relevant to some of these conditions. The contributors who are members of this SIG have shared their experience in some of the conditions where they have published.

We request all IADVL members to share their experiences in any of the disorders in this group and reach to a wider readership through the future newsletters.

Editor's Desk

Parul Verma

"The importance of Neglected ones"

SIG Neglected tropical diseases (NTD) aims at revisiting, exploring the forgotten tropical dermatological diseases. This is our first edition of NTD-newsletter and on behalf of the SIG NTD, I would like to thank IADVL, IADVL academy and entire team for making this possible. The newsletter includes the latest update regarding three important neglected tropical diseases, Cutaneous leishmaniasis, mycetoma and scabies, followed by an interesting crossword puzzle in the end. We hope this will help all our readers to get important and useful information regarding these diseases.

Finally, we hope this newsletter will help dermatologist to further strengthen knowledge regarding NTDs and promote research in this field.

Parul Verma

Conference Report

DERMACON 2020, Pune (30th Jan to 2nd Feb 2020)

Dr Archana Singal

SIG Neglected Tropical Disease Scientific Session

The prefix 'Neglected' is so true with respect to a group of diseases prevalent in tropical and subtropical countries amongst the resource poor communities and neglected alike by both the clinicians and researchers. However, NTDs were recognised by IADVL (President PN Rao, in 2019) that led to the formation of SIG on NTDs sans leprosy that have predominant skin manifestations.

A dedicated one-hour long session was granted to the SIG NTD during DERMACON 2020 held in Pune on 31st Jan. It was very disheartening to see very poor audience attendance but it didn't dampen the spirits of the speakers. The session was chaired by Dr S R Narahari and Dr Archana Singal. **Dr Chanderkant Revankar** was the first speaker who talked about the **'Unmet needs of NTDs in India'** and highlighted the scope of work to be done in the area of NTDs esp cutaneous leishmaniasis, mycetoma, scabies and filariasis and emphasized the role of dermatologists.

Dr SR Narahari discussed the 'Aetiological diagnosis of lymphoedema'; a condition that results from the failure of lymph drainage resulting in swollen legs due to accumulation of lymph and hypertrophy of tissues. Lymphoedema can be separated into secondary and primary. Primary lymphoedema is due to intrinsic abnormalities of the lymphatic system (LS). It is an error in the development of the LS, which can present at birth (congenital) but may also develop later in life (praecox or tarda). Extrinsic factors cause secondary lymphoedema by damaging LS. Causes could be trauma, cancer (and its treatment) and infection, such as lymphatic filariasis (LF) and Kaposi sarcoma. Venous hypertension and deep vein thrombosis cause lipodermatosclerosis and phlebo-lymphoedema. Any chronic oedema of more than three months due to any cause such as cardiac failure indicates the failure of LS. Physiologically there is little difference from lymphoedema. Recently it is better classified on the genetic basis; as part of the known medical syndrome or associated with dysfunction of known working systems such as vascular, liver and lungs. The fault may be in the tissues or genes such as VEGRF3 (Milroy), VEGFC (Milroy like), 45X0 (Turner), KIF11.

An interesting lecture was then taken by **Prof A K Khare** on, **'Cutaneous Leishmaniasis (CL)- experience from non-endemic area of Rajasthan'.** The deliberation described the clinical profile of CL from south Rajasthan which is non endemic area. During a period of 10 years (2010-2019), a total of 37 patients of CL were diagnosed. There were 18 males &19 females with age ranging from 4 months to 72 years. The duration of disease ranged from 7 days to10 months. Common morphology were nodulo-ulcerative lesions & crusted plaques. One HIV+ case presented as diffuse CL while 3 cases had lupoid leishmaniasis. Thirty five cases were treated with azoles while one patient received intralesional inj. Sodium stibogluconate. A newer approach in the form of CO2 LASER was used successfully in one case. And the session concluded with the last lecture on, '**Establishing Etiological Diagnosis of Mycetoma; Challenges and Impact on Treatment'** by **Prof Archana Singal.** Mycetoma is a mutilating chronic subcutaneous inflammatory disease caused by either true fungi (eumycetoma) and bacteria (actinomycetoma). All 10 patients seen over 4 years, presented with the clinical triad of painless subcutaneous mass, multiple sinuses and discharge containing grains of different colours (6/10) with predominant involvement. Laboratory diagnosis is challenging as culture is frequently negative due to bacterial contamination, improper sampling and frequent previous treatment. **Direct microscopy** of the granules often

demonstrates aggregates of microcolonies of causative organism. Identification by PCR provided diagnosis in one case of culture negative case of eumycetoma. Histopathology from a wedge deep biopsy gave a clue to diagnosis in majority; **Splendore-Hoeppli phenomenon** and presence of grains of the causative organism in the tissue sections is diagnostic. Treatment lacks standardization. However, response in 8/10 cases of actinomycetoma by 6-12 months course of antibiotics (Amoxy-clav + trimethoprim-sulphamethoxazole) in Actinomycetoma patients and tissue debridement with itraconazole in 2 patients of eumycetoma was rewarding. A high index of suspicion and early recognition can improve treatment outcome and reduce deformities.

IADVL Academy & SIG Coordinators Meeting

The meeting was held on 31st Jan 2020 in Pune.

It was attended by Dr Archana Singal on behalf of SIG NTD. After a brief introduction about SIG, she detailed the activities undertaken by SIG-NTD members. She presented the SIG NTD Road map and activities planned for 2020 and discussed the constraints faced by the SIG NTD.

- There was a 2-week long interactive session for SIG NTD, on **ACAD Yahoo Group** where all our members interacted and participated in responding to the queries raised on the platform concerning Cut TB, Scabies, Mycetoma and cutaneous leishmaniasis. The activity was well appreciated and saw participation of dermatologist colleagues from all over the country.
- An E-Newsletter is in the process for tentative submission in July 2020.
- We have planned to conduct 'an open labelled therapeutic trial for the treatment of localized cutaneous Leishmaniasis using two different dosing schedules of intra-lesional Sodium Stibogluconate (SSG)'.
- It was also suggested to the IADVL academy to direct IADVL State Branches to voluntarily opt for certain SIG activities (We would like to hold at least two such symposia (one day each) in the year 2020.

CME (Webinar) Proceedings
27th September 2020

CME (Webinar) was conducted on Neglected Tropical Diseases under the IADVL-SIG Neglected Tropical Diseases (NDT) , IADVL Academy on 27th September 2020 along with IADVL Delhi state branch. The webinar was attended by around 130 delegates. It started with welcome note by Dr Sujay Khandpur and Introduction on Neglected tropical diseases by Dr V Ramesh. First session was a panel discussion on **"cutaneous leishmaniasis-how to diagnose and manage"** under moderation of Dr V Ramesh, followed by another Panel discussion on **"Diagnostic dilemma and management challenges in Mycetoma!"** with Dr Archana Singal as moderator. The panelist for the session were Dr A K Khare, Dr V K Mahajan, Dr Shagufta Praveen for Leishmaniasis and Dr M Ramam, Dr Ravi Vadrevu, Dr Parul Verma and Dr Vineet Relhan for session two on Mycetoma. Both the sessions continued for an hour each with elaborate discussion on the topics. Session three was a short talk on **"Diagnosis of scabies-what's new ?"** by Dr Ishmeet Kaur. She highlighted the role of newer diagnostic techniques with their practical uses. At last interesting and atypical cases in NDT's were presented by Dr Vijay Zawar, Dr Sujay Khandpur, Dr Paschal D'souza and Dr Dilip Kchhawa. Cases were discussed with their unique presentation, diagnosis and therapeutic outcomes. The CME was closed by vote of Thanks by Dr Gulhima Arora.

Cutaneous Leishmaniasis

Shagufta Rather
Associate Professor,
Postgraduate institute. Department of Dermatology,
Government Medical College, University
of Kashmir, Srinagar, Jammu and Kashmir

Ankita Chauhan
Senior Resident
Dept of Dermatology
Swami Dayanand Hospital, Shahdara, Delhi

Introduction

Leishmaniasis is a common neglected tropical anthropozoonosis caused by an intracellular protozoan parasite of genus *Leishmania (L)*. The bite of infected female sand fly of genus *Phlebotomus* and *Lutzomyia* is responsible for disease transmission in Old world (Africa, Asia, Middle East, India) and New world (Central and South Africa, Brazil) leishmaniasis respectively.[1, 2] The clinical spectrum of leishmaniasis is wide and ranges from a mild, self-resolving to mutilating cutaneous and mucocutaneous lesions and even to a fatal visceral involvement.

Cutaneous leishmaniasis (CL) is the most common and least severe type with a global prevalence of around 12 million cases spread across 82 countries and an annual incidence of 0.7 -1.2 million cases occurring worldwide.[2, 3, 4] Depending mainly on the *Leishmania* species and the host immune response, CL can be further broadly classified into localized cutaneous leishmaniasis (LCL), diffuse and disseminated CL (DCL) and mucocutaneous leishmaniasis (MCL) (Box 1). Many advancements have been made in the field of management of cutaneous leishmaniasis in the past decade. This article provides an insight into various available and emergent treatment options and the guidelines.

