INSTITUTE OF TROPICAL MEDICINE ANTWERP

State of the Art
Treatment of Tropical Diseases
Version June 2024

How to use the State of the Art in 2024?

Welcome to the June 2024 edition of the "**State of the Art Treatment of Tropical Diseases**" of the Institute of Tropical Medicine (ITM), Antwerp. This comprehensive clinical guidance is now accessible on the WikiTropica platform, hosted by the ITM. Formerly an internal document, it is now publicly available to enhance the treatment of tropical diseases in Belgium and beyond.

Originally developed by Prof. Dr. Alfons Van Gompel over 20 years ago, this guide has served as a crucial resource for the treatment of tropical diseases at ITM and throughout Belgium. It was meticulously compiled through regular literature reviews and the extensive clinical experience of ITM experts. The 2018 update was conducted by a dedicated team from ITM's Department of Clinical Sciences and the University of Antwerp, including Prof. Dr. Emmanuel Bottieau, Dr. Steven Van Den Broucke, Prof. Dr. Chris Kenyon, Dr. Eric Florence, and Prof. Dr. Erika Vlieghe, with technical assistance from Jan Kennis. The June 2024 update benefited from the additional contributions of Dr. Caroline Theunissen and Dr. Ula Maniewski, alongside technical and layout support from Dr. Maria Zolfo, Stefaan Vande Walle, Dr. Susan Dierickx, Nadia Dahchour, and Steffie De Landtsheer.

The guide is currently structured into seven chapters, each dedicated to the main categories of infectious pathogens, within which diseases appear in alphabetic order. It provides two forms of references: introductory references at the beginning of each disease section for comprehensive information, and in-text references supporting specific therapeutic recommendations. A complete list of references is provided at the end of the manuscript.

Due to the limited evidence available for many rare tropical diseases, the guide does not provide graded recommendations. However, it describes the level of evidence where possible, ranging from randomized controlled trials to expert opinions, and includes formal grading when available in the literature.

Efforts have been made to align the recommendations with the Belgian Center for Pharmacotherapeutic Information (BCFI-CBIP) and the Belgian IGGI guidelines. However, this document offers more detailed information specifically for infectious disease specialists managing complex cases. Both abovementioned guidelines emphasize the importance of consulting the ITM clinical team for tropical disease cases, providing contact information for this purpose.

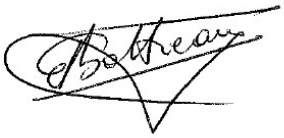
Please note, the information in this guide is accurate as of June 2024, with updates scheduled biennially, and specifically focuses on treatment available in Belgium. Given the rapid evolution of medical knowledge and evolving access, direct consultation with the ITM clinical team is recommended for complex or critical cases to ensure the most current guidance. The ITM can be contacted via email at TROPmail@itg.be, monitored daily, or by phone at 03/247.66.66 for emergencies.

The editorial team welcomes feedback and suggestions for improving the guide. Correspondence should be directed to TROPmail@itg.be to ensure prompt delivery to the relevant expert. While personalized contact details (for supply of specific drugs,…) have been removed for GDPR compliance, they can be obtained by contacting ITM.

We hope this resource will be invaluable for making informed decisions regarding the treatment of (neglected) tropical and infectious diseases.
Antwerp, 14th of June 2024.

Under the scientific responsibility and accountability of:

Prof. Dr. Emmanuel Bottieau
Head of Unit Tropical Medicine



Dr. Steven Van den Broucke
Head of Clinic Tropical Infections

Prof. Dr. Patrick Soentjens
Head of ITM Polyclinic
Head of Unit Travel Medicine

List of abbreviations

od: once daily

bid: bis in die (twice a day)

tid: ter in die (three times a day)

qid: quater in die (four times a day)

po: per os

iv: intravenous

im: intramuscular

sc: subcutaneous

ITM: Institute of Tropical Medicine, Antwerp

NTD: neglected tropical disease

Table of Contents

Chapter 1: Protozoa

1 Amebiasis (Entamoeba histolytica)

1.1 Amebic liver abscess (ALA)

Selected References

1. https://dx.doi.org/10.1503/cmaj.121576 ((Showler and Boggild 2013)
2. https://dx.doi.org/10.1056/NEJMra022710 (Haque et al. 2003)
3. https://dx.doi.org/10.1016/S0140-6736(03)12830-9 (Stanley 2003)
4. https://dx.doi.org/10.1093/clinids/20.6.1453 (Ravdin 1995)
5. https://dx.doi.org/10.1016/j.trstmh.2007.04.001 (Jean François Rossignol et al. 2007)
6. https://dx.doi.org/10.1056/NEJM200210243471722 (Blessmann and Tannich 2002)
7. https://dx.doi.org/10.1002/14651858.CD006085.pub2 (Gonzales, Dans, and Sio-Aguilar 2019a)
8. https://dx.doi.org/10.4103/2229-5070.149887 (Caliari et al. 2015)

Preliminary notes

When amebic liver abscess (ALA) is suspected, empiric treatment should be started whilst waiting for diagnostic results.

A tissue amebicide agent (as described here below) should always be followed by a luminal amebicide agent (as described in intestinal amebiasis).

First-line treatment

Tinidazole (Fasigyn®)

- Adults: 2 gr po od x 3-5 days (depending on severity of the disease).
- Children: 50 mg/kg po od (max 2 gr) x 3-5 days.

A small RCT in India (150 patients with ALA) reported a cure rate of 62.3% in the tinidazole group vs 37.7% in the metronidazole group (Pandey et al. 2018).

NB: as tinidazole is not available any more in Belgium, ornidazole (Tiberal®) could be prescribed instead, at the same dosage as tinidazole, but there is much less evidence with this drug for treating amebiasis. Close follow-up of treatment effectiveness is therefore required

Metronidazole (Flagyl®) (if oral treatment not possible)

- Adults: 750 mg tid (preferably iv for the first few days followed by po) x 10 days.
- Children**:** 15 mg/kg tid (preferably iv for the first few days followed by po) x 10 days.

Consider catheter drainage (better than needle aspiration), in case of:

- Large abscess > 10 cm; (NB: no clear benefit for abscess 5-10 cm; medical treatment for abscess < 5 cm).
- Subcapsular abscess in left lobe (risk of rupture to pericardium).
- (Suspicion) of pyogenic superinfection (seems more frequent than previously thought).
- Clinical deterioration or no clinical response to medical treatment after 3-4 days. Fever can persist for several days (tissue resorption), but general condition usually improves quickly.

Alternative regimen

- Nitazoxanide: only one small RCT (n=60) in India has evaluated nitazoxanide for the treatment of ALA (500°mg po bid x 10 days) and found an efficacy equivalent to that of metronidazole (Goel et al. 2021).

Special situations

Non-hepatic ameboma/amebic abscess.

Other localizations of amebic abscesses (very rare) are treated similarly.

In case of intestinal ameboma add antibiotics covering intestinal bacteria and consider surgery.

Pregnancy:

- Nitroimidazoles: Not contra-indicated during pregnancy (risk/benefit balance for ALA in favor of this treatment).
- Paromomycin: Probably safe (no systemic resorption).
- Nitazoxanide: Probably safe (studies in humans are lacking).

Availability and costs

Only é nitroimidazole derivates (metronidazole, ornidazole) and paromomycin are available in Belgian pharmacies (b category, with prescription). Tinidazole has been removed from the Belgian market in September 2021. Consider using ornidazole (1.5-2g/day for the same duration) instead, although there is no clinical data for the treatment of ALA)

Nitazoxanide is not available in Belgium (very expensive); may be obtained via https://www.inhousepharmacy.vu/p-2027-nizonide-nitazoxanide-500mg.aspx.

