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Guidelines

Diagnosis and Treatment of Leishmaniasis: Clinical Practice Guidelines by the Infectious Diseases Society of America (IDSA) and the American Society of Tropical Medicine and Hygiene (ASTMH)*

Naomi Aronson,[1] Barbara L. Herwaldt,[2] Michael Libman,[3] Richard Pearson,[4] Rogelio Lopez-Velez,[5] Peter Weina,[6] Edgar Carvalho,[7] Moshe Ephros,[8] Selma Jeronimo,[9] and Alan Magill[10]

[1]Uniformed Services University of the Health Sciences, Bethesda, MD; [2]Center for Disease Control and Prevention, Atlanta, GA; [3]McGill University Health Centre, Montreal, Que, Canada; [4]University of Virginia School of Medicine, Charlottesville, VA; [5]University of Alcalá, Madrid, Spain; [6]Walter Reed Army Institute of Research, Silver Spring, MD; [7]Universidade Federal da Bahia, Salvador, BA, Brazil; [8]Carmel Medical Center, Haifa, Israel; [9]Federal University of Rio Grande do Norte, Natal, RN, Brazil; [10]Bill and Melinda Gates Foundation, Seattle, WA

EXECUTIVE SUMMARY

Guidelines for the clinical management of persons with leishmaniasis were prepared by a Panel of the Infectious Diseases Society of America (IDSA) and the American Society of Tropical Medicine and Hygiene (ASTMH). The guidelines are intended for internists, pediatricians, family practitioners, and dermatologists, as well as infectious disease specialists, practicing in the United States and Canada (for simplicity, referred to here as North America). The Panel followed a guideline development process that has been adopted by IDSA, which includes a systematic method of grading both the quality of evidence (very low, low, moderate, or high) and the strength of the recommendation (weak or strong) [1] (Figure 1).

In these guidelines, we describe our approaches to the diagnosis and management of cases of cutaneous, mucosal, and visceral leishmaniasis, the three main clinical syndromes caused by infection with *Leishmania* parasites. Less common or rare syndromes that may require specialized expertise are beyond the scope of these guidelines. Whenever possible, our recommendations are based on randomized clinical trials. However, because of the diversity encompassed by leishmaniasis, which includes a spectrum of diseases caused by >20 *Leishmania* species found in many areas of the world, many of the recommendations are based on observational studies, anecdotal data, or expert opinion. Although there may be disagreement with some of our recommendations and suggestions, the approaches we describe have been both useful and feasible in North America.

Cutaneous leishmaniasis (CL) is the most common leishmanial syndrome worldwide and the one most likely to be encountered in patients in North America. The skin lesions of CL are usually painless and chronic, often occurring at sites of infected sand fly bites. Slow spontaneous healing as cell-mediated immunity develops is the usual natural history, accelerated by antileishmanial therapy. A minority of cutaneous infections caused by *Leishmania* (*Viannia*) *braziliensis* (*L.* [*V.*] *braziliensis*) and related species in the *Viannia* subgenus, including *L.* (*V.*) *panamensis* and *L.* (*V.*) *guyanensis*, are associated with concomitant or late mucosal leishmaniasis (ML), which can cause destructive lesions of the naso-oropharyngeal/laryngeal mucosa. No universally applicable treatment has been identified for CL; the choice of agent, dose, and duration of therapy should be individualized. Parasite and host factors must be considered, as well as clinical characteristics (Table 1).

Visceral leishmaniasis (VL), which reflects dissemination of *Leishmania* parasites throughout the reticuloendothelial system, is potentially life threatening without treatment. VL is an opportunistic infection in persons with HIV/AIDS or other causes of cell-mediated immunosuppression.

The primary goals of therapy for VL and CL/ML are to prevent mortality and morbidity, respectively. The only Food and Drug Administration (FDA)-approved medications for the treatment of leishmaniasis are intravenous liposomal amphotericin B (L-AmB) for VL and oral miltefosine for CL, ML, and VL caused by particular species. For prevention of leishmaniasis in travelers, no vaccines or chemoprophylaxis currently are available; personal protective measures to minimize exposure to sand fly bites are recommended.

Our recommendations for the diagnosis and clinical management of leishmaniasis are listed below. Background information about leishmaniasis, a description of our methods, and the evidence summaries that support our recommendations can be found online in the full text, tables, figures, and appendix of the guidelines.

RECOMMENDATIONS FOR THE DIAGNOSIS OF LEISHMANIASIS (CUTANEOUS, MUCOSAL, AND VISCERAL)

I. In a person with a compatible skin lesion(s) and exposure history, what specimen(s) should be collected for diagnostic testing for CL?

*The content and views expressed in this document are the sole responsibility of the authors and do not necessarily reflect the views or policies of the U.S. Department of Defense, the U.S. Department of Health and Human Services, or the Centers for Disease Control and Prevention. It is important to realize that guidelines cannot always account for individual variation among patients. They are not intended to supplant physician judgment with respect to particular patients or special clinical situations. The IDSA and ASTMH consider adherence to these guidelines to be voluntary, with the ultimate determinations regarding their application to be made by the physician in the light of each patient's individual circumstances.

Corresponding author:
Naomi Aronson
Uniformed Services University of the Health Services
Infectious Diseases Division
4301 Jones Bridge Road, Room A3060
Bethesda, MD 20814
TEL: 301 295 3621
FAX: 301 295 3557
e-mail: naomi.aronson@usuhs.edu

Dedication: The Panel dedicates these guidelines to Alan Magill

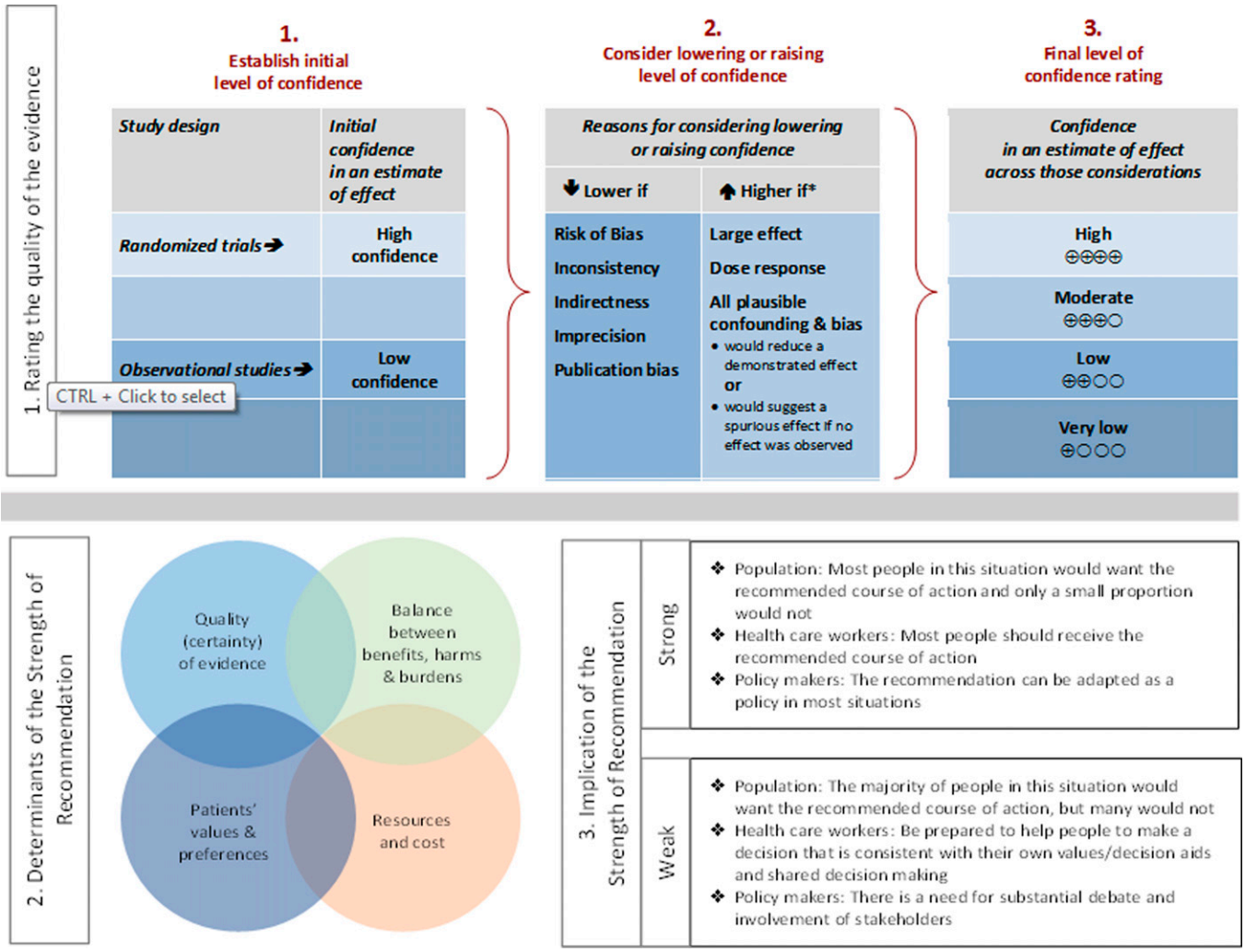

Figure 1: Approach and implications to rating the quality of evidence and strength of recommendations using the GRADE methodology (unrestricted use of the figure granted by the U.S. GRADE Network) [1]

Recommendations

1. Tissue specimens should be collected from a lesion(s) when a clinical suspicion for CL exists. Full-thickness skin biopsy specimens allow for simultaneous testing for other diagnoses, such as by histopathology and cultures [Strong, moderate].
2. Obtain a sample from a cleansed lesion, from which cellular debris and eschar/exudates have been removed [Strong, very low].