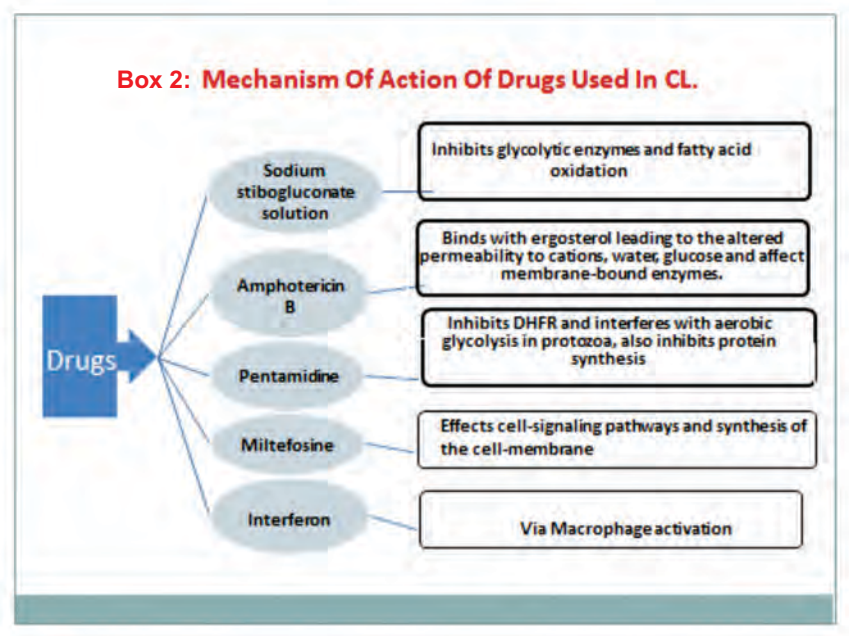
Box 1: VARIANTS OF CUTANEOUS LEISHMANIASIS

1) **Localized cutaneous**
   - Characterized by localized skin ulceration
   - Mostly resolves spontaneously with scarring
2) **Diffuse and disseminated**

   Multiple, pleomorphic lesions in ≥ 2 non-contiguous areas

   - Can present as leonine facies
3) **Mucocutaneous**
   - Mutilating, severe tissue destruction
   - Involvement of skin and mucous membrane
4) **Leishmaniasis recidivans**
   - Recurrence of lesions at site of healed disease
   - Mostly involves face and resembles lupus vulgaris
5) **Post kala azar dermal leishmaniasis**
   - Develops post visceral leishmaniasis
   - Hypopigmented macules to erythematous papules, nodules; might persist for decades

Most lesions of CL are self-resolving and heal spontaneously with scar formation. However, treatment is necessary to minimize the degree of scar formation and in severe cases. Numerous treatment modalities have been used in the management of CL, with pentavalent antimonial compounds being the oldest and most effective of them all and yielding favorable results in both adults and children.[5] **[Figure 1 a-f]. Box 2** illustrates various drugs used in CL along with their mechanism of action. Several factors need to be considered before initiating any particular therapy and different variants of CL have to be treated accordingly. **Box 3, 4, 5** provide an overview of an initial approach to treatment of localized CL, MCL and indications to start systemic therapy. **Table 1** and **Table 2** summarizes various conventional treatment regimens used for CL, mucocutaneous leishmaniasis (MCL) and PKDL. **Table 3** highlights various topical, systemic, physical modalities of treatment that have been tried in management of CL with varying success.



Box 3: Treatment consideration in LCL[6,7,8]

- Pentavalent antimonials form the mainstay of treatment. However, many oral and topical treatment alternatives have become available in recent past.
- Factors that influence the choice of therapy include
  - Size, number, degree of ulceration of lesions
  - Duration of disease
  - Sex and age
  - Relapse and re-infection
  - Mucosal or diffuse involvement
  - Immunosuppressed condition
  - Co-infections
  - Knowledge of resistance to anti-*Leishmania* drugs
  - Anatomical location of the lesion
- Local wound care should be continued and bacterial superinfection should be treated.
- Mild disease is often self-healing. Topical and local therapies are appropriate for early self-limiting lesions in OWCL, on out-patient basis.

Box 4: Indications for systemic therapy in CL

- Size of individual lesion ≥ 5 cm
- ≥ 5 lesions of significant size (disseminated disease)
- Lesions involving cosmetically sensitive areas (face, fingers, toes) or joints
- Associated with presence of nodular lymphangitis or regional lymphadenopathy
- Underlying immunosuppression
- Treatment failure with local therapy, or where local therapy not feasible

Box 5: Treatment consideration in MCL[8,9]

- Choice of anti-leishmanial agent, duration of treatment and dose, should be individualized and therapy should be initiated after assessing severity of mucosal disease.
- Conventional treatment options include pentavalent antimonial (SbV) compounds, Amphotericin B deoxycholate (AmB), liposomal amphotericin B (LAmB), oral miltefosine.
- Hospitalization, co-administration of prophylactic corticosteroid therapy and strict monitoring is recommended for patients with laryngeal/pharyngeal involvement due to increased risk of respiratory obstruction following initiation of anti-leishmanial therapy.

Table 1: Selected treatment regimens for CL (WHO grade evidence) [4,6,7]

†Disease type	Local treatment regimes	††Evidence -grade	Systemic treatment regimes	††Evidence -grade
OWCL - *(L major)*	15% paromomycin +12% methylbenzethonium ointment x 20 days	A	Oral fluconazole 200 mg x 6 weeks	A
	Intralesional antimonials + cryotherapy, both every 3–7 days for up to 5 sessions	A	Pentavalent antimonials 20 mg/kg per day x 10–20 days	D
			Pentavalent antimonials 20 mg/kg per day + pentoxifylline, 400 mg three times daily x 1–20 days	A
OWCL- (*L tropica* & *L infantum)*	Thermotherapy, 1–2 sessions with localised heat (50°C for30 s)	A	Pentavalent antimonials 20 mg/kg per day x 10–20 days	D
			Pentavalent antimonials 20 mg/kg per day x 15 days + oral allopurinol 20 mg/kg x 30 days to treat recidivans caused by *L tropica*	C

NWCL (L Mexicana)	15% paromomycin plus 12% methylbenzethonium ointment for 20 days	B	Ketaconazole 600 mg once daily x 28 days (adult)	B
			Oral miltefosine 2·5 mg/day x 28 days	B
NWCL *(L braziliensis)*	Thermotherapy, 1–2 sessions with localised heat (50°C for 30 s	A	Pentavalent antimonials 20 mg/kg per day x 10–20 days	C
			Liposomal amphotericin B 2–3 mg/kg per day up to 20–40 mg/kg total dose	C
NWCL *(L panamensis L guyanensis)*	Intralesional antimonials 1–5 mL per session every 3–7 days for up to 5 sessions	B	Pentamidine isothionate IM on alternate days x 3 doses	C
			Pentavalent antimonials 20 mg/kg per day x 10–20 days	C
			Oral miltefosine 2·5 mg/day x 28 days	B

†Abbreviations: DCL - diffuse cutaneous leishmaniasis, LCL - localised cutaneous leishmaniasis, NW- New World, OW- Old World

††WHO evidence grading system: evidence obtained from at least one properly designed randomized controlled trial was graded **A**; evidence obtained from well-designed trials without randomization was graded **B**; and opinions of respected authorities based on clinical experience, descriptive studies, or reports of expert committees were graded **C**, and expert opinion without consistent or conclusive studies was graded **D**. (WHO)

Table 2: Selected treatment regimens for MCL and PKDL (WHO grade evidence) [4,6,7]

†Disease type	Systemic treatment regimes	††Evidence-grade
MCL (Any New World *Leishmania species*)	Pentamidine isothionate IM on alternate days x 3 doses	C
	Pentavalent antimonials 20 mg/kg per day + pentoxyfylline, 400 mg three times daily x 1–20 days	A
	Liposomal amphotericin B 2–3 mg/kg per day up to 40–60 mg/kg total dose	C
PKDL (Bangladesh, India, and Nepal)	Oral miltefosine 100 mg daily x 12 weeks (>25 kg); 50 mg daily x 12 weeks, (<25 kg)	A
	Amphotericin B : iv infusion 1mg/kg daily 60–80 doses over 4 months period	C
	Lamb : IV infusion 5 mg/kg daily, twice weekly x 3weeks (total dose of 30 mg/kg)	C
PKDL (East Africa)	Pentavalent antimonials (20 mg Sb per kg per day IM or IV) x 17–60 days + paromomycin (15 mg in 11 mg base per kg per day IM) x 17 days when indicated	C
	Pentavalent antimonial 20 mg Sbv-5 per kg per day, IM or IV x 30–60 days, when indicated	C
	Liposomal amphotericin B: 2·5 mg/kg per day, IV infusion x 20 days.	C
	Miltefosine100 mg per day x 28 days might be beneficial in patients co-infected with HIV & PKDL, when indicated.	C
	Miltefosine100 mg per day x 28 days might be beneficial in patients co-infected with HIV & PKDL, when indicated.	C

†Abbreviations: MCL- Mucocutaneous leishmaniasis, PKDL – post kala-azar dermal leishmaniasis.