1.2 Intestinal amebiasis

Selected References

1. https://dx.doi.org/10.1016/j.meegid.2011.07.023 (De Jonckheere 2011b)
2. https://dx.doi.org/10.1016/j.trstmh.2007.04.001 (Jean François Rossignol et al. 2007)
3. https://dx.doi.org/10.4269/ajtmh.15-0458 (Reyna-Fabián et al. 2016)
4. https://dx.doi.org/10.1179/2047773212Y.0000000021 (Sánchez-Aguilar et al. 2012)
5. https://dx.doi.org/10.1111/j.1445-2197.2010.05494.x (S. S. Gupta et al. 2011)
6. https://pubmed.ncbi.nlm.nih.gov/23991750/ (Marie and Petri 2013)
7. https://doi.org/10.1002/14651858.cd006085.pub3 (Gonzales, Dans, and Sio-Aguilar 2019b)

Preliminary note

Entamoeba histolytica – diagnosis relying only on PCR or on the presence of red blood cells in moving trophozoites – is the only species with confirmed pathogenicity (treatment is always needed). In case of suspicion of *E. histolytica* infection, serology is positive after 5-7 days but cannot distinguish between acute and past infection. Antigen testing can distinguish between *E. histolytica* and *E. dispar* infection.

There is controversy on the possible pathogenicity of *E. moshkovskii*, *E. polecki*, and *E. Bangladeshi*: treat only if symptoms. *E. dispar, E. coli* and *E. hartmanni* are always apathogenic.

The treatment of a symptomatic infection consists of a course of "tissue amebicide" agent followed by a course of "luminal amebicide" agent (to eradicate intestinal cysts and avoid late relapse). For asymptomatic infection, see "Special situations".

First-line treatment

Tissue amebicide

Tinidazole (Fasigyn®):

- Adults: 2 g po od x 3 - 5 days (depending on severity of the disease).
- Children: 50 mg/kg po od (max 2 g) x 3 - 5 days.

Ornidazole (Tiberal®):

- Adults: 500 mg po bid x 5 days.
- Children: 7,5 mg/kg po bid x 5 days.

According to a recent Cochrane Review (Gonzales, Dans, and Sio-Aguilar 2019c), tinidazole may be more effective than metronidazole in reducing clinical failure and may be associated with fewer adverse events.

FOLLOWED BY

Luminal amebicide

Paromomycin (Gabbroral®):

- Adults: 500 mg po tid x 7 days (practically: 3 boxes of 16 tablets of 250 mg = 3 x 2 tablets per day x 7 days).
- Children: 10 mg/kg po tid x 7-10 days.

A recent Cochrane review (Gonzales, Dans, and Sio-Aguilar 2019c) concluded that combination drug therapy (tissue-luminal amebicide agents) may be more effective for reducing parasitological failure compared with metronidazole alone. However, these results are based mostly on small trials conducted over 20 years ago with a variety of poorly defined outcomes.

Alternative tissue amebicide agents

Metronidazole (Flagyl®): (less effective (Redulla 2021)):

- Adults: 500 - 750 mg po tid (or iv if severe) x 7-10 days.
- Children: 15 mg/kg po tid (or iv up to 10 mg/kg if severe) x 7-10 days.

Nitazoxanide (Alinia® 500 mg tablets and 100mg/5 ml oral suspension):

- 500 mg po bid for an adult (100 mg po bid for children 1-3 years; 200 mg po bid for children 4-11 years), x 3 days, to take with meal. Very effective (cure rate: 80-95%) as a tissue AND lumen amebicide. Not FDA-approved in this indication. To consider in case of nitroimidazole allergy/intolerance.

Alternative luminal amebicide agents

Diloxanid furoate (Furamide®):

- 500 mg po tid x 10 days. Cysticidal efficacy: 50%. Not available in Belgium).

Clioquinol (iodochloroxyquinoleine, compounding):

- 250 mg po tid x 20 days. Not available in Belgium.

Special situations

Pregnancy:

- Nitroimidazoles: not contra-indicated during pregnancy (but risk/benefit different than for ALA).
- Paromomycin: probably safe (no systemic resorption).
- Nitazoxanide: probably safe (studies in humans are lacking).

Toxic megacolon and/or intestinal perforation:

- Surgery associated antibiotics for gram-negative enteric organisms.

Asymptomatic infection/cyst carriage:

- Treat asymptomatic (*E. histolytica*) carriers with a luminal amebicide agent only.

Carriers of cysts (or presence of serum antibodies against E. histolytica) with equivocal intestinal complaints:

- Treat with a combined tissue and luminal amebicide therapy (not evidence-based)

Availability and costs

Only 3 nitroimidazole derivates (metronidazole, tinidazole, ornidazole) and paromomycin are available in Belgian pharmacies (b category, with prescription). Tinidazole has been removed from the Belgian market in September 2021.

Nitazoxanide is not available in Belgium (very expensive); may be obtained via internet.

2 Ameba, free-living

2.1 Amebic keratitis

Mainly due to *Acanthamoeba spp,* in immunocompetent contact-lens wearers.

Selected References

1. https://dx.doi.org/10.1051/parasite/2015010 (Lorenzo-Morales, Khan, and Walochnik 2015)
2. https://dx.doi.org/10.1097/ICO.0000000000000804 (Maycock and Jayaswal 2016)
3. https://dx.doi.org/10.1016/j.ophtha.2016.01.020 (Carnt et al. 2016)

First-line treatment

Treatment of *Acanthamoeba spp.* keratitis is difficult. Surgery (debridement, keratoplasty, corneal transplantation or even enucleation in case of unresponsiveness) may be necessary: specialized ophthalmologist advice needed.

Topical treatment is currently recommended with at least two of the following anti-amebic products (the first two being considered as the most efficacious):

- Polyhexamethylene biguanide (PHMB) 0,02% (Lavasept® or magistral)
- Chlorhexidine 0,02% (magistral)
- Propamidine isethionate 0,1% (Brolene®, Sanofi, UK)
- Dibromopropamide 0,15% (magistral)
- Hexamedine 0,1% (Desomédine, Chauvin, France)
- Neomycin

To administer every hour for at least 3 days and then every 3 hours for at least 3-4 weeks; some experts recommend 6 to 12 months of treatment.

NB: Use of topical corticosteroids is controversial. A recent study (n=196) showed symptomatic improvement (pain and discomfort) with no increasing risk of adverse outcome.

Alternative regimens

Oral miltefosine (Impavido®) 50 mg 3 times daily: used with PHMB in some Austrian cases and successful treatment of recalcitrant *Acanthamoeba* keratitis (case report). (Dewan et al. 2019)
Future (but still in-vitro experiments):

- Synthetic dihydropyridines have in vitro activity against *Acanthamoeba castellanii* (Anwar et al. 2020).
- 3-aryl-6,7-dimethoxyquinazolin-4 (3H)-one derivates (Shahbaz et al. 2020).

2.2 Granulomatous amebic encephalitis (GAE)

- High fatality rate (> 90%).
- Acute/subacute meningoencephalitis affecting mainly immunosuppressed individuals.
- Etiological agents: *Acanthamoeba, Balamuthia and Sappinia spp*.

Selected References

1. https://dx.doi.org/10.1016/j.meegid.2011.07.023 (De Jonckheere 2011a)
2. https://dx.doi.org/10.1001/jama.285.19.2450 (Gelman et al. 2001)
3. https://dx.doi.org/10.1086/653609 (Martínez et al. 2010)
4. https://dx.doi.org/10.1086/589747 (Tunkel et al. 2008)
5. https://dx.doi.org/10.4103/2152-7806.132239 (Zamora, Henderson, and Swiatlo 2014)

6. https://dx.doi.org/10.1093/jpids/piu103 (Capewell et al. 2015)
7. https://dx.doi.org/10.1093/cid/civ1021 (Cope et al. 2015)
8. https://dx.doi.org/10.1128/AAC.01293-15 (Grace, Asbill, and Virga 2015)
9. https://dx.doi.org/10.1016/j.arcmed.2004.11.003 (Vargas-Zepeda et al. 2005)

2.2.1 Acanthamoeba spp.

First-line treatment
No known effective treatment. Combination treatments preferred over single-drug regimens. A single cerebral lesion should be removed if feasible (J. Nelson and Singh 2018).