II. In a person with manifestations suggestive of New World mucosal leishmaniasis (ML), what types of specimens should be obtained for diagnostic testing?

Recommendations

3. The initial and most prominent mucosal manifestations typically are nasal (e.g., chronic unexplained congestion/secretions). Oral/palatal, pharyngeal, and laryngeal involvement may develop as ML progresses or, in some persons, may be the first or the only noted abnormalities. The clinical signs, which may evolve over time, may include erythema, edema, hyperemia, infiltration, nodules, erosion, ulceration, and tissue destruction (e.g., perforation of the nasal septum) [FACT, no grade].
4. Mucosal areas that have macroscopic abnormalities are recommended for specimen collection; biopsy specimens, obtained by an otolaryngologist, are useful for confirming the diagnosis by molecular and traditional methods and for excluding other etiologies [Strong, low].

III. During the initial and subsequent evaluations of persons with CL acquired in Central or South America who may have or be at risk for mucosal leishmaniasis (ML), what should be done to assess the possibility of mucosal disease?

Recommendations

5. All persons at risk for ML—on the basis of the etiologic agent of the *Leishmania* infection, if known, and the region in the New World in which infection was acquired—should be questioned about and examined for mucosal symptoms and signs, respectively, even during the initial evaluation [Strong, low].
6. During all evaluations (i.e., initial and subsequent), persons at risk for ML should be questioned explicitly about the development, evolution, and other characteristics of

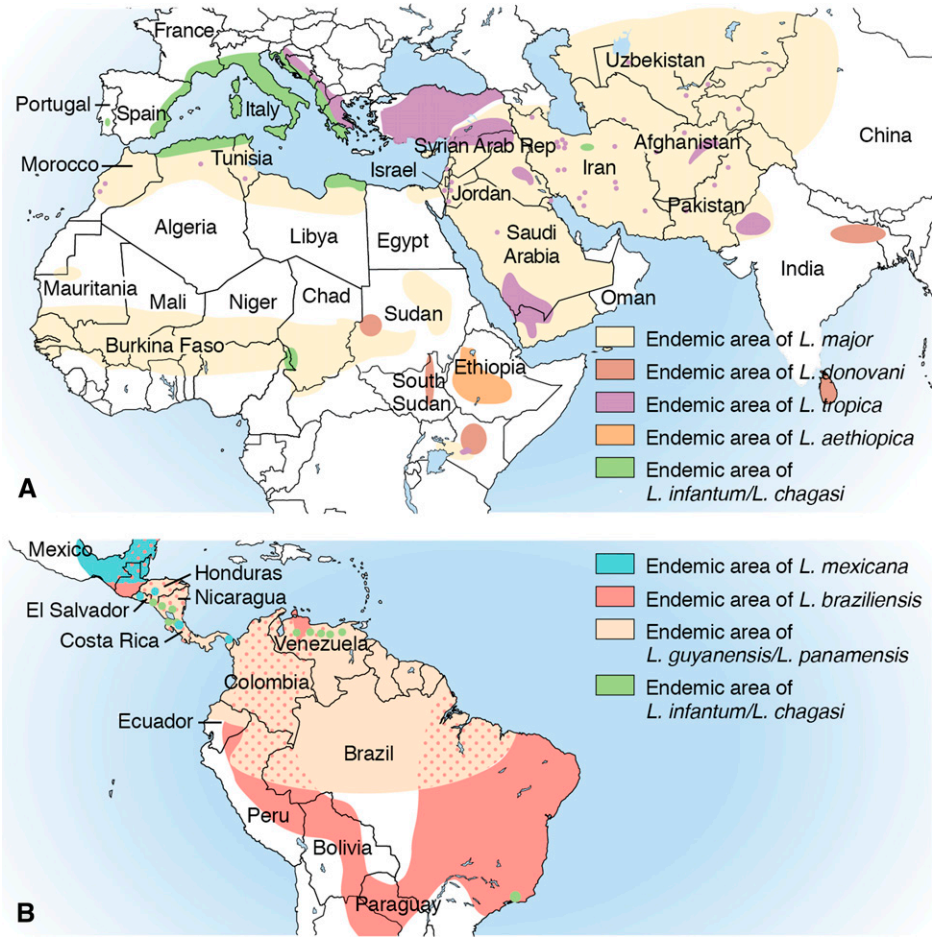

Figure 2: Maps of the Geographic Distribution of Cutaneous Leishmaniasis (CL). Notes: ***Adapted and modified from Chapter 277, Leishmania species. Principles and Practice of Infectious Diseases [31]*** [1]In Guatemala, the reported cases of CL have been acquired in the northern departments (particularly, El Petén and Alta Verapaz but also Izabal, El Quiché, Baja Verapaz, and Jalapa). [2]The etiologic agents of CL in Israel primarily include *L. major* and *L. tropica* but also *L. infantum-chagasi*. [3]The species *L.* (*Leishmania*) *martiniquensis*, which was formally named in 2014, has been identified as the etiologic agent of cutaneous and visceral leishmaniasis in the French West Indies (Martinique Island) and Thailand, where it previously was referred to as "*L. siamenensis*" (not considered a taxonomically valid name). [4]In Sri Lanka, *L. donovani* has been identified as the etiologic agent of cutaneous and visceral leishmaniasis. [5]Not all *Leishmania* species that cause CL are included in this map (eg, *L. amazonensis* in South America).

mucosal symptoms; and they should have a thorough examination of the naso-oropharyngeal mucosa even if they do not have any mucosal symptoms [Strong, low].

7. Persons at risk for ML should be educated and provided personalized documentation about the importance of seeking medical attention for possible ML if they ever develop persistent, atypical (unusual for the person) naso-oropharyngeal/laryngeal manifestations that do not have a clear etiology [Strong, low].
8. Persons at risk for ML who have persistent mucosal symptom(s) or compatible abnormalities of the naso-oropharyngeal mucosa should be referred to a specialist for an otorhinolaryngologic examination, which typically should include fiberoptic endoscopy [Strong, low].
9. Clinicians might refer some at-risk persons without documented mucosal symptoms or signs to an otolaryngologist, especially if it was not possible to conduct a thorough review of systems and mucosal examination or if the assessments may not have been adequate or reliable [Weak, very low].

IV. In a person with a compatible clinical course and epidemiologic context, what types of samples should be collected to evaluate for the diagnosis of VL?

Recommendations

10. We recommend the collection of tissue aspirates or biopsy specimens for smears, histopathology, parasite culture, and molecular testing [Strong, low].
11. Bone marrow aspiration is the preferred first source of a diagnostic sample. Liver, enlarged lymph nodes, and whole blood (buffy coat) are other potential sources of tissue specimens [Strong, low].
12. Serum should be collected for detection of anti-leishmanial antibodies (see VIII) [Strong, moderate].
13. In immunocompromised persons, blood should be collected for buffy coat examination, *in vitro* culture, and molecular analyses [Strong, very low].

Table 1: Clinical Characteristics of Cutaneous Leishmaniasis (CL) that may Modify Management in North America

Simple CL	Complex CL
Caused by a *Leishmania* species unlikely to be associated with mucosal leishmaniasis (ML)	Caused by a *Leishmania* species that can be associated with increased risk for ML, particularly *Viannia* spp. in the "mucosal belt" of Bolivia, Peru, and Brazil♦
No mucosal involvement noted	Local subcutaneous nodules*
Absence of characteristics of complex CL	Large regional adenopathy*
Only a single or a few skin lesions	>4 skin lesions of substantial size (eg, >1 cm)
Small lesion size (diameter <1 cm)	Large individual skin lesion (diameter ≥5 cm)
Location of lesion feasible for local treatment	Size or location of lesion such that local treatment is not feasible
Nonexposed skin (ie, not cosmetically important)	Lesion on face, including ears, eyelids, or lips; fingers, toes, or other joints; or genitalia
Immunocompetent host	Immunocompromised host (especially with respect to cell-mediated immunity)
Lesion(s) resolving without prior therapy	Clinical failure of local therapy
	Unusual syndromes: leishmaniasis recidivans, diffuse CL, or disseminated CL

*It is somewhat controversial whether the presence of small subcutaneous nodules is always associated with complex CL, but certainly complex CL applies if bubonic-like adenopathy is present in regional drainage area of lesions. These findings have been linked to complications or treatment failure when only local treatment is administered. Some experts would not consider systemic therapy needed for a few, small subcutaneous nodules in Old World CL.

♦The highest risk areas for mucosal leishmaniasis (ML) are south of the Amazon basin in parts of Bolivia, Peru, and Brazil (defined here as the "mucosal belt"). Moderate-risk areas are south of Nicaragua to the Amazon basin. Low-risk areas for ML are in NWCL (*Viannia*)-endemic regions north of Costa Rica.

♦High therapeutic failure rates after treatment with pentavalent antimonial drugs have been observed in CL acquired in Amazonian Bolivia (eg, Madidi National Park) and Southeastern Peru (eg, Manu National Park and Puerto Maldonado). Poor efficacy after using miltefosine in the treatment of *L.(V.) braziliensis* was reported in Guatemala

Leishmania species with an increased risk of causing mucosal leishmaniasis (ML) include *L.* (*V.*) *braziliensis* mainly, but also *L.* (*V.*) *guyanensis* and *L.* (*V.*) *panamensis.* There are other species that can be associated with ML less frequently. In this document, we refer to these three species as "increased-ML risk species."