††WHO evidence grading system: evidence obtained from at least one properly designed randomized controlled trial was graded **A**; evidence obtained from well-designed trials without randomization was graded **B**; and opinions of respected authorities based on clinical experience, descriptive studies, or reports of expert committees were graded **C**, and expert opinion without consistent or conclusive studies was graded **D**. (WHO)

Table 3: Range of treatment modalities tried in CL [6-10]

S No.	Mode of therapy	Drug agent used
1	**Non-antimonial systemic therapy**	Oral dapsone, allopurinol, pentoxifylline, zinc sulphate, oral antibiotics (metronidazole & cotrimoxazole), oral artesunate
2.	**Non-antimonial intralesional (i/L) therapy**	Intralesional zinc sulphate, hypertonic saline, interferon-gamma (IFN-γ), metronidazole
3.	**Non-antimonial topical therapy**	Topical miltefosine, dapsone, aminoglycoside ointment, imiquimod, 0.045% pharmaceutical chlorite (DAC N-055), Thio-Ben
4.	**Physical therapy**	CO2 lasers, Trichloracetic acid, cryotherapy, thermotherapy, photodynamic therapy, mesotherapy, hydrocolloid polymer dressings

The individual efficacy of intralesional (i/L) SSG in LCL has been proven in several studies and may be considered as a first line preferential treatment to avoid toxicity associated with systemic administration of antimonials. However, non-compliance due to intolerable pain was observed as a major drawback, especially in younger age group. The WHO recommends one i/L injection of 1-3 ml SSG repeated at 2-days intervals until complete subsidence of the lesion. Sharma et al and Tallab et al administered three i/L injections of SSG (1-5 ml) given on alternate day schedule till 5-7 doses in adult population while Aara et al followed a schedule of once or twice weekly i/L injections till 5-7 doses. Zaraa et al. and Agrawal et al found 86·25% and 84.4% efficacy of i/L antimonial treatment in paediatric CL patients. Similar results were documented by Sharma et al and Aara et al in adult cases.[4,6-10]

In the current scenario of ever growing drug resistance and non-availability of antimonial compounds, use of alternative treatment for LCL is on the rise. A recent Indian study found i/L AmB to be a safe and cost-effective alternative with no relapse during 6 months follow up. Furthermore, they also evaluated the efficacy of two different concentrations of i/L amphotericin B (2.5mg/ml vs 5mg/ml) in patients with CL and found the difference to be statistically insignificant. [11] **Table 4** and **Table 5** represent the therapeutic ladder for treatment of leishmaniasis and various adverse effects associated with commonly used anti-leishmanial drugs and their monitoring respectively.

Table 4: Therapeutic ladder for systemic management of Leishmaniasis

S no.	Pathogen	Recommended drug in order of preference
1.	Old world leishmaniasis	
a)	Leishmania major	Miltefosine 1.5-2.5 mg/kg/day for 28 days orally, or Oral fluconazole 200 mg x 6 weeks, or Ketaconazole 600 mg once daily x 28 days, or Liposomal amphotericin B: 2-3 mg/kg/day iv for 5 to 14 days Pentavalent antimonials 20 mg/kg per day x 10–20 days plus Pentoxifylline 400 mg orally three times a day for 20 days
b)	Leishmania tropica	Oral fluconazole, or Liposomal amphotericin B, or Pentavalent antimonials iv ± oral allopurinol 20 mg/kg x 30 days
c)	Leishmania infantum/ L. aethiopica	Liposomal amphotericin B, or Miltefosine, or Pentavalent antimonials iv (± pentoxifylline)
2.	**New world leishmaniasis**	
a)	Leishmania braziliensis	Pentavalent antimonial iv plus pentoxifylline, or Miltefosine, or Liposomal amphotericin B
b)	Leishmania guyanensis	Miltefosine, or Pentamidine isothionate IM on alternate days x 3 doses, or Pentavalent antimonial iv plus pentoxifylline
c)	Leishmania mexicana	Ketoconazole, or Miltefosine, or Pentavalent antimonial iv plus pentoxifylline

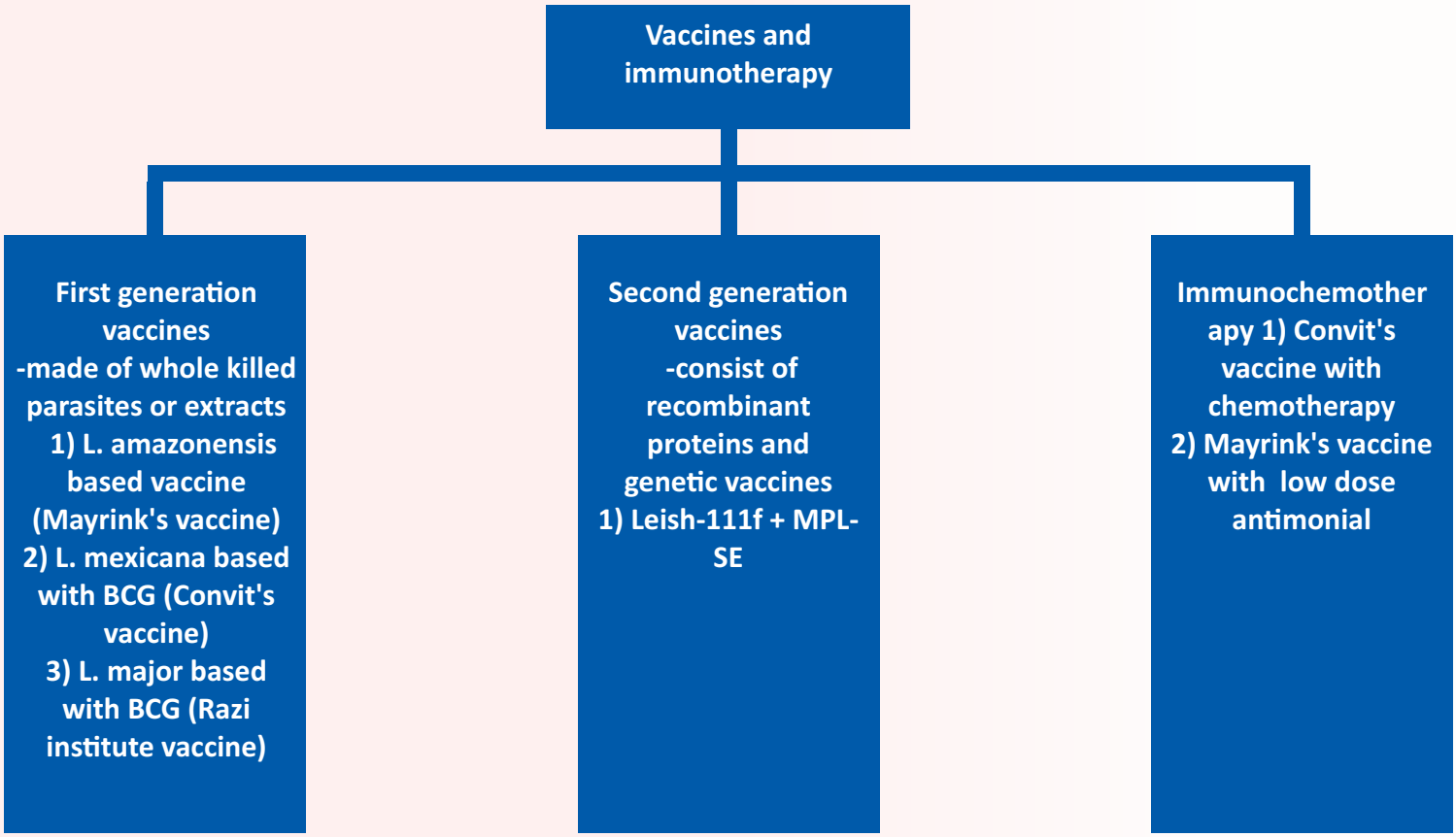
Table 5: Adverse effects associated with anti-leishmanial drugs and monitoring required

S no.	Drug	Adverse effects	Monitoring
1.	Pentavalent antimonials	Musculoskeletal pain, nausea, vomiting, diarrhoea, pain abdominal, headache, anorexia, injection site pain, pancreatitis, hepatitis, marrow suppression, QT prolongation Dose dependent and resolve after discontinuation of drug	Periodic evaluation of cardiac conduction with ECG monitoring; Laboratory assessment in the form of complete blood counts, renal function tests, lipase, amylase and serum transaminases levels
2.	Pentamidine	Nausea, vomiting, diarrhea, pancytopenia, hypotension, arrhythmias, nephrotoxicity, bronchospasm, confusion, hallucinations, risk of hypoglycaemia as well as diabetes mellitus	Periodic evaluation of complete blood counts, renal and hepatic function tests, serum amylase and lipase levels, regular ECG and cardiac evaluation, blood sugar levels and serum electrolytes (potassium and magnesium)
3.	Amphotericin B	Hypotension, nephrotoxicity, anemia, hepatitis, hyperpyrexia, thrombophlebitis	In case of anaphylaxis, stop infusion immediately and no further infusions to be given; Laboratory evaluation of renal, hepatic, hematopoietic function and serum electrolytes (specially magnesium and potassium).
4.	Miltefosine	Vomiting, diarrhea, mild rise in aminotransferases and creatinine levels	Approved for use in patients aged >12 years. Renal and liver functions need to be monitored; severe vomiting, diarrhea, nephrotoxicity or hepatotoxicity require treatment discontinuation

Immunotherapy/immunomodulation and vaccines for CL and MCL

Recombinant *Leishmania* antigen alone or in combination with other antigens, such as BCG, has been used to treat CL with partial success. Pentoxifylline, (TNF-α inhibitor), and imiquimod Toll-like receptor 7 activator and a mediator of cytokine production (IFN-α, TNF-α, IL-1 and IL-12) as local immune response enhancer, have been used in combination with a systemic antimonial in the treatment of both LCL and MCL with a cure rate of up to 90%. The combination of antimonials and immunomodulators could serve as an alternative treatment for patients refractory to antimonial treatment but further evaluation is required.[12] Several anti-*Leishmania* vaccines with partial protective efficacy are currently available.[13]Figure 2 provides an overview on vaccines and immunotherapy available for CL and MCL.