- Miltefosine + fluconazole or voriconazole + pentamidine isethionate. To this regimen can be added: trimethoprim-sulfamethoxazole, rifampicin and/or a macrolide (azithromycin or clarithromycin).
- Hyperbaric oxygen, according to some case reports (Maritschnegg et al. 2011)

2.2.2 Balamuthia mandrillaris

First-line treatment
No known effective treatment. A single cerebral lesion should be removed if feasible (Orozco et al. 2011).

- Albendazole 400 mg po bid + fluconazole/itraconazole + miltefosine (50 mg tid x 12 days, then bid for an extended period) +/- pentamidine 4 mg/kg iv or im od.
- Some experts would add TMP-SMX, azithromycine or flucytosine to the combination treatment.
- In a retrospective study from China 12/28 survived and most received the combination of lincomycin, interferon-y and azithromycin (L. Wang et al. 2020).

2.2.3 Sappinia pedata

First-line treatment
Worldwide only 1 case reported in the literature. The patient recovered with the following treatment:

- Azithromycin (250 mg po od x 31 weeks) + pentamidine isethionate (300 mg iv od x 6 weeks) + itraconazole (200 mg po bid x 25 weeks) + flucytosine (2.75 g po qid x 25 weeks) (Gelman 2001).

2.3 Primary amebic meningoencephalitis (PAM)

Etiological agent: *Naegleria fowleri* (ubiquitous).
Mortality > 95%, survival depends on early diagnosis and early amphotericin treatment.

First-line treatment
No established optimal treatment; duration from 9 to 30 days.

- Early treatment with Amphotericin B deoxycholate: (0.75 mg/kg iv bid x 3 days, followed by 1 mg/kg iv od X 6 days) + (1,5 mg intrathecally od x 2 days followed by 1 mg every other day intrathecally x 8 days), possibly associated with rifampicin 5 mg/kg po or iv bid (max 600 mg/day) and/or fluoconazole 10 mg/kg po or iv od and/or azithromycine 25 mg/kg po or iv od (max 500 mg) and miltefosine 50 mg bid (< 45 kg) or tid (> 45 kg)
- Add dexamethasone to control cerebral edema.

NB: Conventional amphotericin B deoxycholate is preferable as compared to the liposomal formulation since it has a lower MIC (Jahangeer et al. 2020a).

In vitro data: (1) Posaconazole improved survival rate in mice (Colon et al. 2019); (2) an orphan drug designation for corifungin is approved by the US FDA given the good in vitro activity (Jahangeer et al. 2020b); the HMG-CoA reductase inhibitors fluvastatin and pitavastatin have good in vitro activity (Rizo-Liendo et al. 2019; Hahn et al. 2020).

3 Babesiosis (Babesia microti; Babesia divergens)

Selected References

1. https://dx.doi.org/10.1056/NEJMra1202018 (Vannier and Krause 2012b)
2. https://dx.doi.org/10.1016/j.idc.2008.03.010 (Vannier, Gewurz, and Krause 2008)
3. https://doi.org/10.3390/pathogens10091120 (Renard, Pathogens, and 2021 2021)
4. https://doi.org/10.1093/cid/ciaa1216 (Krause et al. 2021b)
5. https://pubmed.ncbi.nlm.nih.gov/30690090/ (Krause 2019)
6. https://doi.org/10.3390/pathogens10091165 (Hildebrandt et al. 2021)

3.1 *Babesia divergens* (Europe), or severe *Babesia microti* (North America)

First-line treatment

- Adults: Clindamycin 600 mg iv or po tid+ quinine 500-650 mg iv or po tid for 7-10 days.
- Children: Clindamycin 7-10 mg/kg iv or po tid + quinine 8-10 mg/kg iv or po tid for 7-10 days.

Consider associating with (partial or complete) exchange transfusion or erythrocytapheresis (better) if organ dysfunction or parasitemia > 10% (weak recommendation for IDSA 2020), (Krause et al. 2021a)

NB: The IDSA guideline 2020 recommends the combination atovaquone and azithromycin (dosages as below) as preferred treatment ALSO for severe patients, but this means that both drugs must be administered intravenously. Since they are not immediately available in Belgium, the classic combination clindamycin and quinine (mentioned as an alternative) remains the proposed first-line therapy here.

3.2 Mild-to-moderate *Babesia microti* (North America)

First line treatment

- Adults: Azithromycin 500 mg od (Day 1) and 250 mg po od (Day 2-10) + atovaquone 750 mg po bid x 7-10 days.
- Children: Azithromycin 10 mg/kg od (Day 1) and 5 mg/kg po od (Day 2-10) + atovaquone 20 mg/kg po bid x 7-10 days.

Special situations

Immunosuppression (asplenia/splenectomy, lymphoma…):

- The above-described treatment should be prolonged up to 6 weeks, including 2 weeks after *Babesia* is not detected any more in blood smear.

In immunocompromised patients:

- Higher doses of azithromycin (600-1000 mg od) have been associated with better outcome (and is therefore recommended).

Asymptomatic infection (50% of children; 25% of adults):

- Supportive treatment only (in young and non-immunocompromised individuals); treatment indicated however if parasitemia positive more than 3 months, or if blood donation is considered.

Persistent/relapsing infection (low-grade parasitemia may persist for months):

- Re-treatment should be considered regardless of symptom status if parasitemia is detectable either by microscopy or PCR > 3 months.

Suspicion of resistance:
There is some rising concern that resistance could emerge (in particular against azithromycin). Some alternative drugs appear promising in animal studies and are under clinical investigation, such as tafenoquine, clofazimine and endochin-like quinolones. No clinical data so far.

Pregnant women: Use exclusively clindamycin + quinine

Availability and costs
Atovaquone (Wellvone, GSK) expensive and not reimbursed for this indication. The combination atovaquone/proguanil is well available in Belgium and could be considered, but there is no clinical data (off-label use).

4 Balantidiasis (*Balantidium coli*)

Selected Reference

1. https://dx.doi.org/10.1128/CMR.00021-08 (F. L. Schuster and Ramirez-Avila 2008)

First-line treatment

Tetracycline (no publication with doxycycline)

- Adults: 500 mg po qid x 10 days.
- Children (> 8 years): 10 mg/kg po qid x 10 days.

Alternative regimens

Metronidazole

- Adults: 750 mg po tid x 5 days.
- Children (> 8 years): 15 mg/kg po tid x 5 days.

Very limited data with paromomycin and ampicillin.

Special situations

Rare cause of urinary tract infection, osteomyelitis, as well as disseminated infection (in immunocompromised individuals): treatment not well established.

5 Blastocystiasis (Blastocystis hominis)

Classically considered as nonpathogenic, with no need of treatment! Little evidence of clinical utility of therapy and in many studies most treatments did not achieve any eradication. Subtype 3 is the only of 9 subtypes that 'might' be pathogenic.
Spontaneous clearance occurs in 22% of the infections. A treatment may be considered in the presence of severe/persisting symptoms in the absence of other pathogens, or in immunosuppressed patients.

Selected References

1. https://dx.doi.org/10.4103/2229-5070.113901 (Sekar and Shanthi 2013)
2. https://dx.doi.org/10.1093/cid/cis699 (Anne Line Engsbro 2012)
3. https://dx.doi.org/10.1128/CMR.00022-08 (Tan 2008)
4. https://dx.doi.org/10.1016/S1542-3565(05)00427-1 (Jean François Rossignol et al. 2005)
5. https://dx.doi.org/10.1007/s10156-012-0496-2 (Van Hellemond et al. 2012)
6. https://dx.doi.org/10.1016/S0002-9270(99)00588-2 (Ok et al. 1999)
7. http://iraq-git.com/pdf/issue05page82.pdf (Mahdi and Strak 2005)
8. https://dx.doi.org/10.1007/s100960050314 (Giacometti et al. 1999)
9. https://dx.doi.org/10.1097/MCG.0b013e3181bb86ba (Stensvold et al. 2010)
10. https://dx.doi.org/10.1186/1757-4749-6-17 (T. Roberts et al. 2014)

First-line treatment

- Metronidazole (Flagyl®) 500-750 mg po tid (or 15 mg/kg bid) x 10 days or tinidazole (Fasigyn®) 2gr (50mg/kg) po od for 5 days (not available in Belgium anymore) or ornidazole (Tiberal®) 500 mg po bid (or 25mg/kg od) x 5 days.
- Very variable efficacy (from 30 to 80% according to the studies).