Geographic regions in which there is an increased risk for ML are defined above. Amazonian-basin regions up to an altitude of approximately 2,000 meters are referred to as "increased-ML risk regions."

V. What laboratory tests should be used to diagnose leishmaniasis?

Recommendations

14. We recommend using multiple diagnostic approaches to maximize the likelihood of a positive *Leishmania* result, using methods such as visualization of the characteristic amastigote in smears or tissue (histopathology); parasite isolation by *in vitro* culture; molecular detection of parasite DNA; and, for VL, serologic testing (see VI–VIII and Table 2). Simultaneous testing for other diagnoses (e.g., by histopathology and culture) should be considered [Strong, low].
15. We recommend attempting parasite isolation with the assistance of reference laboratories. We recommend that clinicians contact their leishmaniasis reference laboratory before collecting specimens (Table 2). If *Leishmania* parasites are isolated in culture, reference laboratories can identify the species by DNA-based assays or isoenzyme analysis [Strong, low].
16. Molecular amplification assays typically should be performed because they are the most sensitive *Leishmania* tests currently available (see VII) [Strong, moderate].
17. *Leishmania* skin testing is not recommended or available in the United States or Canada; there are no standardized, approved, or commercially available skin-test products in North America [Strong, very low].

VI. In a person with leishmaniasis, why could it be helpful to identify the infecting *Leishmania* species?

Recommendation

18. We suggest that identification of the infecting parasite to the species level be attempted in cases of suspected CL. Species identification may help inform clinical management decisions for individual persons (e.g., whether and how to treat) [Weak, moderate].

VII. What is the role of DNA-based assays in the diagnosis of leishmaniasis?

Recommendation

19. DNA-based assays should be performed, especially if other diagnostic testing is unrevealing. They are emerging as the most sensitive assays for the diagnosis of leishmaniasis [Strong, moderate].

VIII. What is the role of serologic testing in the diagnosis of leishmaniasis?

Recommendations

20. Serologic testing is recommended for persons with suspected VL in whom definitive diagnostic tests for the parasite (microscopic identification, culture, and molecular tests for parasite DNA) cannot be conducted or have negative results. The sensitivity and specificity of serologic tests depend on the assay and antigens used,

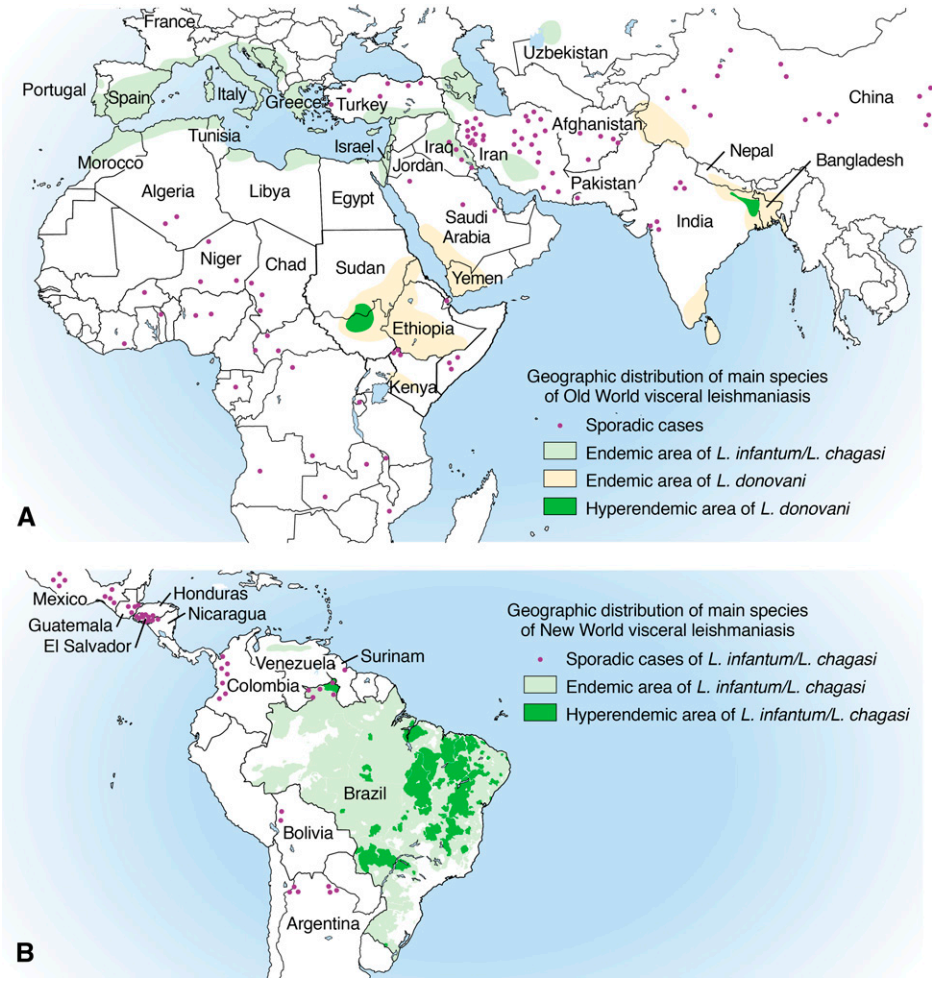

Figure 3. Maps of the Geographic Distribution of Visceral Leishmaniasis (VL)

as well as host factors. Serologic tests cannot be used to assess the response to treatment. Antileishmanial antibodies can be detected years after clinically successful therapy in some persons [Strong, moderate].

21. We suggest that tests for antileishmanial antibodies not be performed as the sole diagnostic assay. Antibodies may be undetectable or present at low levels in persons with VL who are immunocompromised because of concurrent HIV/AIDS or other reasons. The potential for false-negative test results limits the utility of serologic assays in this setting [Weak, low].
22. Serologic testing is not recommended as part of the diagnostic evaluation for CL. The currently available serologic assays are neither sensitive nor specific for the diagnosis of CL [Strong, moderate].

RECOMMENDATIONS FOR THE TREATMENT OF LEISHMANIASIS

CUTANEOUS LEISHMANIASIS

IX. In a person with a consistent travel history and compatible skin lesion(s), is it necessary to obtain parasitologic confirmation of the diagnosis of leishmaniasis before starting treatment?

Recommendation

23. After a careful diagnostic evaluation in which neither leishmaniasis nor another diagnosis is confirmed, empiric treatment may be indicated on the basis of an individualized risk-benefit assessment [Weak, very low]. *Remark: This should be discussed with the patient and reevaluated periodically, taking into account the clinical evolution.*

X. Is treatment of clinically manifest cutaneous infection (CL) always indicated?

Recommendations

24. We recommend that immunocompetent persons with skin lesions that are caused by infection with *Leishmania* species that are not associated with increased risk for ML, that are defined as clinically simple lesions (Table 1), and that are healing spontaneously may be observed without treatment if the patient concurs with this management [Strong, moderate].
25. For persons with CL when the *Leishmania* species is not known but the infection was not acquired in an increased ML-risk region (Table 1, Figure 2), treatment of clinically simple or healing skin lesions is not required in an immunocompetent patient who concurs

Table 2: Leishmaniasis Reference Diagnostic Laboratories in North America

Laboratory[1]	Testing available	Submitting samples[2]	Point of Contact
McGill University, Montreal, CANADA	- Culture - PCR (conventional and real time) - Species determination (DNA sequencing, DNA probes) - Antibody detection (DAT, rK39, ELISA Crude Antigen)	Shipment instructions provided on request. Shipment preferred using McGill transport medium. In most cases, specimens should be sent to the relevant provincial public health laboratory, which will forward samples as appropriate.	Momar Ndao, DVM, MSc, PhD National Reference Centre for Parasitology Research Institute of the McGill University Health Centre Room E03 5375 1001 Décarie Blvd Montreal, QC H4A 3J1 Email: momar.ndao@mcgill.ca Tel 1: +1-514-934-8347 Fax: +1-514-934-8261 https://www.mcgill.ca/tropmed/nrcp
Centers for Disease Control and Prevention (CDC), Atlanta, GA, USA	- Microscopic evaluation - Culture - PCR (conventional and real time) - Species determination (DNA sequencing analysis; also cellulose acetate electrophoresis) - Antibody detection rK39 Rapid Test)	Shipment instructions provided on request. Shipment preferred using CDC transport medium. Clinicians are encouraged to notify their State Public Health Laboratory regarding specimen submission to CDC.	Marcos E. de Almeida, PhD Centers for Disease Control and Prevention Division of Parasitic Diseases and Malaria 1600 Clifton Road NE, Mailstop D-64 Building 23, 9th Floor, Room 439 Atlanta, GA 30329-4027 Tel: (404) 718- 4175/718-4126 Fax: (404) 718-4191 Email: bnz0@cdc.gov http://www.cdc.gov/parasites/leishmaniasis/health_professionals/index.html#dx
Walter Reed Army Institute of Research (WRAIR), USA	- Microscopic evaluation - Culture - PCR (real time) - Species determination (Cellulose acetate electrophoresis) - Xenodiagnosis (mice and hamsters) - Antibody detection (rK39)	Shipment instructions provided on request. Shipment preferred using WRAIR transport medium. Services restricted to samples from U.S. military beneficiaries and DoD civilian workers.	Sheila A. Peel, MSPH, PhD Leishmania Diagnostic Laboratory Walter Reed Army Institute of Research 503 Robert Grant Avenue Silver Spring, MD 20910-7500 24-hour cell – (240) 595-7353 usarmy.detrick.medcom-wrair.mbx.leishmania-diagnostic@mail.mil http://www.wrair.army.mil/OtherServices_LDL.aspx

PCR = polymerase chain reaction rK39 = recombinant K39 antigen
DAT = direct agglutination test ELISA = enzyme-linked immunosorbent assay
DoD= Department of Defense
Note: Please visit http://apps.who.int/whocc/List.aspx?cc_subject=Leishmaniasis& to access additional laboratories that are World Health Organization (WHO) Collaborating Centers, http://www.who.int/leishmaniasis/collaborating_centres/en/
[1] Additional WHO leishmaniasis laboratories are listed in WHO Technical Report Series 949 "Control of the leishmaniasis" pages 162–3 [42].
[2] Recommend contact with reference laboratories in advance for instructions to optimize specimen collection and shipping. Tests performed in the above laboratories are provided free of charge.

with this management [Strong, low; E.C. dissents, recommending that all persons with NWCL receive treatment]. *Remark: See XXIV and XXV regarding the management of CL in immunocompromised persons*.