Figure 2: Vaccines and immunotherapy in treatment of CL



Treatment guidelines in special group patients

Treatment for leishmaniasis needs to be modified and regularly monitored in special group of patients (paediatric age group, pregnant and lactating females, immunocompromised patients). **Box 5, 6, 7** highlight various modifications required in these cases.

Box 5: Treatment in pediatric population [6-8,14]

- No specific guidelines are available for treatment of pediatric CL and MCL cases.
- Intralesional SbV therapy should be the preferential mode of treatment wherever feasible.
- Rifampicin, cryotherapy, meglumine antimonate are the recommended interventions for OWCL, while miltefosine and meglumine antimoniate are preferred for pediatric MCL.
- No unusual side effects have been reported and no need for pediatric-specific dosage regimens in cases treated with systemic anti- leishmanial drugs, including L-AmB.
- Its better to avoid SbV or select an alternative antileishmanial agent in children. If needed lower daily dose in mg/kg of Sb V should be used.

Box 6: Management of CL/MCL in immunosuppressed [6-8]

- Lack of well-designed controlled studies; recommendations are based on limited anecdotal studies.
- Use of systemic anti-leishmanial therapy is recommended even for treatment of "focal CL" in presence of moderate to severe immunosuppression.
- L-AmB is considered to be the drug of choice due to its good efficacy and safety profile
- The recommended treatment regimens in persons with HIV/AIDS-associated CL/MCL are usually the same as those in immunocompetent persons.
- Increased risk of toxicity and drug interactions of antiretroviral agents is seen when used in conjunction with SbV, miltefosine therapy and azole/triazoles.
- Initiation of HAART and in accordance with standard practice for HIV/AIDS is the feasible approach. Worsening of Leishmania infection after starting of HAART should be managed with anti-leishmanial agents and, if indicated, corticosteroid therapy.
- Decreasing the dose of immunosuppressive drugs and using higher doses for longer duration of anti-leishmanial drugs may be considered.

Box 7: Treatment of CL In Pregnancy and Lactation [6-8]

- Local wound care in combination with some physical modality should be the initial approach in patients of CL presenting during pregnancy. Specific anti-leishmanial therapy can be postponed.
- **L-AmB:** Pregnancy category B; close monitoring for adverse events is mandatory.
- **SbV therapy:** Pregnancy category D; increased risk of abortions/miscarriages and preterm deliveries in humans, and risk of embryo toxicity and genotoxicity conducted in murine models.
- **Miltefosine:** Contraindicated during pregnancy. FDA recommends that "women with reproductive potential should have a negative pregnancy test before starting therapy and should use effective contraception both during the treatment course and for 5 months thereafter."
- **Lactation:** Amphotericin B and SbV therapy are considered to be compatible with breastfeeding. Miltefosine should be avoided during lactation as significant amount of drug gets transferred into breastmilk.

Definition of cure and end point of treatment

There are several parameters that help us to decide the end point of instituted therapy. Person is referred to be clinically cured when papular, nodular or ulcerative lesions are clinically resolved and the macular lesions show repigmentation at 12 month follow up. However, parasitological cure is considered when parasites can no longer be demonstrated at the end of treatment and at follow up. The size of area of ulceration, size and thickness of induration, color of lesion borders and the extent of scarring are some of the parameters that help to determine treatment endpoints.

Post treatment follow-up and monitoring

Skin lesions in all CL patients should be monitored clinically for 6–12 months after treatment to assess the response to treatment, therapeutic failure and / or relapse. WHO expert consensus group does not recommend repeat parasitological testing if the skin lesion appears to be healing.[9]

Therapeutic failure

Therapeutic failure of a particular drug while treatment of CL, is considered if:

- Incomplete healing of lesions even after 3 months of completion of the treatment course.
- Worsening of existing lesions while on therapy
- Development of new skin lesions while on therapy.

There are several factors that can act as predictors of therapeutic failure; some of them have been enlisted in **Box 8.** Such cases can benefit with a repeat course of antimonials (i/L or systemic), addition of an immunomodulatory agent, use of combination treatments and use of L-AmB.

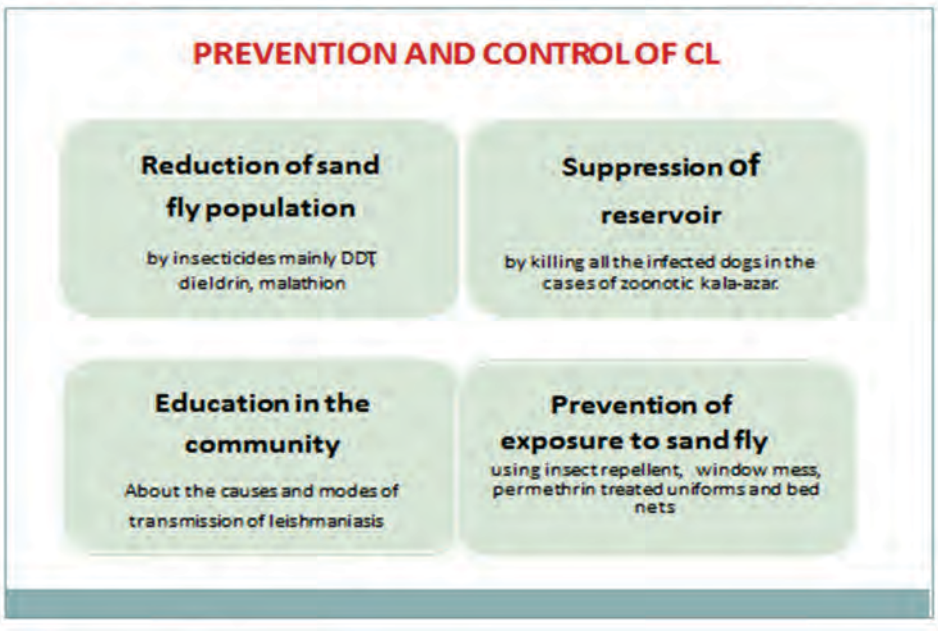
Box 8: Predictors of therapeutic failure

1. **Host factors:** Host's immunological status (CMI), use of corticosteroids, immunosuppressive agents, prior treatment history, incomplete treatment, body weight>68 kg, local trauma.
2. **Parasite factors:** Intrinsic and acquired resistance of parasite to anti-leishmanials.

Prevention and control

Prevention of CL can be achieved by measures directed towards elimination of disease vector and breaking the chain of transmission. **Box 9** provides a four-pronged approach that helps in control of disease.

Box 9



Future challenges

Despite being a well known disease entity for decades, CL still remains to be a major health problem especially in the tropical countries. Various modalities (topical, systemic, i/L) are available for treatment. However, rising trend of drug resistance in certain regions poses a great challenge in treatment of difficult and severe cases. So, research work on newer, better diagnostic methods and novel drugs is need of the hour. Large well conducted randomized trials are desperately needed to reevaluate and formulate treatment protocols for CL. Development of a safe, effective, single dose and low-cost prophylactic vaccine that will provide a long-term protection against leishmaniasis also remains a difficult challenge.

Conclusion

Leishmaniases is a complex disease spectrum that involves cutaneous, mucocutaneous and visceral involvement. Management of patients can be improved by formulation of treatment guidelines, evaluation of presently available and upcoming novel therapeutic modalities using well-conducted randomized controlled trials, vaccine development and control measures to curb transmission.