Alternative regimens

Trimethoprim/Sulfamethoxazole (Eusaprim®):

- Adults: 800/160 mg po bid x 7-10 days (2 x 1 compr Forte/d).
- Children: 25/5 mg/kg po bid x 7-10 days.

Eradication: 90%

Paromomycin (Gabbrorral®):

- Adults: 500 mg po tid x 10 days.
- Children: 8-10 mg/kg po tid x 10 days.

Eradication rate: 77%

(Nitazoxanide (Alinia®)

- 500 mg po bid x 3 days or 4 mg/kg po bid x 3 days).

Reported efficacy at 85%. Not available in Belgium and very expensive.

Special situations

No need of treatment if incidental finding in asymptomatic individual.

Availability and costs

(Nitazoxanide is not available in Belgium (very expensive); may be obtained via https://www.inhousepharmacy.vu/p-2027-nizonide-nitazoxanide-500mg.aspx)

6 Chagas disease (*Trypanosoma cruzi*)

Selected References

1. https://dx.doi.org/10.1001/jama.298.18.2171 (Bern et al. 2007)
2. https://dx.doi.org/10.1371/journal.pntd.0001250 (Carlier et al. 2011)
3. https://dx.doi.org/10.1016/S1473-3099(10)70098-0 (Lescure et al. 2010)
4. https://dx.doi.org/10.1016/S0140-6736(10)60061-X (Rassi, Rassi, and Marin-Neto 2010)
5. https://dx.doi.org/10.1016/S1473-3099(15)00243-1 (Pérez-Molina et al. 2015)
6. https://dx.doi.org/10.1016/S1473-3099(01)00065-2 (Prata 2001)
7. https://dx.doi.org/10.1086/656917 (Y. Jackson et al. 2010)
8. https://dx.doi.org/10.1016/S0140-6736(96)04128-1 (Sgambatti de Andrade et al. 1996)
9. https://dx.doi.org/10.1016/0002-8703(94)90521-5 (Viotti et al. 1994)
10. http://www.ncbi.nlm.nih.gov/pubmed/15569790 (Andrade et al. 2004)
11. https://dx.doi.org/10.1056/NEJMoa1507574 (Morillo et al. 2015a)
12. https://dx.doi.org/10.7326/0003-4819-144-10-200605160-00006 (Viotti et al. 2006)
13. https://dx.doi.org/10.4269/ajtmh.2000.63.111 (Lauria-Pires et al. 2000)
14. https://dx.doi.org/10.1128/CMR.14.3.659-688.2001 (Herwaldt 2001)
15. https://doi.org/10.1161/CIR.0000000000000599 (Nunes et al. 2018)

The precise indications of anti-parasitic treatment of Chagas disease remain an area of controversy. It depends mainly on the stage of the disease, of which features and diagnosis are briefly summarized here under.

Acute phase, symptomatic (5-10%) or not (90%):

- Diagnosis by blood microscopy or PCR.

Indeterminate phase, asymptomatic:

- Diagnosis is made if AT LEAST 2 different serological assays (with 2 different antigens/techniques, such as ELISA, IIF, IHA) are positive, and if no damage of target organs can be demonstrated; sensitivity of PCR is 50-70% in this phase and therefore negative PCR cannot exclude the diagnosis.

Chronic (or determinate) phase, asymptomatic or symptomatic (in about 30% of infected individuals, after 10-30 years):

- Diagnosis by serology +/- PCR and demonstration of cardiac or gastro-intestinal abnormalities (ECG, cardiac ultrasound, GI imaging…) (Nunes et al. 2018).

Reactivation, symptomatic (atypical features such as myocarditis, meningoencephalitis…in case of immunosuppression):

- Diagnosis by microscopy or PCR.

Congenital infection, symptomatic or not:

- Risk of neonatal infection of 2-5% if mothers seropositive for Chagas, up to 15% if positive PCR in mothers.
- Diagnosis by (1) positive microscopy (buffy coat) or PCR on cord blood at delivery, OR (2) positive microscopy or PCR at 4-6 weeks, OR (3) positive serology (2 different tests) at 9 months.

6.1 Congenital infection, acute infection and reactivation

ABSOLUTE indication of anti-parasitic treatment (respective cure rates: 90-100%, 75-85% and unknown).

First-line treatment
Initial comment: both anti-parasitic drugs (benznidazole and nifurtimox) have similar efficacy (although no formal head-to-head comparison has been performed), but the safety profile favors benznidazole in first line (rather than nifurtimox). No evidence of additional benefit by combining both drugs (just cumulative toxicity). No evidence of sustained effect of posaconazole and ravuconazole beyond the treatment itself. (Malone et al. 2021)

Benznidazole:
Remark: side-effect in up to 30% of patients, mainly cutaneous, but also hematotoxicity, peripheral neuropathy…)

- (Immunocompetent) adults and children > 12 years: 2,5-5 mg/kg (max 300 mg) po bid x 60 days.
- (Immunocompetent) children < 12 years and neonates: 5 mg/kg po bid x 60 days.
- Reactivation in immunosuppressed individuals: 2,5 mg/kg po bid x 60 days (with PCR follow-up).
    - Consider extended administration until PCR negativation (cave toxicity).
    - Consider secondary prophylaxis (5 mg/kg/d po three times a week or 5 mg/kg/week, or 200 mg daily until "immune recovery").

Alternative regimens
Nifurtimox:
Remark: frequent side-effect, bad tolerance and treatment discontinuation in > 50% of the cases.

- (Immunocompetent) adults and children > 12 years: 2,5-3,75 mg/kg po qid x 60-(90) days.
- (Immunocompetent) children < 12 years and neonates: 3,75-5 mg/kg po qid x 60 days.
- Reactivation in immunosuppressed individuals: 2-2,5 mg/kg po qid x 60-90 days (with PCR follow-up).

6.2 Indeterminate and chronic phases

The recommendation for anti-parasitic treatment varies greatly:
Recommended:

- In early indeterminate/chronic phases, in children/adolescents < 18 years: cure rate of 60-90% at this age and almost no further disease progression in the long-term.
- In women of reproductive age with pregnancy wish (to prevent vertical transmission).
- In patients with (planned) immunosuppression (to prevent reactivation).
- In individuals wishing to donate organs (to prevent reactivation in recipient).

Optional (low cure rates, and likely limited/no clinical benefit):

- “Late” (no clear cutoff) indeterminate phases.
- Chronic (established) cardiac or gastrointestinal phases, after preliminary data demonstrated conflicting results: reduction of disease progression versus no effect. The large BENEFIT trial did not demonstrate any clinical benefit in this group of patients (despite parasitological cure as assessed by PCR negativation). (Morillo et al. 2015b).

Contra-indicated:

- Pregnancy (both drugs are teratogenic).
- Severe renal or hepatic insufficiency.
- Advanced cardiomyopathy or megaesophagus.

First-line treatment
Benznidazole:

- (Immunocompetent) adults and children: 2,5-3,75 mg/kg po bid x 60 days.
- Immunosuppressed individuals: 2,5 mg/kg po bid x 60 days (followed by careful PCR follow-up post-immunosuppression/transplantation).