26. We suggest that systemic treatment be offered for persons even with healing/recently healed CL lesions caused by increased ML-risk species or when the species is unknown but the infection was acquired in an increased ML-risk region. Risks and benefits of such treatment should be discussed with the patient [Weak, low]. *Remark: In some cases, watchful waiting, with vigilance for signs and symptoms of ML, may be a reasonable approach.*
27. We recommend that any decision to observe a patient with CL without treatment should be reevaluated periodically, and the decision not to treat should be reconsidered if healing does not progress as anticipated [Strong, very low].
28. In all cases of CL, wound care, individualized documentation of lesion evolution, and patient education regarding the manifestations and detection of local therapeutic failure/relapse and ML should be routine components of management (see III and XV) [Strong, low].

XI. In a person with CL, what could be the consequences of no treatment or suboptimal therapy, and how should persons who received no or suboptimal therapy be monitored?

Recommendations

29. Potential consequences of inadequate treatment include poor cosmetic outcome due to scarring or superinfection, the persistence of a chronic wound(s), and, with some *Leishmania* species, destructive and disfiguring

ML. In immunocompromised persons, cutaneous, mucosal, and visceral dissemination may occur [FACT, no grade].
30. Persons with CL should be actively monitored by clinical appearance, including by performing a careful nasal and oropharyngeal examination periodically up to 1 year, or at least 2 years if at increased risk for ML. They should be educated about the signs and symptoms of relapse and ML and instructed to seek medical attention anytime these appear [Strong, low].
31. Symptoms such as chronic nasal stuffiness, epistaxis, or hoarseness or findings such as septal perforation that occur anytime in a person with a prior or current diagnosis of CL or a scar consistent with prior CL should prompt evaluation for ML, including fiberoptic examination of the affected area if relevant (see II and III) [Strong, moderate].

XII. In a person with CL, what factors should prompt consideration of use of a systemic (oral or parenteral) agent for initial therapy?

Recommendations

32. Systemic treatment is recommended for persons with complex CL as defined in Table 1 [Strong, moderate].
33. Initial systemic therapy (see XIII) may be used in persons with CL in whom it is not practical to use local therapy or (possibly) if more rapid healing of large, cosmetically or functionally concerning lesions is preferred [Weak, very low].
34. Less common cutaneous syndromes, such as leishmaniasis recidivans (caused by *L. tropica* and occasionally other species), diffuse cutaneous leishmaniasis (caused by *L. mexicana, L. amazonensis*, and *L. aethiopica*), and disseminated cutaneous leishmaniasis (caused by *L.* [*V.*] *braziliensis*), usually require systemic therapy [Strong, low].

XIII. What systemic treatment options are available in North America for CL, and what factors should be considered when selecting a medication for an individual patient?

Recommendations

35. The parenteral options for systemic therapy currently available in North America include **conventional amphotericin B deoxycholate, lipid formulations of amphotericin B, pentavalent antimonial (Sb^V) compounds, and pentamidine (listed in alphabetical order). Oral options include miltefosine and the "azole" antifungal compounds, including ketoconazole (if potential benefits outweigh risks for hepatotoxicity and QT prolongation) and fluconazole [FACT, no grade].**
36. To maximize effectiveness and to minimize toxicity, the choice of agent, dose, and duration of therapy should be individualized [Strong, moderate]. *Remarks*: *No ideal or universally applicable therapy for CL has been identified. Some therapies/regimens appear highly effective only against certain Leishmania species/strains in certain areas of the world. Both the parasite species and host factors (e.g., comorbid conditions and immunologic status) should be considered.*
37. Factors that should be considered when selecting CL treatment for an individual patient include the risk for ML; the *Leishmania* strain/species and published response rates for antileishmanial agents in the pertinent geographic region; the potential for adverse events; age extremes; childbearing competence and pregnancy; obesity; hepatic, pancreatic, renal, and cardiac comorbid conditions; preference for and convenience of various routes of administration; the rapidity with which one wishes to control the infection; the impact of lesions on daily activities and patient self-confidence; the patient/provider comfort level with logistics (e.g., Investigational New Drug protocols); and other practical issues (e.g., drug availability, various types of cost, insurance reimbursement) (see XII and XXVI; Tables 3 and 4) [Strong, low].

XIV. In which clinical settings can local therapy be used effectively in a person with CL?

Recommendations

38. Local therapy is preferred for treatment of OWCL lesions defined as clinically simple (Table 1) and may be useful for localized NWCL caused by *Leishmania* species not associated with increased risk for ML [Strong, moderate]. *Remark: Local therapy includes heat and cryotherapy, topical ointments/creams with paromomycin and other ingredients, intralesional injections of pentavalent antimonial drugs (±cryotherapy), and photodynamic or laser treatment.*
39. Eschar(s) overlying ulcers should be debrided before administration of local therapy and any secondary infection managed to maximize treatment effect [Strong, very low].

XV. What are the recommended timeframes and findings to assess response to treatment in a person with CL?

Recommendations

40. Response to treatment is assessed by clinical criteria; repeat parasitologic testing is not recommended if the skin lesion appears to be healing [Strong, low]. *Remark: The healing process may continue after the treatment course is completed especially for large ulcerative lesions.*
41. Persons with CL should have their skin lesions monitored for 6–12 months after treatment for clinical evidence of therapeutic failure, which is initially seen at the border of a healed lesion [Strong, low]. *Remark: The first sign of healing is usually flattening of the skin lesion. By 4–6 weeks after treatment, the lesion size should have decreased by >50%, ulcerative lesions should be reepithelializing, and no new lesions should be appearing. Ulcerative lesions are generally fully reepithelialized and clinically healed by approximately 3 months after treatment.*

XVI. What are the recommended approaches for additional management in a person with CL that does not respond to therapy?

Recommendations

42. Additional therapy is recommended (but not necessarily always with a different agent or approach) when there is development of new skin lesions or worsening of existing lesions. Additional therapy is also recommended if there is incomplete healing by 3 months after completion of the treatment course [Strong, low].
43. We recommend that therapeutic failure be assessed by physical appearance. Relatively little improvement

Table 3: Approach to Syndromic Treatment of Leishmaniasis in North America[1,2]

Syndrome	Treatment Classification	Drug/treatment	Proprietary Name	Source	Route of Administration	Regimen	FDA Approval and Availability	Comments
Cutaneous leishmaniasis (CL)								
	Treatment of choice	There is no generally applicable treatment of choice; choice should be individualized.						For cases of CL associated with increased risk for ML,[3] the choices include miltefosine, amphotericin B formulations, and pentavalent antimonials.
	Parenteral alternatives							
CL		**Amphotericin B deoxycholate**	Fungizone®	Bristol Myers Squibb	IV	0.5–1.0 mg/kg per dose daily or every other day for cumulative total of ~15–30 mg/kg	Yes, but not for CL; off-label use	
		Pentavalent antimonials[4]						In some settings, treatment for as few as 10 days has been effective.
CL		Sodium stibogluconate	Pentostam®	GlaxoSmithKline, via CDC Drug Service or USAMMDA for military health care beneficiaries via Special Access Program in Canada	IV, IM (IV preferred in North America[1])	20 mg Sb^V/kg/day for 20 days	No; but available in the US under a CDC-sponsored IND protocol. For military health care beneficiaries, contact Force Health Protection Division, US Army Medical Materiel Development Activity (USAMMDA).[13] In Canada, via Special Access Program	Supplied as 100 mg Sb^V/mL. Dilute dose in D5W (~50–100 mL) for IV, ~10–30-minute infusion. Use of an in-line filter is recommended.