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Legends

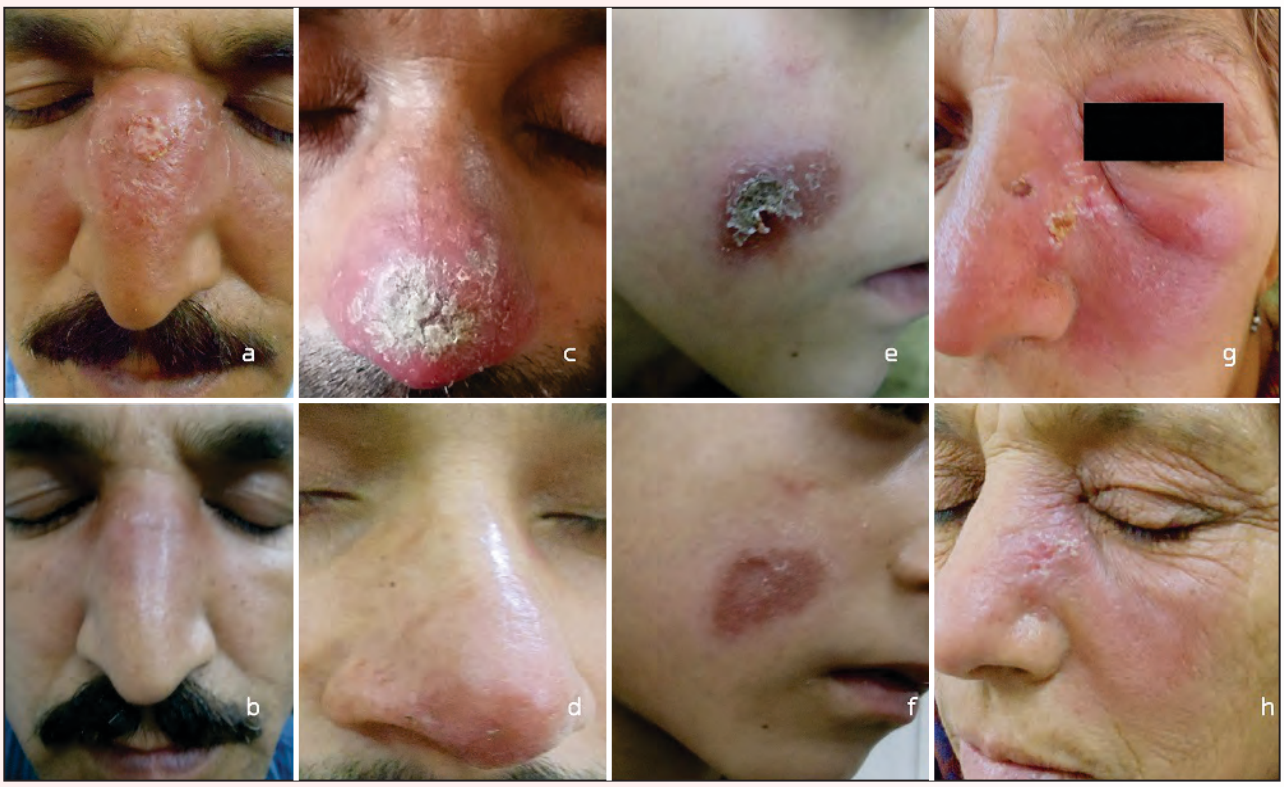
Fig 1: Treatment response to different modalities in patients of CL (Pre- treatment and post-treatment pictures)

a&b) Before and after treatment with intralesional SSG thrice - weekly schedule.

c&d) Before and after treatment with intralesional SSG twice - weekly schedule.

e&f) Before and after treatment with intralesional amphotericin B once - weekly.

g&h) Before and after treatment with systemic treatment with SSG, given IM, daily for 21 days



Mycetoma Current Indian Scenario

Dr Parul Verma
Associate Professor
Dept. Dermatology Venereology & Leprosy
King George's Medical University (KGMU)
Lucknow (UP)

Dr Prakriti Shukla
Senior Resident
Dept. Dermatology Venereology & Leprosy
King George's Medical University (KGMU)
Lucknow (UP)

Introduction and Epidemiology

Mycetoma identified as neglected tropical disease by WHO in 2016, is a chronic disfiguring disease of skin, soft tissues, muscle and bone. Described in Sanskrit texts dating back to 1000 years BCE, it was known as "Padavalmika" (foot anthill) in Atharva-veda. Mycetoma was first reported from the Indian town of Madurae in the mid-19th century and is commonly known as "Madura foot".Reported globally mycetoma is presentpreferably in countries which have short rainy season and long dry season, accordingly "Mycetoma belt" which stretches between the latitudes of 15° south and 30° north of the equator, includes varies tropical and subtropical countries, Bolivarian Republic of Venezuela, Yemen, Arab, India, Mexico, Senegal, Somalia, Sudan and Yemen.[1]Initiated by traumatic implantation, with subtle difference in clinical presentation both bacteria and fungi cause mycetoma, described as actinomycetoma and eumycetoma respectively. Although the exact data on incidence and prevalence is lacking on Mycetoma, actinomycetoma is thought to be more frequent than eumycetoma. In a meta-analysis performed by Wendy et al in 2013 included 8763 cases, most of which were from Mexico, Sudan and India (1392 cases).Rajasthan reported maximum cases per year (33.3), followed by Tamil Nadu (16.8 reported cases/year) and West-Bengal (13.2 reported cases/year).[2] Actinomycetoma is seen more in south India, south -east Rajasthan and Chandigarh whereas eumycetoma more in North India and central Rajasthan.[3]

Table 1 Shows varies mycetoma reports from India.

E: Eumycetoma, A: Actinomycetoma

	Year	Place	No of patients	Type	Age years	Sex M:F	Organisms isolated	Site M/C	M/C occupation
Dubey et al[3]	2017	Delhi	30	All E	15-45	24:6	*A. flavus , A. nidulans F. solani , S. kiliense, C. lunata, E. jeanselmei , M. mycetomatis, Acremonium blochii, F. incarnatum, S. apiospermum complex, M. romeroi, L. theobromae, A. alternata, A. terreus and Phanerochaetechrysosporium.*	Lower extrematies (sp foot)	Agriculture workers and labourers
Swatkar et al[4]	2015 -16	Central India (Nagpur)	11	7 A 4 E	18-55	8:3	Phialophora Fusarium	Foot and lower extremity	Farmer
Padhi et al[5]	2000 - 2009	South India	13	8 A 5 E	22-65	11:2	Madurellamycetomatis, Neoscytalidiumdimidiatum, Aspergillus flavus. *Actinomaduramadurae*, *Actinomadurapelletieri*, Nocardia.	Foot and lower extremity	
Bakshi et al[6]	2001 -5	Western Rajasthan	73	25 A 48 E	21-30	1.61: 1	Madurellamycetomatis (MC), *Madurellagrisea* , *Aspergillus nidulans* , *Actinomadurasomaliensis* (M/C A), *Actinomaduramadurae* , and one case was of *Actinomadurapelletieri* .	Foot	Farmers
Maiti et al[7]	1981 - 2000	West Bengal	264	197 A 67 E	16-25	183: 81	*Nocardia brasiliensis*, *N. caviae*(now called *N. otitidiscaviarum*), *N. asteroides*, *Streptomyces* spp., *Actinomadura*spp., *Madurellagrisea, M. mycetomatis*, *Pseudallescheria boydii*, *Acremonium* spp., *Pyrenochaetaromeroi*, *Exophialajeanselmei,* Unidentied eumycetoma agents	Exposed body parts	Farmers
Venugopal et al[8]	1964 - 1987	Tamil Nadu	210	All eumycetoma			*Actinomaduramadurae*	Foot	
Talwar et al9	1979	North India	20	14 A 6 E	20-40	9:1	*Nocardia, madurellamycetomi, A. pelletieri, Actinomaduramadurae, Phialophorajeanselmei, unidentified.*	Foot/lower extremities	

Vulnerable group

Mycetoma is more common in males than females, this may be attributed to more outdoor and farming activities by males.Majority of the patients reported are in the age group of 20-40, although any age group including children, infantscan be affected.People living in villages and those involved in agriculture work, daily labourers are more commonly affected. Walking barefoot on land and working without proper protective gear increases the risk of infection. In developing countries like India, lack of education, lack of proper health facility and low socioeconomic status also contributes to its vulnerability and associated morbidity.

Causative organisms

Madurellamycetomatis(most common), *Madurellagrisea,Pseudoallescheria boydii and Leptosphaeria senegalensis* cause 90% of eumycetomas reported worldwide.[10] Actinomycetoma is commonly caused by Nocardia spp.(mostly in region with higher humidity) *Nocardia brasiliensis*, *Nocardia asteroids*, *Nocardia otidiscaviarum.*In India, *Nocardia* species and *Madurellagrisea* are the most common causes of mycetoma.[11]

Bakshi et al in 2008 reported the ratio of prevalence of maduromycotic mycetoma to the prevalence of actinomycotic mycetoma has decreased from 4:1 to 1.91:1 during the last five years in western Rajasthan.[6]

Table 2: Causative agents of Mycetoma [10,12]

Eumycetoma	***Actinomycetoma***
Common pathogens *Madurellamycetomatis, (most common)* *Madurellagrisea,* *Pseudoallescheria boydii,* *Leptosphaeria senegalensis*	Actinomadura spp. *Actinomaduramadurae,* *Actinomadurapelletieri* Nocardia spp. *Nocardia brasiliensis* *Nocardia asteroids* *Nocardia otidiscaviarum* *Nocardia caviae* *Nocardia transvalensis*
Others *Leptosphaeria tompkinsii,* *Pyrenochaetaromeroi, Pyrenochaetamackinonii,* *Cladophialophorabantiana, Cladophialophoramycetomatis,* *Curvulariageniculata,* *Exophialajeanselmei,* *Phialophoraverrucosa,* *Acremonium falciforme* *Acremonium kiliense,* *Neotestudinarosatii,* *Fusarium moniliforme,* *Fusarium solani,* *Aspergillus nidulans,* *Aspergillus flavus,* *Aspergillus fumigatus,* *Cylindrocarponcyanescens* *Dermatophytes (Trihophytonspp, Microsporumaudouini)* *Hormonemaspp* *Scedosporium boydii* *Trematosphaeriagrisea* *MedicopsisromeroiGeotrichumcandidumRhinocladiellaatrovirens* *Biatriosporamackinnonii,* *Falciformispora senegalensis* *Cochlioboluslunatus* *Neoscytalidiumdimidiatum*	Others *Streptomyces Somaliensis* *Actinomyces Israeli*

Pathogenesis

Mycetoma organism enters the human skin and subcutaneous tissue through abrasion or prick. In vulnerable individuals initially non specific immune response is initiated,in this initial phase neutrophils play an important role.As the disease progress the response becomes more cellularand TH2 cytokine mediated response is linked to progression of disease. Recent literature also points to a possible role of IL-35 and IL-37 in the pathogenesis of Eumycetoma caused by *Madurellamycetomatis*. Gradually the lesions enlarge to form firm to hard swelling with pustules which break to form sinuses.Host and pathogen related Genetic factors may play some role in the pathogenesis. Verwer et al [13] demonstrated increased risk of M. mycetomatis mycetoma with decreased chitotriosidase activity.