A recent phase 2 RCT (BENDITA) exploring different dosages and durations of benznidazole therapy with parasitological endpoint (sustained parasite clearance at 6 months follow-up as assessed by PCR) showed that a duration of one month and even 2 weeks of benznidazole 300 mg/day was not inferior to two months (about 85% cure rate for all three regimens). Of note adjunction of fosravuconazole to benznidazole did not improve the cure rate. While these results need to be confirmed in larger trials with clinical endpoints, this suggests however that the benznidazole course could be shortened in patients experiencing adverse event/toxicity (often cumulative) (Torrico F. Lancet Infect Dis 2021).
NB: A recent clinical observation at ITM (still to be published) showed a spectacular improvement of benznidazole-related (oxidative) adverse event immediately after administration of ascorbic acid. It is therefore worth a try in such situations.

Alternative regimens
Nifurtimox:

- (Immunocompetent) adults and children: 2-2,5 mg/kg po qid x 60-(90) days.
- Immunosuppressed individuals: 2-2,5 mg/kg po qid x 60-90 days (followed by careful PCR follow-up post-immunosuppression/transplantation).

NB: no conclusive evidence of additional activity through adjunction of allopurinol or itraconazole.

Special situations
Pregnancy:

- Contraindicated, except in life-threatening acute infection (risk-benefit assessment).

Post-exposure prophylaxis (laboratory accident):

- Benznidazole 2,5-3,75 mg/kg po bid or nifurtimox 2-2,5 mg/kg po qid x 10-14 days.

Availability and costs
Benznidazole (and nifurtimox) are easily obtained for free via WHO, Geneva, by sending a mail to the group of NTD experts (updated address to be obtained at ITM), with a short clinical summary about the indication. An authorization for importation is needed (a template can be obtained at ITM). Order should now be placed through the WHO Integrated Medical System (WIMEDS). Once your request has been processed through WIMEDS, you will receive an acknowledgment by email to confirm that the request has been approved and that the shipment is being prepared. When the shipment is ready for dispatch from WHO, you (i.e. the requestor) will receive another email notification.

7 Cryptosporidiosis (*Cryptosporidium spp.*)

Disease mainly caused by *C. hominis* and *C.parvum; C. felis* and *C. meleagritis* have also been implicated. Disease considered as self-limiting in immunocompetent individuals. There is no effective therapy in immunosuppressed patients, except, if possible, the immune restoration.

Selected References

1. https://dx.doi.org/10.1056/NEJMra013170 (X.-M. Chen et al. 2002)
2. https://dx.doi.org/10.1586/eri.09.24 (Pantenburg B, Cabada M 1989)
3. https://dx.doi.org/10.1007/s40475-015-0056-9 (Sparks et al. 2015)
4. https://dx.doi.org/10.1016/S1473-3099(14)70772-8 (Checkley et al. 2015)
5. https://dx.doi.org/10.1111/j.1365-2125.2007.02873.x (Abubakar et al. 2007)
6. https://dx.doi.org/10.1086/321008 (J F Rossignol, Ayoub, and Ayers 2001)
7. https://dx.doi.org/10.1016/S0140-6736(02)11401-2 (Amadi et al. 2002)
8. https://dx.doi.org/10.1001/jama.279.5.384 (Holmberg et al. 1998)
9. https://dx.doi.org/10.1097/00002030-200012220-00010 (Fichtenbaum et al. 2000)

Immunocompetent patient

First-line treatment

Symptomatic treatment (self-limiting illness).

Alternative regimens

Nitazoxanide (Alinia®):

- Children 1-3 years 100 mg; 4-11 years 200 mg; > 12 years 500 mg; po bid x 3 days.
- Only FDA-approved drug for this indication; cure rate: 56-96%.

Paromomycin (Gabbroral® 16 x 250 mg) 1000 mg po bid x 2-4 weeks (children 10-15 mg/kg po bid).

- Anecdotal evidence of success; no controlled trial

Immunocompromised patient (including HIV/AIDS)

First-line treatment

Restoration of immunity, with antiretroviral treatment.

Alternative regimens

None has demonstrated efficacy in this subgroup of patients. If treatment is considered:

- Nitazoxanide (Alinia®) 500-1000 mg po bid for up to resolution of symptoms, elimination of oocysts AND CD4 count > 200/µl. (Not FDA-approved in this indication; lack of demonstrated efficacy).

- Combination of paromomycin (1000 mg po bid) (or Nitazoxanide) and azithromycin (500 mg od) for 4 weeks, followed by paromomycin 500 mg po bid for 8 weeks as maintenance treatment. (Anecdotal evidence of success)

- Rifabutin/rifaximin 550 mg po bid x 14 days.
  Uncontrolled studies have shown absence of cryptosporidiosis in AIDS patients receiving rifabutin prophylaxis for MAC infection.

NB: responses have been described with rifaximin (Targaxan®) but the drug is expensive.

Availability and costs

Nitazoxanide is not available in Belgium (very expensive); may be obtained via internet.

8 Cyclosporiasis (Cyclospora cayetanensis)

Selected References

1. https://dx.doi.org/10.1097/01.qco.0000433320.90241.60 (Legua and Seas 2013)
2. https://dx.doi.org/10.1128/CMR.00026-09 (Ortega and Sanchez 2010)
3. https://dx.doi.org/10.1016/0140-6736(93)91330-O (Madico et al. 1993)
4. https://dx.doi.org/10.1093/clinids/24.5.977 (Madico et al. 1997)
5. https://dx.doi.org/10.7326/0003-4819-132-11-200006060-00006 (Verdier et al. 2000)
6. https://dx.doi.org/10.1086/510744 (Zimmer 2007)

Immunocompetent patient

First-line treatment

Trimethoprim/Sulfamethoxazole (TMP/SMX)

- Adults 160/800 mg po bid x 7 - 10 days (cure rate 95%).
- Children 5/25 mg/kg po bid x 3 - 10 days (cure rate 100%).

NB: in case of incomplete clinical response, administer TMP/SMX one additional week.

Alternative regimens

- Ciprofloxacin 500 mg bid x 7 days (cure rate: 90%).
- Nitazoxanide (Alinia®) 500-1000 mg bid x 7 days; Children 1-3 years 100 mg bid; 4-11 years 200 mg bid; > 12 years 500 mg bid; not available in Belgium and very expensive.

Immunocompromised patient

First-line treatment

Trimethoprim/Sulfamethoxazole (TMP/SMX)

- Adults 160/800 mg po bid for 3 - 4 weeks.
- Children 5/25 mg/kg po bid for 3 - 4 weeks.

Followed by secondary prophylaxis/maintenance therapy (800/160 mg 3x weekly) as long as immunocompromised status persists.

Alternative regimens

- Ciprofloxacin 500 mg 2 x po bid x 7 days (less effective than TMP/SMX), followed by secondary prophylaxis/maintenance therapy (500 mg 3x weekly).
- Nitazoxanide (Alinia®) 500-1000 mg bid x 7 days; Children 1 - 3 years 100 mg bid; 4-11 years 200 mg bid; > 12 years 500 mg bid; not available in Belgium and very expensive.

9 Cystoisosporiasis (Cystoisospora belli, formely Isospora belli)

Infection that generally spontaneously resolves in two to three weeks in immunocompetent patients. The length of the treatment has not been well defined.

Selected References

1. https://dx.doi.org/10.1097/01.qco.0000433320.90241.60 (Legua and Seas 2013)
2. http://www.ncbi.nlm.nih.gov/pubmed/8993857 (Lindsay, Dubey, and Blagburn 1997)
3. https://dx.doi.org/10.7326/0003-4819-132-11-200006060-00006 (Verdier et al. 2000)
4. https://dx.doi.org/10.1093/infdis/158.3.646 (Musey et al. 1988)
5. https://dx.doi.org/10.1056/NEJM198607103150203 (DeHovitz et al. 1986)
6. https://dx.doi.org/10.7326/0003-4819-109-6-474 (Weiss et al. 1988)
7. https://dx.doi.org/10.1056/NEJM198904203201604 (Pape, Verdier, and Johnson 1989)
8. https://dx.doi.org/10.1371/journal.pone.0042844 (Boyles et al. 2012)
9. https://dx.doi.org/10.1586/14787210.2.1.43 (White Jr 2004)

Immunocompetent patient

First-line treatment

Trimethoprim/Sulfamethoxazole (TMP/SMX)

- Adults 160/800 mg po bid x 7 - 10 days.
- Children 5/25 mg/kg po bid x 7 - 10 days.