(continued)

Table 3
Continued

Syndrome	Treatment Classification	Drug/treatment	Proprietary Name	Source	Route of Administration	Regimen	FDA Approval and Availability	Comments
CL		Meglumine antimoniate	Glucantime®	Sanofi via Special Access Program in Canada	IV, IM (IV preferred in North America[1])	As per Pentostam®	No; in US, would require investigator-sponsored IND protocol. In Canada, via Special Access Program	Supplied as 81 mg Sb^V/mL. Dilute dose in D5W (~50–100 mL) for IV, ~10–30-minute infusion.
CL		**Liposomal** amphotericin B	AmBisome®	Astellas	IV	3 mg/kg/day on days 1–5 and 10 or on days 1–7 (total 18–21 mg/kg)	Yes, but not for CL; off-label use	No standard dosage regimens have been established; other regimens have been described in case reports/series from various settings.
CL		**Pentamidine** isethionate	Pentam 300®	APP Pharmaceuticals	IV, IM (IV preferred in North America[1])	3–4 mg/kg every other day for 3 or 4 doses	Yes, but not for CL; off-label use	*L.* (*V.*) *panamensis*/ guyanensis: an alternative regimen is 2 mg/kg every other day for 7 doses.
	Oral alternatives							
		Azoles						
CL		Fluconazole	Diflucan®	Pfizer	po	**Adults**: 200 mg daily for 6 weeks	Yes, but not for CL; off-label use	See XIII regarding preliminary data for therapy with higher daily doses.
CL		Ketoconazole	Nizoral®	Janssen	po	**Adults**: 600 mg daily for 28 days	Yes, but not for CL; off-label use	Take with acidic drink (eg, coke or citric juice).
CL		**Miltefosine**	Impavido®	In US: Knight Therapeutics, via Profounda, the US marketer. In Canada: via Special Access Program	po	**FDA-approved regimen**: if 30–44 kg, 50 mg bid for 28 days; if ≥45 kg, 50 mg tid for 28 days	Yes, for CL caused by *Viannia* species; off-label use for other species	Target dose is ~2.5 mg/kg/day, but doses >150 mg/day have not been studied. GI side effects may limit higher doses. See Table 4 and XXVI.

(continued)

Table 3
Continued

Syndrome	Treatment Classification	Drug/treatment	Proprietary Name	Source	Route of Administration	Regimen	FDA Approval and Availability	Comments
	Intralesional alternatives							
		Pentavalent antimonials[4]						
CL		Sodium stibogluconate	Pentostam®	GlaxoSmithKline, via CDC Drug Service or USAMMDA for military health care beneficiaries[13]	IL	Various regimens, eg, 0.2–5 mL per session every 3–7 days (or up to every 3 weeks) +/– cryotherapy for 5–8 sessions or until healing. 5 sites/lesion with a 25–27G needle intradermally for 0.1 mL/cm^2 until blanched.	Not currently covered by the CDC-sponsored IND protocol	Use undiluted drug. Consider premedication (eg, with EMLA: lidocaine/prilocaine). In children, sedation/anesthesia may be required. Avoid body sites as per heat therapy (see below).
CL		Meglumine antimoniate	Glucantime®	Sanofi via Special Access Program in Canada	IL	As per Pentostam®	No; in US, would require investigator-sponsored IND protocol. In Canada, via Special Access Program	
	Topical alternatives							
		Paromomycin preparations						
CL		15% paromomycin and 12% MBCL ointment	Leshcutan®	Approximate with compounding pharmacy	Topical	Apply bid for 10 days, rest for 10 days, and reapply bid for 10 days	The capsule formulation of paromomycin is FDA approved for other indications; use of the capsules to compound antileishmanial ointment constitutes off-label use.	Local irritation (from MBCL) may lead some patients to discontinue therapy. Higher response rates noted for infection caused by *L. major* than *L. tropica*.

(continued)

Table 3
Continued

Syndrome	Treatment Classification	Drug/treatment	Proprietary Name	Source	Route of Administration	Regimen	FDA Approval and Availability	Comments
CL		15% paromomycin and 0.5% gentamicin cream	WR 279,396	Expanded-access IND protocol; otherwise, approximate with compounding pharmacy	Topical	Apply once per day for 20 days	See above about paromomycin capsules. Treatment under expanded-access IND protocol currently is limited to US military health care beneficiaries.	Local erythema and/or mild pain are commonly noted. See section XIV for some similar drug compounding instructions and the US military point of contact.
CL		**Heat therapy**	ThermoMed™	TTI, Thermosurgery Technologies, Inc.	Locally applied to skin	Apply under local anesthesia for 30-sec doses in grid-like pattern extending 1–2 mm into surrounding normal-appearing skin. Usually one session (sometimes up to 3).	Yes, cleared for CL indication	Avoid applying over eyelids, tip of nose, lips, mucus membranes, cartilaginous structures, or superficial nerves. Use topical antibiotics for several days after the heat treatment. Keloids may be less common than with cryotherapy.
CL		**Cryotherapy with liquid nitrogen**		No special applicator required	Locally applied to skin	Multiple regimens, eg, freeze 15–20 sec until 1–2 mm of normal circumferential skin frozen, thaw 20–60 sec, and freeze again. Repeat every 3 weeks for up to 3 total applications (fewer, if healed sooner).	Yes, "grandfathered in"	Increased efficacy has been noted if used in combination with IL Sb^V. Avoid applying over eyelids, tip of nose, lips, mucus membranes, cartilaginous structures, or superficial nerves.

(continued)

Table 3
Continued

Syndrome	Treatment Classification	Drug/treatment	Proprietary Name	Source	Route of Administration	Regimen	FDA Approval and Availability	Comments
Mucosal leishmaniasis (ML)								
	Treatment of choice	There is no treatment of choice; choice should be individualized.						
	Alternatives							
ML		**Amphotericin B deoxycholate**	Fungizone®	Bristol Myers Squibb	IV	0.5–1.0 mg/kg per dose daily or every other day for cumulative total of ~20–45 mg/kg	Yes, but not for ML; off-label use	
ML		**Liposomal amphotericin B**	AmBisome®	Astellas	IV	~3 mg/kg/day for cumulative total of ~20–60 mg/kg	Yes, but not for ML; off-label use	
ML		**Miltefosine**	Impavido®	In US: Knight Therapeutics, via Profounda, the US marketer. In Canada: via Special Access Program	po	**FDA-approved regimen**: if 30–44 kg, 50 mg bid for 28 days; if ≥45 kg, 50 mg tid for 28 days	Yes, approved for ML caused by *L.* (*V.*) *braziliensis*	Target dose is ~2.5 mg/kg/day, but doses >150 mg/day have not been studied. GI side effects may limit higher doses. See Table 4 and XXVI.
	-	**Pentavalent antimonials**[4]						
ML		Sodium stibogluconate	Pentostam®	GlaxoSmithKline, via CDC Drug Service or USAMMDA for military health care beneficiaries[13]	IV, IM (IV preferred in North America[1])	20 mg Sb^V/kg/day for 28 days	No; but available in the US under a CDC-sponsored IND protocol. For military health care beneficiaries, available from USAMMDA.[13]	Supplied as 100 mg Sb^V/mL. Dilute dose in D5W (~50–100 mL) for IV, ~10–30-minute infusion. Use of an in-line filter is recommended.
ML		Meglumine antimoniate	Glucantime®	Sanofi via Special Access Program in Canada	IV, IM (IV preferred in North America[1])	As per Pentostam®	No; in US, would require investigator-sponsored IND protocol. In Canada, via Special Access Program	Supplied as 81 mg Sb^V/mL. Dilute dose in D5W (~50–100 mL) for IV, ~10–30-minute infusion.

(continued)

Table 3
Continued

Syndrome	Treatment Classification	Drug/treatment	Proprietary Name	Source	Route of Administration	Regimen	FDA Approval and Availability	Comments
ML	Lesser alternative	**Pentamidine isethionate**	Pentam 300®	APP Pharmaceuticals	IV, IM (IV preferred in North America[1])	2–4 mg/kg every other day or 3 times per week for 15 or more doses	Yes, but not for ML; off-label use	
Visceral leishmaniasis (VL)[5]								
VL	Treatment of choice	**Liposomal amphotericin B**[6]	AmBisome®	Astellas	IV	**FDA-approved regimen**, if **immunocompetent**[5,7]: 3 mg/kg/day on days 1–5, 14, and 21 (total dose 21 mg/kg) **FDA-approved regimen**, if **immunosuppressed**[8]: 4 mg/kg/day on days 1–5, 10, 17, 24, 31, and 38 (total dose 40 mg/kg)	Yes, for this indication	See XIX regarding other regimens that have been used in various settings. For treatment of VL in immunocompetent[7] persons with VL acquired in East Africa, regimens with total doses ≥40 mg/kg may be needed.
	Alternatives[9]							
VL		**Miltefosine**[10]	Impavido®	In US: Knight Therapeutics, via Profounda, the US marketer. In Canada: via Special Access Program	po	**FDA-approved regimen**: if 30–44 kg, 50 mg bid for 28 days; if ≥45 kg, 50 mg tid for 28 days[8]	Yes, for VL caused by *L. donovani*	On the basis of anecdotal experience in Europe and Brazil, not as effective for VL caused by *L. infantum-chagasi*. In general, target dose is ~2.5 mg/kg/day, but doses >150 mg/day have not been studied. GI side effects may limit higher doses. See Table 4 and XXVI.