Clinical features

Classical triad comprising of swelling, discharging sinuses and grains forms the hallmark for mycetoma. (Fig 1)Nodules and pustules are formed on the swelling which may rupture to discharge grains. Grains which are colonies of bacteria or fungi are intermittently discharged and vary in colour, size depending upon the organism (table 3). Cystic, verrucous and swelling without sinuses are other clinical variants described.[10] Clinically eumycetoma and actinomycetoma have similar features with subtle differences.(Table 4)Lower extremities and leg are most common sites involved. Other sites which have been affected are upper extremities, forehead, back, perineum, chest, abdomen, scalp and face. Depending upon the site and care taken it can be complicated by septicaemia , dissemination of disease.

Table 3: Classification of mycetoma agents according to colour of grains

Eumycetoma	
Black grains	*Madurellaspp, Leptosphaeria spp.Exophiala spp., Curvularia spp.Phaeoacremonium spp.Pyrenochaetamackinnonii, Phialophoraverrucosa P. romeroi, corynesporacassiicola, plenodomusavramii, pyrenochaetaromeroi, pseudochaetosphaeronema*
White grains , yellow grains	*Pseudallescheria boydii (Scedosporiumapiospermum) Aspergillus spp., Acremonium spp, Cylindrocarponspp, Fusarium oxysporum, Fusarium moniliforme, Fusarium solani, Polycytella hominis*
Green granules	*Aspergillus flavus*
Actinomycetoma	
White yellow grains	*Actinomaduramadurae, Nocardia spp.*
Brown to yellow grains	*Streptomyces* spp.
Red grains	*A. pelletierii*

Table 4:Differences between eumycetoma and actinomycetoma

	Eumycetoma	Actinomycetoma
Caused by	Fungi common species: *Madurellamycetomatis,Madurellagrisea, Pseudoallescheria boydii, Leptosphaeria senegalensis*	Bacteria Common species : *Actinomaduramadurae, Streptomyces somaliensis, Actinomadurapelletieri, Nocardia brasiliensis and Nocardia asteroides*
Distribution	Common in Africa and India(south India and south east Rajasthan)	Common in Latin America, North India and central Rajasthan
Progression	Slowly progressive	Relatively more inflammatory with rapid progression
Lesions	Well-encapsulated with a clear margin	Margin diffuse, more destructive
Sinuses	Few	Many
Grains characteristics	Coarse, of different colours, but mostly white or black(not red)	Fine, of different colours(white yellow, brown, red) usually not Black
Bone invasion and muscle invasion	After a long time	Rapid
Lymphatic spread	Less frequent	More frequent
Cavities in radiograph	larger in size with clear margins and few in number	small in size, many with unclear margins
Ultrasonographic features [10]	Hyperreflective echoes within thick walled cavities which corresponds to grains, are more pronounced.	Fine closely aggregated echoes usually at the bottom of cavities.
KOH Mount	Fungal hyphae seen	no hyphae
Special stains	PAS, GMS (fungal hyphae seen)	Gram, AFB (bacterial elements seen)
Medical treatment only	Slow and often partial improvement	Useful in most cases

Diagnosis

Clinically presence of classical triad in a patient from endemic area should guide towards evaluation for mycetoma. More than one diagnostic methods are needed to know the extent of lesion and aetiology. Morphology of lesion, colour and texture of grains gives some orientation about causative organism. (Table 3) These grains can be collected by either of the ways - by spontaneous extrusion over a saline dressing kept overnight on the swelling, by mechanical compression of the surrounding soft tissue, by obtaining a deep tissue biopsy, or by FNAC (fine needle aspiration cytology). Further investigations include bed side test, imaging, histopathology, FNAC, cell block, culture and molecular diagnosis

Bed side test : Grains are subjected to KOH mount for fungal elements, gram staining and AFB (acid fast bacilli) staining for bacterial colonies.Nocardia species are Gram positive and nearly allare weakly acid fast while actinomadura grains are gram positive and AFB negative.

Imaging: Radiographs of the affected area done is important to know the underlying bony involvement in the form of cavities, bony sclerosis, soft tissue swelling osteoporosis, pathological fractures etc. Similarly ultrasonography, MRI (magnetic resonance imaging) of the affected area helps in, diagnosis, knowing the extent of lesions and help to some extent in differentiating eumycetoma from actinomycetoma. (Table 4)"Dot in circle" sign on MRI is an important indicator for mycetoma it represents high signal granulation tissue with small central hypointense foci within the granulomata representing the grains.[10]

Histopathology: skin tissue subjected to histopathology shows suppurative granulomas along with grains. Skin biopsy is best taken from the site of impending sinus and taking multiple (2-3) biopsy specimen is often helpful. Special satins like AFB, gram stain are used for actinomycetoma and Periodic Acid Schiff(PAS),Gomori methenamine silver for Eumycetoma. Cytodiagnosis can also be done by cell block technique that can provide us the combined advantages of direct smears and histopathology.

Culture and molecular diagnosis: The isolation of the causative agent can be done from grains and tissues, it requires prolonged bacterial cultures in aerobic and anaerobic conditions. Culture media used are Sabouraud Dextrose Agar ,Columbia agar, Brain Heart Infusion, Lowenstein-Jensen etcculture isolates are used for species identification based on micromorphological and cultural properties. Molecular diagnostic procedures are need of an hour to overcome the difficulties associated with the accurate identification of the known causative agents of mycetoma using phenotypic criteria. Rapid identification of causative agent will not only help in accurate diagnosis but to initiate proper treatment on time which could significantly reduce the morbidity associated with mycetoma.Polymerase chain reaction (PCR), Rolling circle amplification(RCA), are methods used for molecular diagnosis.

Matrix-assisted laser desorption ionization-time of flight (MALDI-TOF) mass spectrometry is newer emerging technique.

Treatment:

The treatment of mycetoma depends upon its aetiology. Where actinomycetoma is mostly managed by antibiotic therapy, surgical intervention may be required for eumycetoma. Nevertheless, a prolonged course of treatment is necessary to obtain cure in both conditions.

Actinomycetoma responds to cotrimoxazole, dapsone, streptomycin, trimethoprim (TMP), rifampicin, and amoxicillin-

clavulanic acid. Netilmicin with cotrimoxazole, amikacin with cotrimoxazole and rifampicin, ciprofloxacin, linezolid, imipenem and meropenem have also shown success. Combination therapy is preferred to avoid the risk of drug resistance.(Table 5)Renal, hepatic and audiometric assessment is prerequisite for starting the above therapy, as well as later during the treatment cycles. Monotherapy with amoxicillin-clavulanic acid is preferred in pregnant patients.

Eumycetoma usually requires a combination of medical and surgical therapy for cure. Itraconazole (400mg/kg/day in 2 divided doses for adults) for up to 1-2 years may be required and is the mainstay antifungal agent used against eumycotic mycetoma. Posaconazole and voriconazoleare the other antifungals used for Eumycetoma, although there are limited studies to demonstrate the efficacy of newer antifungals and their role is as of yet questionable. Recently fosravuconazole an new oral antifungal drug is being tried for eumycetoma [14]

Prevention: Preventive measures such as avoiding walking barefoot, using back shield, maintaining proper hygiene especially in endemic areas such as our country might help avoid acquiring infection. Though no one measure may be entirely protective, early diagnosis and treatment may help prevent long-term sequelae and disfiguring amputation.This may be made possible through health education, control programmes and by increasing awareness among venerable groups and health care workers regarding the disease.

Learning points

1. Mycetoma included under neglected tropical disease by WHO in 2016
2. Actinomycetoma is more common than Eumycetoma
3. Most common cause of Eumycetoma world wide is MadurellaMycetomatis
4. Nocardia species are common cause of Actinomycetoma
5. “Dot in Circle” sign is important diagnostic indicator for Mycetoma on MRI
6. Future diagnostic advancements for mycetoma includes molecular methods including PCR, Sequencing and MALDI-TOF
7. Fosravuconazole is new antifungal under trial for eumycetoma

Table 5: varies treatment regimens described for actinomycetoma

Regimen	Intensive phase	Maintenance
1. Welsh regimen[15]	Inj. Amikacin for 21 days, 1–3 cycles with intervals of 15 days between cycles +cotrimoxazole continuously for 35–105 days	
2. Two step regimen[16]	Crystalline Penicillin + Gentamicin + Tab Cotrimoxazolefor 5 to 7 weeks	Tab Cotrimoxazole+ Tab Amoxicillin for 2–5 months after disease becomes inactive
3. Modified two step regimen [16]	Gentamicin(80 mg twice daily, IV), and Cotrimoxazole (320/1600 mg twice daily)weeks for 4 weeks	Doxycycline(100 mg orally, twice daily), and Cotrimoxazole (320/1600 mg twice daily) Till 5-6 months after complete healing of all sinuses.