Alternative regimens

Ciprofloxacin 500 mg bid x 7 days.

Immunocompromised patient

First-line treatment

Trimethoprim/Sulfamethoxazole (TMP/SMX)

- Adults 160/800 mg tid or po qid x 3-4 weeks.
- Children 5/25 mg/kg tid or po qid x 2-4 weeks.

Followed by a secondary prophylaxis/maintenance therapy (800/160 mg 3x weekly).

Alternative regimens

- Ciprofloxacin 500 mg 2 x po bid x 7 days, followed by secondary prophylaxis/maintenance therapy (500 mg 3x weekly).
- Pyrimethamine 50 - 75 mg/d po + folinic acid 10 - 25 mg/d po, followed by secondary prophylaxis/maintenance therapy pyrimethamine 25 mg/week, with or without sulfadoxine or sulfadiazine.
- In case of malabsorption or lack of response after 10 days, give iv instead of oral treatment.
- In some cases, infection and symptoms may persist despite treatment, secondary prophylaxis and immune recovery.
- Nitazoxanide has some activity 500 mg BID po for 3 days: but drug not available in Belgium, and extremely expensive.

10 Dientamoebiasis (Dientamoeba fragilis)

There is a persistent debate on the need to treat this infection or not. Rate of symptomatic infection is estimated at 15-30%. In addition, spontaneous clearance is observed in 40% of infection. Few studies on efficacy have a placebo arm: metronidazole vs placebo in children showed no difference in symptom resolution, even with 62% initial parasite clearance rate (Röser et al. 2014). However, treatment can be necessary in case of symptoms and in the absence of other pathogens.

Selected References

1. https://dx.doi.org/10.1128/JCM.00400-16 (L. S. Garcia 2016)
2. https://dx.doi.org/10.1016/j.ijpddr.2012.08.002 (Nagata et al. 2012)
3. https://dx.doi.org/10.1128/CMR.17.3.553-570.2004 (Johnson, Windsor, and Clark 2004)
4. https://dx.doi.org/10.1016/j.ijpddr.2012.03.002 (Van Hellemond et al. 2012)
5. https://dx.doi.org/10.1097/01.inf.0000247139.89191.91 (Vandenberg et al. 2007)
6. https://dx.doi.org/10.1111/j.1469-0691.2008.02002.x (Kurt et al. 2008)
7. https://dx.doi.org/10.1046/j.1469-0691.2003.00504.x (Girginkardeşler et al. 2003)
8. https://dx.doi.org/10.1093/cid/ciu188 (Röser et al. 2014)
9. https://dx.doi.org/10.1016/j.ijid.2016.05.027 (Boga et al. 2016)
10. https://doi.org/10.1128/CMR.00076-15 (Stark et al. 2016)

First-line treatment

Paromomycin (Gabbroral®)

- Adults 500 mg po tid x 7 days (cure rate: 98%).
- Children 10 mg/kg po tid x 7 days (cure rate: 100%).

Ornidazole/tinidazole (Tiberal®/Fasigyn®)

- Adults 2 g po single dose (cure rate: 93%).
- Children 30 mg/kg po single dose (idem).

NB: similar results with secnidazole (not available in Belgium).

Alternative regimens

- Metronidazole: 500 mg (or 10-15 mg/kg) po tid x 10 days.
- Doxycycline 100 mg po bid x 10 days; recommended by CDC (but on weak evidence: 3 case reports).
- Iodoquinol 650 mg po tid for 10-20 days; recommended by CDC, on weak evidence (less than 50 patients); not available in Belgium.

Special situations

In case of eosinophilia and/or in case of recurrent symptoms/infection, investigate for co-infection with *E. vermicularis* (or other helminths). Some studies have suggested *E. vermicularis* eggs to be a vector of *D. fragilis*, and a study suggested treatment failure with metronidazole in case of *E. vermicularis* co-infection: a serious limitation of this study is that it only considered parasitological cure and not clinical symptoms (Boga et al. 2016).'

11 Giardiasis (Giardia duodenalis)

Selected References

1. https://dx.doi.org/10.1016/j.actatropica.2016.06.026 (Escobedo, Lalle, et al. 2016)
2. https://dx.doi.org/10.1002/14651858.CD007787.pub2 (Granados et al. 2012)
3. https://dx.doi.org/10.1016/j.actatropica.2015.09.023 (Escobedo, Ballesteros, et al. 2016)
4. https://dx.doi.org/10.3201/eid2010.140073 (Meltzer, Lachish, and Schwartz 2014)
5. https://dx.doi.org/10.1007/s11908-014-0396-y (Watkins and Eckmann 2014)
6. https://dx.doi.org/10.1097/QCO.0b013e32834ad401 (Tejman-Yarden and Eckmann 2011)
7. https://dx.doi.org/10.1016/j.tmaid.2012.10.004 (Muñoz Gutiérrez et al. 2013)
8. https://dx.doi.org/10.1016/j.cmi.2015.04.019 (Nabarro et al. 2015)

First-line treatment

Tinidazole (Fasigyn®); not available anymore in Belgium

- Adults 2 gr (= 4 tablets of 500 mg) po od single dose.
- Children 50 mg/kg po od single dose.

Ornidazole (Tiberal®)

- Adults: 1,5 - 2 gr po od x 1 day (or 500 mg po bid x 5 days).
- Children: 40 mg/kg po od x 1 day (or 15 mg/kg po od x 5 days).

NB: Both regimens have > 90% cure rate (although decreasing). Some experts recommend 2 days instead of 1 single day.

Alternative regimens

Metronidazole (Flagyl®):

- Adults: 500 mg po tid x 7 days.
- Children: 5 mg/kg po tid x 7 days.

NB: lower efficacy than first-line treatment, due to more side effects.

Albendazole:

- Adults: 400 mg daily po bid x 5 - 7 days.
- Children: 5 - 7,5 mg/kg po bid for 5 - 7 days

NB: similar efficacy as metronidazole, with fewer adverse events; lower efficacy than tinidazole.

Special situations

Giardiasis refractory to nitroimidazoles:

In refractory cases consider the following general actions on top of re-treatment:

- Treatment of household contacts, regardless of symptoms.
- Test for IgA deficiency, hypogammaglobulinemia or HIV.
- Consider a lactose-free diet to exclude Giardia-induced lactose intolerance.

Consider one of the following treatment options.

- Quinacrine (mepacrine):

Small studies suggested about 100% efficacy, including the recent TropNet study.(Neumayr et al., 2021a) A systematic review concludes that quinacrine appeared highly effective but more data on safety are needed (Bourque et al. 2021).

  - Adults: 100 mg po tid x 5 days.
  - Children 2 mg/kg po tid x 5 days.

NB: Beforehand, it is better to exclude a G6PD deficiency; caution with the risk of psychiatric adverse events.

- Albendazole + nitroimidazole (dosage as here above): Cure rate of about 80% in refractory cases.

- Albendazole (as above) + chloroquine 250 mg po bid x 5 days, also appears as inferior to quinacrine in the abovementioned TropNet study, but used as first-line treatment for refractory cases in European countries where quinacrine is not available; but chloroquine not available in Belgium since 2016.
  NB: Other less efficient possibilities (tested in very few cases refractory to nitroimidazoles).
- Paromycine (Gabboral®) 10 mg/kg po tid x 7 days (cure rate of 30% in refractory cases).
- Nitazoxanide (Alinia®) 500 mg po bid x 3 days (or 3-4 mg/kg bid in children) combined with a second agent; not available in Belgium and extremely expensive.