(continued,

Table 3
Continued

Syndrome	Treatment Classification	Drug/treatment	Proprietary Name	Source	Route of Administration	Regimen	FDA Approval and Availability	Comments
	-	**Pentavalent antimonials**[4,11]						
VL		Sodium stibogluconate	Pentostam®	GlaxoSmithKline, via CDC Drug Service or USAMMDA for military health care beneficiaries[13] via Special Access Program in Canada	IV, IM (IV preferred in North America[1])	20 mg Sb^V/kg/day for 28 days[8]	No; but available in the US under a CDC-sponsored IND protocol. For military health care beneficiaries, available from USAMMDA.[13] In Canada, via Special Access Program	Supplied as 100 mg Sb^V/mL. Dilute dose in D5W (~50–100 mL) for IV, ~10–30-minute infusion. Use of an in-line filter is recommended.
VL		Meglumine antimoniate	Glucantime®	Sanofi via Special Access Program in Canada	IV, IM (IV preferred in North America[1])	As per Pentostam®	No; in US, would require investigator-sponsored IND protocol. In Canada, via Special Access Program	Supplied as 81 mg Sb^V/mL. Dilute dose in D5W (~50–100 mL) for IV, ~10–30-minute infusion.
VL		**Amphotericin B deoxycholate**[6]	Fungizone®	Bristol Myers Squibb	IV	1 mg/kg per dose daily or every other day for a total of 15–20 doses[8]	Yes, but not for VL; off-label use	

(continued)

Table 3
Continued

Syndrome	Treatment Classification	Drug/treatment	Proprietary Name	Source	Route of Administration	Regimen	FDA Approval and Availability	Comments
VL		**Amphotericin B lipid complex**	Abelcet®	Sigma-Tau Pharmaceuticals	IV	**Immunocompetent**[5,7]: 2–3 mg/kg/day for 5–10 days **Immunosuppressed**[8]: 3–5 mg/kg/day for 10 days[12]	Yes, but not for VL; off-label use	Liposomal amphotericin B (L-AmB) is the treatment of choice for VL. Bioequivalence between amphotericin B lipid complex (ABLC) and L-AmB for treatment of VL has not been established; ABCL has been less well studied in VL treatment trials and, anecdotally, may not be as effective as AmBisome® (rough conversion: 3 mg/kg of liposomal amphotericin B is about 5 mg/kg of ABLC).
VL	Lesser alternative	**Pentamidine isethionate**	Pentam 300®	APP Pharmaceuticals	IV, IM (IV preferred in North America[1])	4 mg/kg every other day or three times per week for ~15–30 doses[8]	Yes, but not for VL; off-label use	Considered second-line therapy because of toxicity (see Table 4) and lower efficacy.

[1]For simplicity, the terminology North America is used to refer to the United States and Canada.
[2]All treatment-related decisions should be individualized. The lists of treatment approaches/drugs and regimens are not all inclusive. For the listed systemic drugs, see Table 4 regarding adverse events, monitoring for toxicity, and mitigation approaches. See XXIII-XXV regarding treatment considerations applicable to HIV-coinfected persons and to persons who are immunocompromised for other reasons. See XXVI for considerations for other special populations of patients (eg, young children).
[3]See Table 1 and X-XIII for additional perspective.
[4]The pentavalent antimonial drugs—sodium stibogluconate (Pentostam®) and meglumine antimoniate (Glucantime®)—are considered comparable when dosed on the basis of Sb^V content. In general, the daily dose does not have an upper limit in mgs (ie, the daily dose no longer is limited to 850 mg); however, see XXVI for additional perspective and cautionary notes.
[5]Persons newly diagnosed with VL should be assessed for concurrent HIV/AIDS or other causes of cell-mediated immunosuppression.
[6]Liposomal amphotericin is approved by the U.S. Food and Drug Administration for the treatment of VL. The off-label use of amphotericin B deoxycholate is likely to be effective but is generally more toxic (see Table 4).
[7]An immunocompetent person is defined as someone without an identified congenital or acquired immune defect (eg, HIV/AIDS). In general, *L. donovani* (India) may be treated with a shorter course of ABLC, whereas *L. infantum* in Europe requires 10 days duration [300, 377].
[8]See XXIII regarding secondary prophylaxis in patients with HIV/AIDS-associated VL. Chronic maintenance therapy (secondary prophylaxis) should be given until the CD4 T-lymphocyte cell count consistently remains >200–350/mm^3 (see XXIII).
[9]See XIX and XX for additional perspective about treatment alternatives. Parenteral paromomycin appeared promising in clinical trials in India, but it is not available in North America.
[10]Miltefosine has been effective in treating VL in India and adjacent areas of South Asia where resistance to pentavalent antimonials is prevalent. There is some evidence to support the use of miltefosine for VL acquired in East Africa. There is less available evidence to support its use in southern Europe and Latin America.
[11]Resistance to pentavalent antimonials is well documented in India and has been reported from other areas. In general, pentavalent antimonial therapy should not be used for persons who acquired VL in India.
[12]Personal communication Pierre Buffet, on the basis of expert opinion.
[13]Contact information for use in military beneficiaries:
Force Health Protection Division's 24-hour cell phone: 301-401-2768
Force Health Protection Division's email: usarmy.detrick.medcom-usammda.mbx.force-health-protection@mail.mil
CDC Drug Service (telephone: 404-639-3670; email: drugservice@cdc.gov)
Canada's Special Access Program

List of Abbreviations: CDC (Centers for Disease Control and Prevention), CL (cutaneous leishmaniasis), D5W (5% dextrose in water), EMLA (lidocaine and prilocaine topical anesthetic), FDA (Food and Drug Administration), GI (gastrointestinal), IL (intralesional), IM (intramuscular), IND (Investigational New Drug), IV (intravenous), kg (kilogram), MBCL (methylbenzethonium chloride), mg (milligram), mL (milliliter), ML (mucosal leishmaniasis), mm (millimeter), po (by mouth), Sb^V (pentavalent antimony), sec (second(s), US (United States), VL (visceral leishmaniasis).

Table 4: Drugs Used in North America for Systemic[a] Antileishmanial Therapy: Adverse Events, Monitoring for Toxicity, and Mitigation Approaches[b]

Drug[c]	Route(s) of Administration	Adverse Events[d,e]	Laboratory Monitoring for Toxicity[d,f]	Mitigation and Management Approaches[d,f]	Pregnant Patients[f,g]	Breastfeeding Patients[f,h]	Comments
Parenteral							
Amphotericin B formulations							
Amphotericin B deoxycholate	IV	Infusion-related reactions[i] (eg, fever, rigors, headache, nausea, vomiting, hypotension, tachypnea), electrolyte abnormalities (eg, hypokalemia, hypomagnesemia), nephrotoxicity, anemia	Baseline and frequent (eg, once or twice weekly) serum chemistry values and CBC. More frequent and/or additional testing (eg, ECG, urinalysis) may be indicated or prudent for some patients.	Examples: premedication; saline loading; test dose; slow infusions (~2–6 h); electrolyte supplementation, increased intervals between doses, and/or drug holidays, if indicated. Avoid/ minimize use of other nephrotoxic agents (eg, nonsteroidal anti-inflammatory drugs).	FDA pregnancy category B[j]	Probably compatible (see text XXVI); interruption of breastfeeding may be prudent.	
Liposomal amphotericin B (*also other lipid-associated formulations of amphotericin B*)	IV	Usually better tolerated than amphotericin B deoxycholate but similar types of toxicity (eg, renal). Infusion-related reactions to liposomal amphotericin B also can be caused by liposome-induced complement activation-related pseudoallergy (CARPA; see text XIX and XX).	See above.	See above (eg, minimize use of other nephrotoxic agents) but modify as appropriate (eg, liposomal amphotericin B typically is infused over ~2 h; minimum of ~1 h).	FDA pregnancy category B[j] (see text XXVI)	See above.	

(continued)

Table 4
Continued

Drug[c]	Route(s) of Administration	Adverse Events[d,e]	Laboratory Monitoring for Toxicity[d,f]	Mitigation and Management Approaches[d,f]	Pregnant Patients[f,g]	Breastfeeding Patients[f,h]	Comments
Pentavalent antimonial (Sb^V) compounds—sodium stibogluconate (Pentostam®) and meglumine antimoniate (Glucantime®)	IV, IM[a]	Various symptoms (eg, myalgia, large-joint arthralgia, headache, malaise, fatigue, anorexia, nausea) commonly noted as treatment course progresses. Laboratory abnormalities usually reversible (during or after treatment), including elevated aminotransferase, lipase, and amylase values (see comments); also, ECG abnormalities (eg, nonspecific ST-T-wave changes; less often, clinically relevant QTc prolongation) and cytopenias (in VL, pretreatment cytopenias typically improve during therapy).	Baseline and weekly serum chemistry values (eg, aminotransferases, lipase/amylase, potassium, creatinine, BUN, glucose), CBC, and ECG. More frequent monitoring may be indicated or prudent for some patients (see text XXVI).	Avoid/minimize use of other agents (eg, drugs linked to QTc prolongation). Interrupt Sb^V therapy if QTc prolongation (eg, if QTc >0.50 sec), concave ST-segments, clinically relevant arrhythmias, or moderate-to-severe clinical pancreatitis; thresholds for interrupting therapy if asymptomatic laboratory abnormalities (eg, elevated aminotransferase levels) should be individualized. Nonsteroidal anti-inflammatory drugs may be used for symptomatic therapy; avoid rigorous physical activity.	Not formally assigned to an FDA pregnancy category (see text XXVI)	Probably compatible (see text XXVI); interruption of breastfeeding may be prudent.	Patients with advanced immunosuppression (eg, AIDS) may have life-threatening pancreatitis or cardiotoxicity (see text XXIII). See XXVI regarding considerations for other special populations (eg, children).