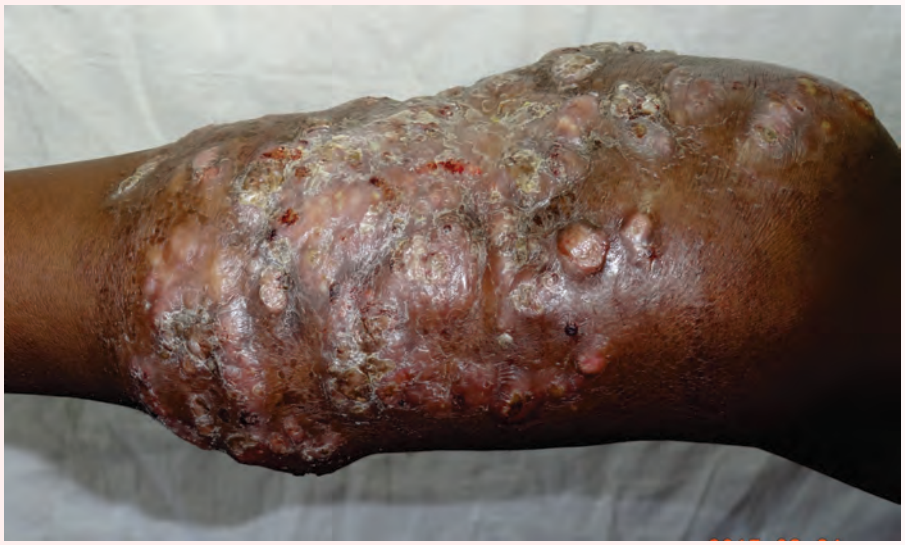


Fig 1

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Legends to figure 1

Swelling with, discharging sinuses

Courtesy: Dr Swastika Suvirya

Scabies: An Update

Dr Simi SM
Professor,
Department of Dermatology,
Sree Gokulam Medical College & Research Foundation, Thiruvananthapuram, Kerala

Dr Usha Chandra
Senior Resident
Dept. Dermatology Venereology& Leprosy
King George's Medical University, KGMU, Lucknow

Scabies is an itchy skin condition caused by an infestation by microscopic itch mite sarcoptes scabiei var hominis. As per The World Health Organisation (WHO) report around two hundred million peoples are globally affected with scabies at any time with a prevalence of around 0.2% to 71%.The World Health Organisation has included scabies in the list of neglected tropical diseases (NTDs) in 2017.

The mite & the transmission.

Transmission of scabies is predominantly through direct skin-to-skin contact, with fomite playing a minor role except in crusted scabies as they have millions of mite as compared to with ordinary scabies patient which may have an average of 12 mites. Scabies mite stay for 24-36 hrs outside human skin at normal room temperature. Overcrowding, young age, poor hygiene, chronic debilitating conditions and poor personal care makes an individual prone to this infection. It is also considered as sexually transmitted infection and immunocompromised states like HIV are associated with crusted scabies.

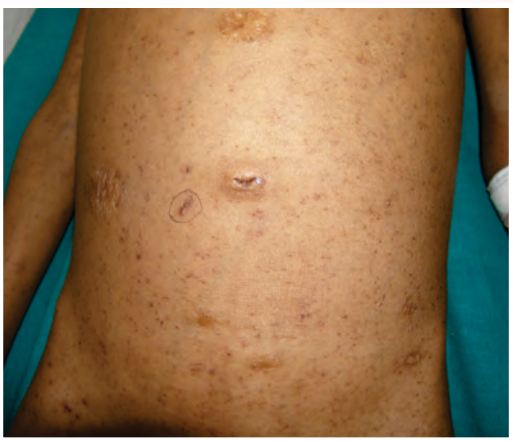
Clinical features

Classically presents as itchy papular eruptions distributed over web space, wrist, genitals, breast in females, axilla, thighs and abdomen.(Fig 1, 2)Palms and soles may be involved in infants. (Fig 3) First episode requires an incubation period of 3-6 weeks for host to sensitize. The skin eruptions are a part of hypersensitivity reaction to the mite and subsequent exposure may results in rapid development of lesions due to prior sensitization. Crusted scabies is characterized by hyperkeratotic and crusted plaques, minimal itching and with millions of mites. Highly infectious and commonly seen in patients with chronic debilitating diseases and immunosuppression. It is thought to develop in patients with defective T cell response, decreased cutaneous sensation and some studies have association with HLA-A11.[1]Davis et al. developed grading system for crusted scabies and classified it as mild, moderate and sever. It can be used as a guide for classifying and treating crusted scabies.[2]

Scabies however can have diverse and atypical presentations described as Scabies surrepticius.[3]These variants are more commonly seen in elderly, children, infants, immunosuppressed patients and patient with crusted scabies. variants described includes,

- Nodules resembling prurigo nodularis,
- Malar erythema as seen in systemic lupus erythematosus,
- Pityriasis rosea likescaly papule[3],
- Resembling dermatitis herpetiformis[3]
- Resembling Langerhan's histiocytosis[3]
- Bullous lesions resembling bullous pemphigoid[4]
- Scabies of the scalp resemblingseborrheic dermatitis
- Erythroderma (in crusted scabies)[1]
- In AIDS patients pruritic papular dermatitis and presentation resembling Dariers disease or psoriasis have been described.
- Subungual scabies: subungual debris and nail dystrophy can be seen as part of normal or crusted scabies.[1]Requires additional treatment to prevent relapse.

A nationwide 14 year-long population-based matched-cohort study done in Taiwan showed that patients with scabies had a higher risk of subsequent psoriasis. T-helper 17 cell-mediated inflammatory pathway may be involved in this association.[5]



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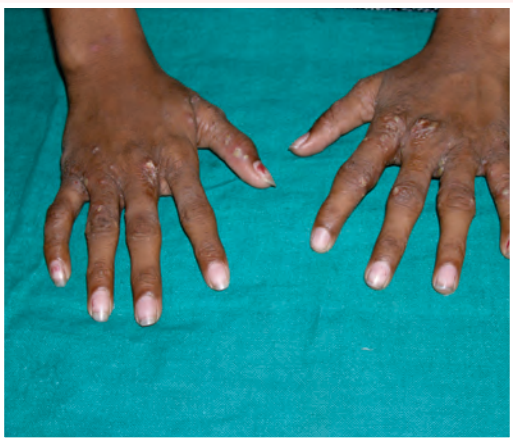

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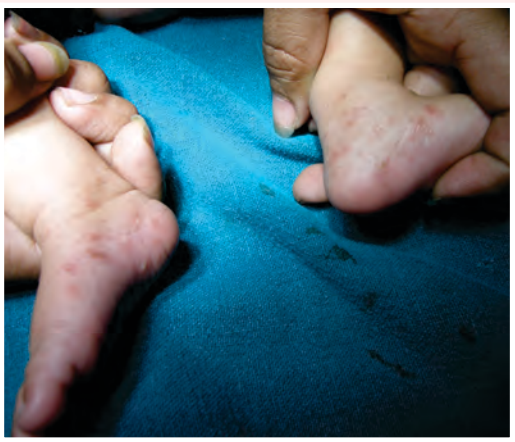

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Diagnosis

Clinical diagnosis: based on classical clinical features

Skin scraping and microscopy: material obtained from scraping of burrow is examined under the microscope to look for mite, eggs or scybala and is diagnostic of scabies.

Burrow ink test: cover the lesion with ink and remove it later with alcohol to look for ink tracking in burrow.

Dermatoscope: scaly burrow is visualised better and one can see "jet with contrail" that is mite at the end of the burrow as a dark triangular structure.The "mini triangle sign" refers to scabies eggs that show the head of the maturing mite within the egg.[6]

Videodermatoscopy, reflectance confocal microscopy and Polarising microscopy: provide a more detailed inspection of the mite.

Histopathology: finding mite or its parts, eggs on skin biopsy section is diagnostic. Dermal infiltrate are superficial and deep with perivascular eosinophilia and neutrophils. It is also characterized by numerous plasma cells.

Nested PCR: assay based on the cox1 gene (mitochondrial cytochrome c oxidase subunit 1) of S. scabiei[6]

The Delphi (consensus) study categorised the scabies into three levels of diagnostic certainty which are "confirmed scabies," "clinical scabies" or "suspected scabies". Each level was based on set of different diagnostic methods. These criteria can be used for clinical trials and field studies.[7]

Treatment

Treatment is justified in suspected and confirmed cases. There are limited studies regarding comparison of effectiveness and safety of scabicides and there are no treatment guidelines for recurrent scabies. It may take 6 weeks for symptoms and signs to go, as hypersensitivity takes a longer time to resolve.