Availability and costs
Quinacrine: see additional and updated information via contact with ITM.
Albendazole: see additional and updated information via contact with ITM.

12 Leishmaniasis

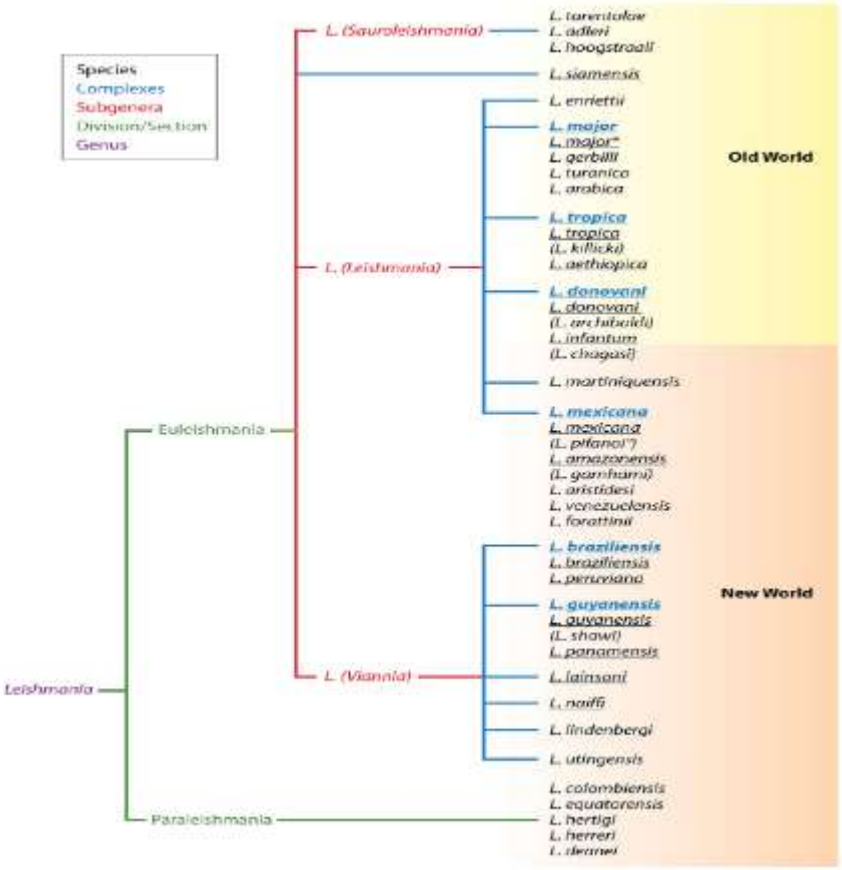
Preliminary comments

Evidence about leishmaniasis treatment (especially cutaneous leishmaniasis) is often limited or context dependent. Therefore, guidelines of national expert bodies are often not consistent between each other. The recommendations developed here are somehow arbitrary and represent a compromise between (weak) evidence and other factors like drug availability, experience,…

The current trend (although not yet fully endorsed by all expert groups, such as IDSA) is to try obtaining a species diagnosis by PCR (available at ITM CLKB) since it allows refining the management. The recommendations here below are therefore PCR-guided.

Unfortunately, the *Leishmania* taxonomy is complex (and still evolving). In addition, epidemiology also appears increasingly complex, with many species clinically and geographically overlapping. The situation is even "worse" for immunocompromised individuals. This makes the classic approach based on clinical features and epidemiology somehow obsolete (although still helpful if molecular assays are not available/feasible). The recommendations also consider this reality.

12.1 Current Leishmania taxonomy



Source figure: Van Der Auwera G & Dujardin JC. Species Typing in Dermal Leishmaniasis. *Clin Microbiol Rev.* 2014

12.2 Cutaneous leishmaniasis (CL)

Selected References

1. https://dx.doi.org/10.1128/CMR.00104-14 (Van der Auwera and Dujardin 2015)
2. https://dx.doi.org/10.1517/14656566.2015.973850 (Sundar and Chakravarty 2015)

3. https://dx.doi.org/10.1111/1469-0691.12556 (J. Van Griensven et al. 2014)
4. https://dx.doi.org/10.1371/journal.pntd.0004495 (Johan van Griensven et al. 2016)
5. WHO, "control of the leishmaniases," World Health Organization, pp. 1-202, 2010 http://apps.who.int/iris/bitstream/handle/10665/44412/WHO_TRS_949_eng.pdf;jsessionid=3F3F3607683DEEB3EA6FD0DE76713B42?sequence=1 (WHO 2010)
6. https://dx.doi.org/10.1016/j.lpm.2010.09.023 (Buffet et al. 2011)
7. https://dx.doi.org/10.1111/jtm.12089 (Blum et al. 2014)
8. https://dx.doi.org/10.1371/journal.pntd.0002832 (Hodiamont et al. 2014)
9. https://dx.doi.org/10.1093/cid/ciw742 (Aronson et al. 2016)
10. https://dx.doi.org/10.1056/NEJMoa011882 (Alrajhi et al. 2002)
11. https://dx.doi.org/10.1086/517634 (Wortmann et al. 1998)
12. https://doi.org/10.1016/j.tmaid.2020.101885 (Vandeputte et al. 2020)
13. https://doi.org/10.1371/journal.pntd.0009863 (Guery et al. 2021)

In the Old World (Africa/Europe/Asia), mainly due to *L. tropica* and *L. major,* and to a lesser extent to *L. infantum* and *L. aethiopica.*

In the new World, mainly due to:

- *L. mexicana* complex (*L. mexicana/L. amazonensis/L. venezuelensis*).
- *L. (Viannia) braziliensis* complex [*L. (V). braziliensis* and *L. (V.) peruviana*].
- *L. (V.) guyanensis* complex [*L. (V.) guyanensis* and *L. (V.) panamensis*].

Preliminary note

The decision for the type of treatment of CL should mainly rely on (1) the *Leishmania* species, (2) the clinical aspects of the lesions, (3) the host immunity and drug availability/local experience. A new classification of CL is emerging in the international literature, with the distinction between "simple CL" and "complex CL". Here under an example reproduced from the IDSA guidelines 2016. In general, for simple CL, observation/simple wound care or local treatment are sufficient, while systemic therapy should be considered for complex CL. Of note there are still slight differences between guidelines about some criteria (especially regarding the size and number of lesions) but treatment decisions should be based on common sense.
Species diagnosis is progressively used to refine the therapeutic decisions, reason why the current recommendations are classified according to the etiological species, and therefore mainly based on the LEISHMAN group guideline.

Treatment failure is defined by the absence of complete re-epithelialization after 3 months. Relapse is defined by reappearance of lesion/ulcer after complete healing, or renewed increase of nodular lesions.

Simple CL	Complex CL
Caused by a *Leishmania* species unlikely to be associated with mucosal leishmaniasis	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[a,b,c]
No mucosal involvement noted	Local subcutaneous nodules[d]
Absence of characteristics of complex CL	Large regional adenopathy[d]
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

Recommendations by etiological species
Source figure: Aronson N *et al*. 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). *Clin Infect Dis.* 2016

12.2.1 Leishmania major

Spontaneous cure rate is 40-90% at 3 months and close to 100% at 12 months.

Simple CL
Consider observation/simple wound care if few, small and non-disturbing lesions.
Local treatment.

First-line treatment

- Intralesional infiltrations of antimonials (2-3 ml Glucantime® 1-3x/week up to 4-6 administrations) AND/OR cryotherapy (2 cycles of 10-30 seconds): cure rate of 70-90% for any method (slightly higher if both methods are combined).