(continued)

Table 4
Continued

Drug[c]	Route(s) of Administration	Adverse Events[d,e]	Laboratory Monitoring for Toxicity[d,f]	Mitigation and Management Approaches[d,f]	Pregnant Patients[f,g]	Breastfeeding Patients[f,h]	Comments
Pentamidine isethionate	IV, IM	Various symptoms (eg, nausea, vomiting, dysgeusia, headache); hypo/hyperglycemia, insulin-dependent diabetes mellitus (may e diagnosed up to several months posttreatment), pancreatitis, hypotension, QTc prolongation, nephrotoxicity, hyperkalemia, hypocalcemia, hepatoxicity, cytopenias (leukopenia/ thrombocytopenia > anemia). If IM: also pain and sterile abscesses at injection sites; rhabdomyolysis.	Assess before, during, and after therapy: serum chemistry values, CBC, and ECG. Monitor fasting \glucose level (and urinalysis) before each dose and ~3 weeks and ~2–3 months posttreatment. If indicated (if potential for rhabdomyolysis), check or monitor CPK level.	To minimize risk for hypotension, infuse drug over 1–2 h; keep patient supine; check vital signs before, during, and after infusion (or injection) until stable. Avoid/ minimize use of other agents, including nephrotoxic drugs.	Typically, not warranted or recommended for antileishmanial treatment during pregnancy	Selection of a different drug or interruption of breastfeeding may be prudent.	
Oral							
Azoles	Oral	GI symptoms (eg, nausea, vomiting, abdominal pain); headache; hepatotoxicity	Baseline and weekly assessment of hepatic function (eg, aminotransferase levels). More frequent and/or additional types of monitoring (eg, ECG, CBC) may be indicated or prudent for some patients.	Avoid/minimize use of other hepatotoxic agents (eg, acetaminophen). Hepatoxicity may warrant interrupting therapy. Both drugs listed below are associated with drug interactions that can be life threatening.	Typically, not warranted or recommended for antileishmanial treatment during pregnancy		
Fluconazole	Oral	See above. Also: reversible hair loss and agranulocytosis	See above.	Can be taken with or without food. (Also see above.)	See above.	Generally considered compatible; on principle, interruption of breastfeeding may be prudent.	

(continued)

Table 4

Continued

Drug[c]	Route(s) of Administration	Adverse Events[d,e]	Laboratory Monitoring for Toxicity[d,f]	Mitigation and Management Approaches[d,f]	Pregnant Patients[f,g]	Breastfeeding Patients[f,h]	Comments
Ketoconazole[k]	Oral	See above. Risk for severe hepatoxicity (fatal or requiring transplantation) may be higher than with other azoles and may occur regardless of dose/ duration of therapy.[k] QTc prolongation may occur and lead to life-threatening ventricular arrhythmias.[k] High-dose therapy may be associated with decreased secretion of adrenal corticosteroids and/or reversible decreases in serum testosterone levels.	See above.	To minimize GI symptoms, take with food; gastric acidity required. (Also see above.) Avoid use of other drugs linked to QTc prolongation, including drugs metabolized by CYP3A4.[k]	See above.	Selection of a different drug or interruption of breastfeeding may be prudent.	
Miltefosine[k]	Oral	GI symptoms (nausea/ vomiting > diarrhea), mainly early in treatment course; dizziness/motion sickness; scrotal pain (decreased/absent ejaculate); nephrotoxicity and/or hepatoxicity	Baseline and weekly assessment of renal function; also (particularly, if VL) monitor hepatic function (aminotransferase and bilirubin levels) and CBC (platelet count).	To minimize GI symptoms, take with food and use divided daily dosing (see text XXVI). Encourage fluid intake if vomiting/diarrhea.	Female patients with reproductive potential[k] should have a negative pretreatment pregnancy test, should use effective contraception during and for 5 months after treatment, and should not rely on hormonal contraception if vomiting/diarrhea.	Breastfeeding not recommended during or for 5 months after treatment (see text XXVI).	Not FDA-approved for patients <12 years of age or <30 kg. See text (XXVI) regarding considerations for children and other special populations. Contraindicated in patients with Sjögren-Larsson Syndrome (congenital ichthyosis).

Abbreviations: BUN, blood urea nitrogen; CBC, complete blood count; CPK, creatine phosphokinase; ECG, electrocardiogram; FDA, U.S. Food and Drug Administration; GI, gastrointestinal; IM, intramuscular; IV, intravenous; QTc, corrected QT interval (on ECG); Sb^V, pentavalent antimony (antimonial); VL, visceral leishmaniasis.

[a] See Table 3 and text (eg, XIV and XXVI) regarding nonsystemic drug therapies, including treatment with intralesional Sb^V and topical paromomycin.

[b] To help ensure safe and effective therapy, see full prescribing information for additional details, including potential drug interactions. Expert consultation also is encouraged regarding such issues as whether to start, continue, or interrupt therapy with a particular antileishmanial agent; to adjust the dosage regimen; or to select a different agent if the patient has or develops laboratory abnormalities or comorbid conditions. On principle, minimize the use of other medications/supplements and avoid alcohol.

[c] In general, drugs are listed alphabetically in the parenteral and oral categories and in the subcategories (eg, azoles); however, "pentavalent antimonial compounds" are listed before "pentamidine isethionate."

[d] Not all-inclusive.

[e] Selected examples are provided (eg, comparatively common or noteworthy adverse events); potential dermatologic effects and phlebitis (if IV) are not addressed. In general, symptoms are listed first. The types and rates of adverse events associated with a particular drug may vary, depending on interrelated factors such as the leishmanial syndrome, dosage regimen, and host characteristics (eg, immunologic status, comorbid conditions, concomitant/recent use of other medications).

[f] Should be individualized.

[g] Use during pregnancy only if clearly indicated (see text XXVI); expert consultation encouraged.

[h] The potential for risk to breastfeeding infants cannot be excluded; expert consultation encouraged.

[i] Some of the examples (eg, headache, GI symptoms) are not necessarily just infusion related.

[j] Reproduction studies in animals have not demonstrated fetal risk; however, data from adequate, controlled studies in pregnant women are not available.

[k] See boxed warning (also known as "black box warning") in prescribing information.

or worsening while on therapy suggests an inadequate response and an alternate treatment approach should be planned [Strong, low]. *Remark: A paradoxical increase in the local inflammatory response may be seen in the first 2–3 weeks of treatment and can be difficult to differentiate from therapeutic failure.*

44. Consultation with a leishmaniasis expert about other treatment options is recommended for management of persons' lesions associated with therapeutic failure [Strong, very low].

MUCOSAL LEISHMANIASIS

XVII. What are the treatment options for American (New World) mucosal leishmaniasis (ML)?

Recommendations

45. All persons with clinically manifest, metastatic, American ML should receive systemic antileishmanial therapy, with the goals of preventing morbidity (e.g., disfigurement) and mortality (e.g., from aspiration pneumonia or respiratory obstruction) [Strong, low].
46. Before treatment is initiated, a complete examination of the naso-oropharyngeal/laryngeal mucosa should be conducted by a specialist to assess the anatomic extension and clinical severity of the mucosal disease, which have prognostic implications [Strong, moderate].
47. We recommend inpatient monitoring and prophylactic corticosteroid therapy for persons with laryngeal/pharyngeal disease and increased risk for respiratory obstruction, as indicated by symptoms and otolaryngologic/radiologic examinations, because of the potential for inflammatory reactions after initiation of antileishmanial therapy [Strong, low].
48. The choice of antileishmanial agent, dose, and duration of therapy for persons with ML should be individualized (Table 3) [Strong, moderate]. *Remarks: The traditional options for ML include treatment with a pentavalent antimonial (Sb^V) compound (20 mg Sb^V/kg daily, IV or IM, for 28–30 days) or with amphotericin B deoxycholate (0.5–1.0 mg/kg per dose, IV, daily or every other day, for a cumulative total of ~20–45 mg/kg). More recently, on the basis of comparatively limited data, the armamentarium has expanded to include lipid formulations of amphotericin B (typically, liposomal amphotericin B [L-AmB], with a cumulative total dose ranging widely from ~20–60 mg/kg), as well as the oral agent miltefosine (~2.5 mg/kg per day [maximum, 150 mg/day] for 28 days).*

VISCERAL LEISHMANIASIS

XVIII. In what circumstances should a person with visceral *Leishmania* infection be treated?

Recommendations

49. We recommend that persons with clinical abnormalities compatible with VL and laboratory evidence of VL be treated (Table 3) [Strong, moderate].
50. We suggest that clinicians closely monitor persons with asymptomatic visceral infection and generally initiate therapy only if clinical manifestations of VL develop [Weak, very low].

XIX. What is the optimal treatment for VL in a symptomatic immunocompetent person (person without an identified immune defect) in North America?

Recommendations

51. For an immunocompetent person with VL, treatment with liposomal amphotericin B (L-AmB) is recommended. The FDA-approved dosage regimen is 3 mg/kg/day IV on days 1–5, 14, and 21 (total dose, 21 mg/kg) (Table 3) [Strong, high]. *Remarks*: *Multiple regimens in which the total L-AmB dose is 18–21 mg/kg have been used effectively in regions other than East Africa. Doses of 40 mg/kg or more may be necessary in persons with VL acquired in East Africa. Other lipid-associated formulations of amphotericin B, such as amphotericin B lipid complex and amphotericin B colloidal dispersion, are not generally recommended: they have not been approved by FDA for treatment of VL; and they have been less well studied in VL treatment trials (i.e., bioequivalence has not been established).*
52. For an immunocompetent person with VL caused by *L. donovani*, acquired in the Indian subcontinent (South Asia), who is ≥12 years of age, weighs ≥30 kg, and is not pregnant or breastfeeding, treatment with the oral agent miltefosine, 2.5 mg/kg per day (maximum, 150 mg, in 3 divided doses) for 28 days, is a possible alternative to L-AmB, particularly in persons weighing <75 kg (see XXVI and Table 3) [Strong, moderate].

XX. What alternative agent(s) can be used for a person with VL who cannot tolerate liposomal amphotericin B or miltefosine or in whom these agents otherwise are contraindicated?

Recommendations

53. Pentavalent antimonial therapy (20 mg Sb^V/kg/day IV or IM for 28 days) is a recommended therapy for immunocompetent persons with VL acquired in areas where the prevalence of antimony-resistant *Leishmania* species is low (<10%) [Strong, high].
54. We do not recommend switching to amphotericin B deoxycholate in persons with contraindications to, or substantial toxicity with, L-AmB, with the exception of persons who develop liposome-induced complement activation-related pseudoallergy (CARPA). Amphotericin B lipid complex is a consideration in this situation [Strong, low].