Treatment	Mechanism of action	Dose	Comments
Cream Permethrin(5 %)	Scabicidal, Disrupt the neuronal sodium channel repolarisation causing insect death	Adults: apply along the hairline, neck, side of the head and other parts of body below neck (In infants, apply same as adult including the scalp, side of the head, and forehead). Leave cream on the skin for 8 to 12 hours (2 hours for pregnant or breast feeding female, children < 2 years) and wash. Repeat in 7 days	Most common and effective treatment Approved for children > 2 month of age Pregnancy category B Resistance reported
Lotion Lindane 1% (γ-benzene hexachloride)	Effects nervous system of parasite	Apply entire skin surface from the neck down, Leave on for 8 to 12 hours, then remove by washing thoroughly Repeat in 7 days	US FDA black box warning (risk of neurotoxicity) Withdrawn in many countries
Cream Crotamiton 10%		Apply entire skin surface from the neck down on day 1, 2, 3,8.	Have anti-pruritic effect Questionable effectiveness
Precipitated Sulfur5-10%		Apply entire skin surface from the neck down on day 1, 2, 3 for 8 hours	Safe in neonates, during pregnancy Malodourous Questionable effectiveness
Lotion Benzyl Benzoate 10%	Neurotoxic to mites	Apply entire skin surface from the neck down for 24 hours	Effective and inexpensive Contraindicated in pregnant and infant
Ivermectin cream/lotion 1%	Inhibits gamma amino benzoic acid transmission in mites	Apply entire skin surface from the neck down at a dose of 400 microg/kg , repeated once the following week [8](as used in studies)	Safe and may be as effective as topical permethrin,
Oral Ivermectin 200µg/kg/dose Scabicidal	Inhibits gamma amino benzoic acid transmission in mites[1]	Two doses each approximately one week apart. Guidelines recommend taking on an empty stomach, few experts recommend taking with a meal to increase bioavailability Used in mass drug administration with good safety profile[6]	Pregnancy category C Contraindicated in patients central nervous system disorders [1] Not approved for children <15kg.
Esdepallethrin(0.63%)aerosol[9]			Can be used in infants [9].
Moxidectin[6]		Single dose around 0.6 mg/kg,	moxidectin is retained in skin throughout the 2-week life cycle of the mite. Safety profile still under evaluation

Other modalities [6]	
Urea based emollients	For hyperkeratotic skin lesions
Fluazuron	Insect growth regulators
Fluralaner	Affects insects nervous system
Tea tree oil, neem oils and turmeric	
Antibiotics	For secondary bacterial infections
Treatment of contacts	

Treatment of crusted scabies:

Crusted scabies is most contagious and a very severe infestation of scabies. Chances of treatment failure is common. Combination of oral and topical medication along with keratolytic agents is must. Repeated dosing of medication is required. Application of topical medication in subungual areas with nail trimming should be consider. Topical Permethrin (5%) should be applied for overnight, on every 2-3 days up to 1 – 2 weeks, to the entire body surface, including sub ungual region.Benzyl benzoate

(25% in adults and lower concentration in children) is used as alternative to topical permethrin. It has found to be effective along with oral Ivermectin in severe crusted scabies. Ivermectin – with the dose 200µg/kg/ dose of multiple regimen depending upon severity has been prescribed. CDC (centers for disease control and prevention) describes according to severity, three doses regimen (days 1, 2, and 8), five doses regimen (days 1, 2, 8, 9, and 15), or seven doses regimen (1, 2, 8, 9, 15, 22, and 29).Keratolytic agent is used to increase efficacy of topical such as 5-10% salicylic acid in petrolatum, 40% urea or by soaking in a hot bath.

Immunotherapy and Vaccines

They might help to combat the emerging drug resistance and scabies outbreaks. In crusted scabies TH2 response predominates while in normal scabies Th1 response is able to control the disease. Immunotherapy in crusted scabies with increasing doses of allergens may be of some value. Hypoallergenic recombinant allergens and immunotherapy with T-cell peptide epitopes are the approaches which have been tried

Scabies control

- Mass drug administration: SHIFT trial found mass drug administration with invermectin to be useful in decreasing the prevalence[6]
- Merging the scabies control activities with already existing skin NTD control activities
- **International Alliance for the Control of Scabies (IACS):** A global network of group of experts from various disciplines who are committed to the cause of scabies.

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Fig 1**:**Papules and excoriation on abdomen. A linear burrow could be seen near umblicus

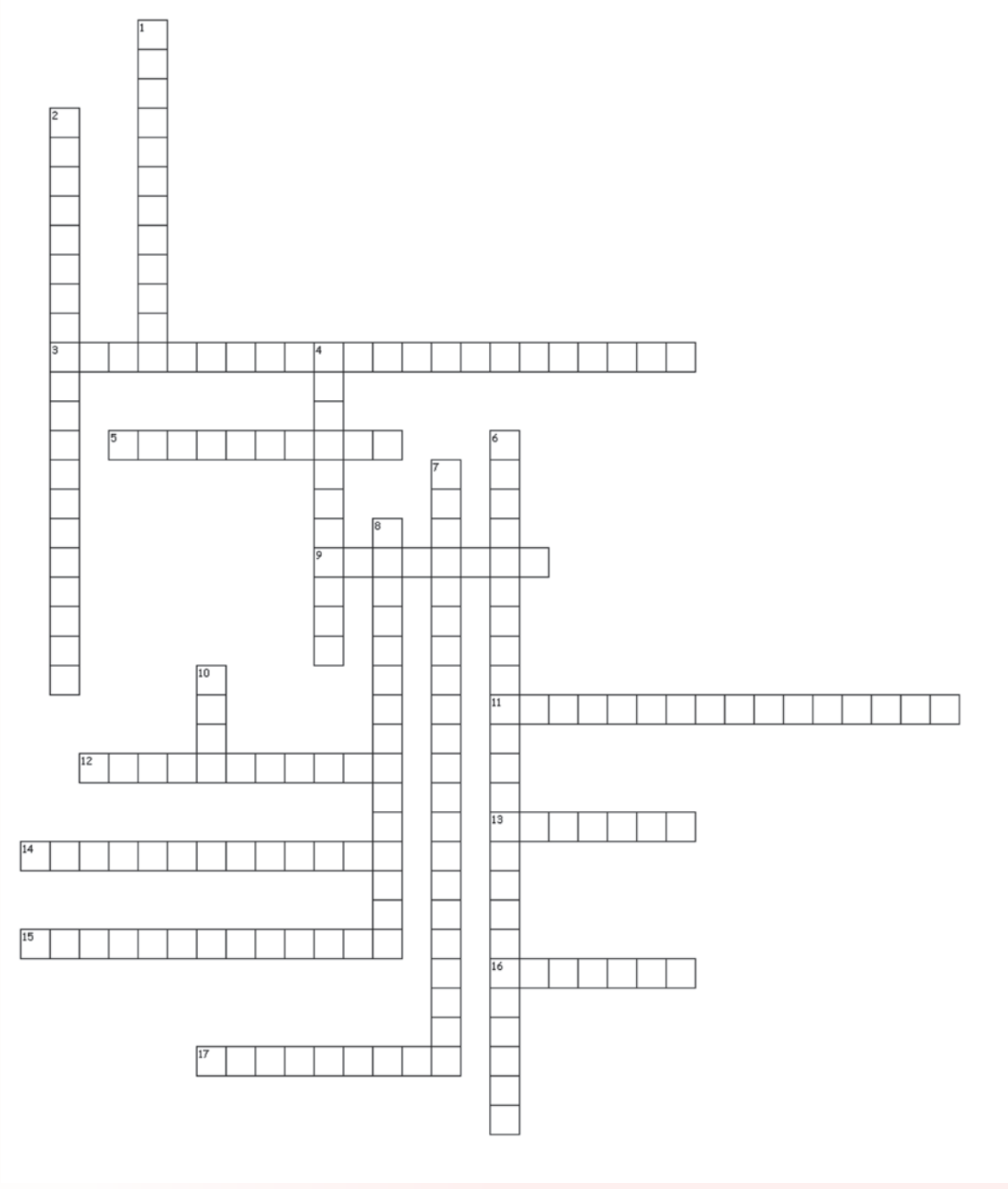
Fig 2: classical web space involvement in scabies

Fig 3: papules and pustules on feet in infant

Fig courtesy: Dr Archana Singal

Crossword

Ankita Chauhan
Senior Resident
Dept of Dermatology
Swami Dayanand Hospital, Shahdara, Delhi



HINTS_PUZZLE

Across

3 Most common cause of Cutaneous larva migrans

5 Characteristic transient eruption caused at the site of penetration of hookworm larvae is also known as

9 Topical pediculocide which is a mixture of tetracyclic macrolides and acts by overstimulating nerve cells by acting like acetylcholine

11 Pathognomonic phenomenon seen on histopathology in mycetoma

12 PCR testing for IS2404 and IS2606 is standard for laboratory confirmation of

13 Pink pig-tail appearance on histopathology seen in

14 In pubis louse infestation, bluish-grey, ill-defined macules seen on thighs, buttocks and trunk

15 An imaginary circle formed by sites of predilection in scabies

16 Intermediate host in guinea worm disease

17 Irregular, brown pigmented ring with central plugged opening corresponding to posterior end of parasite on dermoscopy is seen in

Down

1 New world cutaneous leishmaniasis caused by L. braziliensis and L. mexicana complex is also known as

2 Most common causative agent for eumycetoma

4 FDA approved oral drug for visceral, cutaneous and mucosal leishmaniasis

6 Classification describing the 5 stages describing the clinical manifestations of tungiasis:

7 Causative organism for buruli ulcer

8 Infective stage for humans in hookworm disease

10 Most common cutaneous manifestation of leishmaniasis in India

ANSWERS_PUZZLE

Across

3 Ancylostoma braziliense
5 Ground itch
9 Spinosad
11 Splendore Hoeppli
12 buruli ulcer
13 scabies
14 Macula cerulea
15 Circle of Hebra
16 Cyclops
17 Tungiasis

Down

1 White leprosy
2 Madurella mycetomatis
4 Miltefosine
6 Fortalezas classification
7 mycobacterium ulcerans
8 Filariform larva
10 PKDL

Global NTD day

Globally January 30, 2020 was celebrated as the first-ever World Neglected Tropical Diseases Day (World NTD Day)

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