XXI. In persons with VL, what parameters should be used to assess the clinical response to treatment?

Recommendations

55. Clinical parameters correlate well with parasitologic responses to VL treatment and should be used to monitor the response [Strong, low].
56. Parasitologic confirmation of response (such as by repeat bone marrow aspiration for microscopy and culture after treatment) is not recommended in a patient showing a timely clinical response. Antibody levels fall but over many months or longer [Strong, moderate].

XXII. How should a person with VL be treated who does not respond to initial therapy as assessed by these parameters [or who has a relapse]?

Recommendations

57. Immunocompetent persons with VL who do not respond to therapy with L-AmB should be treated with an alternative drug or with a higher dose or a longer course of L-AmB [Strong, low].
58. Immunocompetent persons with VL who do not respond to initial therapy with miltefosine or a pentavalent antimonial compound should be treated with L-AmB or an alternative drug if L-AmB is unavailable [Strong, low].
59. Immunocompetent persons with VL who respond to initial therapy but subsequently have a relapse should be treated with an alternative drug or with another, potentially longer, course of therapy with the initial drug. If L-AmB was the drug used for initial therapy, use of a higher dose can be considered [Strong, low].
60. Combination therapies may be considered but have not been well studied after therapeutic failure in persons with VL [Weak, low].

LEISHMANIASIS IN IMMUNOCOMPROMISED HOSTS

XXIII. How should HIV/AIDS-associated visceral leishmaniasis (VL) be treated in persons in North America, and what other management issues should be considered?

Recommendations

61. Liposomal amphotericin B (L-AmB) is recommended for the treatment of VL in immunocompromised persons in North America (Table 3) [Strong, low]. *Remark: The FDA-approved dosage regimen of L-AmB for such persons, including those with concurrent HIV/AIDS, is 4 mg/kg/day IV, on days 1–5, 10, 17, 24, 31, and 38 (10 doses over a 38-day period), for a total dose of 40 mg/kg*.
62. Combination therapy (e.g., L-AmB plus miltefosine) might be considered, especially for persons with refractory cases of VL [Weak, very low]. *Remark: The efficacy and optimal duration of miltefosine monotherapy (and combination therapy) for HIV/AIDS-associated VL have not been established.*
63. Because of the importance of effective immune reconstitution in HIV-VL-coinfected persons, antiretroviral therapy (ART) should be initiated or optimized as soon as the person is sufficiently stable to tolerate it (e.g., either during or soon after the initial course of therapy for VL) [Strong, low].
64. *Leishmania* infection that becomes clinically manifest or worsens after initiation of ART should be treated with antileishmanial (and, if indicated, corticosteroid) therapy; leishmaniasis-associated immune reconstitution inflammatory syndrome (IRIS) reactions after initiation of ART have been reported occasionally [Strong, very low].
65. We recommend administering secondary prophylaxis (chronic maintenance therapy) to decrease the risk for posttreatment relapse of VL in persons with HIV/AIDS-associated immunosuppression (e.g., CD4 T-lymphocyte cell counts <200 cells/mm^3) [Strong, moderate].
66. Persons with VL-HIV/AIDS coinfection should be monitored indefinitely (until effective immune reconstitution) for evidence of posttreatment relapse; ART and secondary prophylaxis provide only partial protection against relapse. Antileishmanial treatment is indicated for persons who have clinical and parasitologic evidence of recurrence [Strong, low].

XXIV. How should HIV/AIDS-associated CL or ML be treated in persons in North America who do not have evidence of VL, and what other management issues should be considered?

Recommendations

67. In HIV/AIDS-associated CL/ML, systemic antileishmanial therapy is recommended, particularly in persons who are moderately to severely immunosuppressed (e.g., have CD4+ T-lymphocyte cell counts <200–350 cells/mm^3), who may be at increased risk for suboptimal therapeutic responses, for posttreatment relapses, and for cutaneous, mucosal, or visceral dissemination [Strong, very low].
68. The systemic regimens used for CL/ML in otherwise comparable immunocompetent persons typically are recommended for the initial treatment of coinfected persons, taking into account the potentials for drug interactions and toxicity (Tables 3 and 4) [Strong, very low]. *Remark: Whether coinfected persons who experience multiple posttreatment relapses of CL/ML would benefit from secondary prophylaxis (chronic maintenance therapy) has not yet been established*.
69. Antiretroviral therapy (ART) should be initiated or optimized in accordance with standard practice for HIV/AIDS; no evidence-based, CL/ML-specific recommendations regarding ART have been established [Strong, low].

XXV. What is the preferred treatment of visceral/cutaneous leishmaniasis in immunocompromised hosts with solid organ transplant, persons with lymphatic-hematologic malignancies, or persons receiving immunosuppressive therapy for other reasons?

Recommendations

70. Liposomal amphotericin B (L-AmB) is recommended as the drug of choice for immunosuppressed persons with VL (Table 3) [Strong, low]. *Remarks: The FDA-approved regimen is 4 mg/kg/day IV on days 1–5, 10, 17, 24, 31, and 38 (total dose of 40 mg/kg). Higher doses and longer durations of therapy may be needed depending in part on the level of immunosuppression.*
71. Doses of immunosuppressive drugs should be decreased in persons with VL during antileishmanial therapy whenever possible [Strong, very low].
72. Secondary prophylaxis is not recommended for initial management in persons with VL who have not manifested a relapse [Weak, low]. *Remark*: *Immunosuppressed persons with VL who are not coinfected with HIV typically have higher response rates to initial treatment and lower recurrence rates than HIV-coinfected persons.*
73. Routine serologic screening of organ donors from leishmaniasis-endemic areas is not recommended. If an available donor is known to be seropositive, it is advisable to perform clinical and laboratory monitoring

of the recipient in the post-transplant period rather than to reject the organ for transplant [Strong, low].

74. We suggest that clinicians not routinely perform diagnostic testing to assess persons for evidence of asymptomatic visceral infection, including persons who have lived or traveled in leishmaniasis-endemic regions (Figure 3) and are considering organ transplantation or initiation of therapy with biologic immunomodulating agents. Immunosuppressed persons known or found to be asymptomatically infected and those with a history of VL warrant close monitoring. Neither preemptive treatment nor primary prophylaxis for VL in asymptomatically infected persons is suggested [Weak, very low].
75. Immunosuppressed persons with VL who are not coinfected with HIV should be monitored for a minimum of 1 year (ideally lifelong or until effective immune reconstitution) to assess for posttreatment relapse. During clinical follow-up, assess for symptoms and, if present, pursue parasitologic confirmation of relapse [Strong, very low].
76. Confirmed VL therapeutic failure typically can be managed by retreatment using L-AmB at the same or a higher total dose [Strong, very low]. *Remark: Pentavalent antimonials could be used in some persons with VL under close follow-up.*
77. We suggest that CL/ML associated with the use of tumor necrosis factor (TNF)-alpha antagonist therapy be managed with systemic therapy and standard drug regimens for the pertinent setting/species (e.g., geographic area where the infection was acquired) [Weak, very low]. *Remark: Withdrawal of TNF-α antagonists during antileishmanial therapy may be appropriate: the risks, benefits, and feasibility of this action should be assessed on a case-by-case basis.*

SPECIAL POPULATIONS AND LEISHMANIASIS

XXVI. How should the treatment of leishmaniasis be modified in persons who are pregnant or lactating; are young children or older adults; or have comorbidities such as renal, hepatic, or cardiac dysfunction?

Recommendations

78. In general, clinically manifest cases otf VL and ML should be treated even in these special populations of persons because the benefits of treatment typically outweigh the risks. However, patient-specific factors, including the presence of comorbid conditions, should be considered in the selection of the antileishmanial therapy, dosage regimen, and monitoring approach (Table 4) [Strong, low].
79. Decisions regarding whether and how to treat cases of CL in persons with special characteristics or comorbid conditions should take into account the potential risks and benefits of various approaches, such as initially observing without antileishmanial therapy, deferring treatment (e.g., until after pregnancy/delivery), and using local (vs systemic) therapy as the sole approach or as a temporizing measure, if otherwise appropriate and feasible [Strong, very low].

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Potential Conflict of Interest:

The following list is a reflection of what has been reported to IDSA. To provide thorough transparency, IDSA requires full disclosure of all relationships, regardless of relevancy to the guideline topic. Evaluation of such relationships as potential conflicts of interest (COI) is determined by a review process that includes assessment by the SPGC Chair, the SPGC liaison to the development Panel, the Board of Directors liaison to the SPGC, and, if necessary, the Conflict of Interest (COI) Task Force of the Board. This assessment of disclosed relationships for possible COI will be based on the relative weight of the financial relationship (i.e., monetary amount) and the relevance of the relationship (i.e., the degree to which an association might reasonably be interpreted by an independent observer as related to the topic or recommendation of consideration). The reader of these guidelines should be mindful of this when the list of disclosures is reviewed. For activities outside of the submitted work, N.A. has received payment from Up to Date. For activities outside of the submitted work M.E. has received research grants from the Israel National Institute for Health Policy Research (Rotavirus). For activities outside of the submitted work, R.P. has received personal fees from Merck & Co, Inc. and has a patent Protozoacidal Activity of the Phenothiazines (U.S. patent number 4,407,800), 1983.issued. No conflicts: E.C., M.L., R.L., B.H., P.W., S.J., and A.M.

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