Alternative regimens

- Local heat therapy (50°C for 30 seconds): Thermomed® (expensive device, not readily available).
- 15% paromomycin/12% methylbenzethonium chloride ointment BID for 10-20 days: not available in Belgium; Leishcutan® (Teva) 350 euros on internet

NB: evidence grade A for all regimens; similar efficacy

Complex CL

- Meglumine antimoniate 20 mg SbV/kg od slow iv x 10(-14) days (cure rate: 50-85%; grade D).
- Miltefosine 50 mg po tid x 28 days (cure rate: 85-100%; grade B).
- L-AmB total dose 20 mg/kg; 3 mg/kg Days 1 - 5 and 10 (only some case reports; grade D); experts increasingly recommend a 4- or 5-day regimen (not interrupted) for ease of use.

NB: fluconazole 200 mg po bid x 6 weeks: cure rate of 80% in one small RCT in Saudi Arabia; similar efficacy never reproduced elsewhere). For sure not a first choice.
There is no clear first-line regimen, except that antimoniates have been more used and are readily available.

12.2.2 Leishmania tropica/L. infantum/L. aethiopica

Spontaneous cure rate is 10% at 3 months and up to 65% at 12 months.

Simple CL
Since healing is much slower, observation/simple wound care is usually not an option

First-line treatment
- Intralesional infiltrations of antimonials (2-5 ml Glucantime® 1-3x/week up to 4-6 administrations) AND/OR cryotherapy: cure rate of 80% (slightly higher if both methods are combined).

Alternative regimens
- Local heat therapy (50°C for 30 seconds): expensive device, not readily available.
- (15% paromomycin/12% methylbenzethonium chloride ointment bid for 10-20 days: not available in Belgium; Leishcutan® (Teva) 350 euros on internet).

NB: evidence grade A for only local antimonials, cryotherapy and local heat therapy; only case reports for the ointment.

Complex CL
- Meglumine antimoniate 20 mg SbV/kg slow iv od x 10(-14) days (cure rate: 60%; grade C).
- Miltefosine 50 mg po tid x 28 days (cure rate: 100%; grade D).
- L-AmB total dose 20 mg/kg; 3 mg/kg days 1 - 5 and 10 (cure rate: 85% grade C); same remark as for *L. major* regarding "new" administration schedules.

There is no clear first-line regimen, except that antimoniates have been more used and are more readily available.

12.2.3 Leishmania mexicana complex

Spontaneous cure rate is high (although not well documented; very scarce study data).

Simple CL
Consider observation/simple wound care if few, small and non-disturbing lesions.

First-line treatment
Intralesional infiltrations of antimonials (2-5 ml Glucantime® 1-3x/week up to 4-6 administrations) AND/OR cryotherapy: cure rate?

Alternative regimens
(No study data, although local heat therapy is increasingly used locally).
NB: very low evidence for any type of treatment.

Complex CL

First-line treatment
- Meglumine antimoniate 20 mg SbV/kg slow iv od x 20 days (cure rate: 70%; grade D).

- Miltefosine 50 mg po tid for 28 days (cure rate: 60%; grade B).

NB: there is no data on the use of L-AmB in the treatment of complex CL due to *L. mexicana;* ketoconazole 600 mg/day po for 28 days has produced cure rates of 90% (higher than antimonials), but is not available in Belgium

12.2.4 Leishmania (Viannia) braziliensis complex

Here, there is a 5 - 10% risk of delayed metastatic mucosal localizations. Treatment should therefore be more aggressive; observation is not an option, and local treatment should be an exception (only a few small lesions, with the necessity of long-term clinical follow-up).

Simple CL

Local treatment (no option for observation only; close long-term follow-up necessary).

First-line treatment
- Intralesional infiltrations of antimonials (2 - 5 ml Glucantime® 1 - 3x/week up to 4 - 6 administrations) AND/OR cryotherapy (cure rate: 80%; grade B).

Alternative regimens
- 15% paromomycin/12% methylbenzethonium chloride ointment BID for 10 - 20 days (cure rate: 90%; grade B - but not available in Belgium, see above).

NB: evidence grade A or B for all treatments; cure rate with local heat therapy is low (50%; grade D).

Complex CL

First-line treatment
Meglumine antimoniate 20 mg SbV/kg slow iv od x 20 days (cure rate: 95%; grade A).

Alternative regimens
- L-AmB total dose 20 mg/kg; 3 mg/kg Days 1 - 5 and 10 (cure rate: 85% grade B); see previous comments on simplification of administration schedule.
- Miltefosine 50 mg po tid x 28 days (efficacy about 75%, but inconsistent across the countries, much lower in Peru; grade C).

12.2.5 Leishmania (Viannia) guyanensis complex

There is no data on spontaneous cure rate, but it seems unusual. Exceptionally, *L. (V.) guyanensis* can cause mucosal leishmaniasis, so a good follow-up is necessary.

Simple CL

First-line treatment
15% paromomycin/12% methylbenzethonium chloride ointment bid for 10-20 days: cure rate 90%; grade B, but not available in Belgium (see above).

Alternative regimens

Local heat therapy (50°C for 30 seconds): rather low cure rate: 60% (grade A), but still might be an (expensive) alternative.

NB: no data on the use of intralesional antimonials.

Complex CL

First-line treatment
Pentamidine isethionate 7 mg/kg iv/(i.m) od at D1, D3 and D5 (cure rate: 90%; grade A). An RCT in Brazil suggests that the highest cure rate (>90%) is obtained when 3 doses are administered at one-week intervals (Gadelha et al. 2018).
NB1: The 4 mg/kg dosage which was previously reported was based on another pentamidine formulation atht is not available anymore.
NB2: for limited CL, a single injection of 7 mg/kg might be a good "field" alternative.

Alternative regimens
- Meglumine antimoniate (20 mg SbV/kg slow iv od x 10(-14) days (cure rate: 80%; grade A).
- Miltefosine 50 mg po tid x 28 days (cure rate: 75%; grade A).

Special situations
- CL in immunocompromised patients:
- Look carefully for dissemination/visceralization; in such cases, treatment like VL for immunocompromised patients (see below).

Pregnancy:
- Prefer simple wound care or physical methods (cryotherapy, local heat therapy…); if a systemic treatment is needed, L-AmB has the best benefit/risk ratio.

Diffuse cutaneous leishmaniasis:
- Exclusively due to *L. aethiopica* in the Old World, and sometimes to *L. mexicana* complex in the New World.
- Treatment poorly defined; L-AmB or antimonials as first choices.

CL refractory to L-AmB:
There are few reports of treatment failure with L-AmB; treat such cases with systemic antimonials even if more adverse events; there is some growing evidence of effectiveness of miltefosine for (complex) CL due to different species among travelers (mainly New World species), but the price remains prohibitive at this moment (in Europe) (C. Y. T. Wang et al. 2020).

Availability and costs
Obtaining adequate drugs for complex CL and VL in Belgium is an unsolved issue.

Liposomal anphotericin B (AmBisome®/Gilead; vial of 50 mg or Abelcept®/Teva; vial of 100 mg).
- Total cost for 20 mg/kg: 2000 - 3000 euros + day-clinic/hospital costs.
- Not reimbursed so far in Belgium for this indication.
- Obtained in compassionate use from Gilead after contact with representative.

Miltefosine (Impavido®)
- Not available in Belgium (and not reimbursed).
- About 15000 USD on internet (generic soon?).

Meglumine antimoniate (Glucantime® vial of 5 ml; 85 mg SbV/ml; 7,5 euros).
- Total cost: 500 euros (2 vials/day x 30 days) + day-clinic/hospital costs.

NB1: Sodium stibogluconate (Pentostam® vial of 30 ml; 100 mg SbV/ml) is not available in Belgium.
NB2: Amphotericin B deoxycholate (0,7-1 mg/kg od slow iv for 15-20 doses) is not available anymore in Belgium (cheaper but much more toxic than L-AmB).

12.3 Mucosal leishmaniasis (ML)

Mainly due to *L. (V.) braziliensis* complex and sporadically to *L.(V.) guyanensis* complex (mostly *L. (V.) panamensis*). Exceptionally, *L. infantum* has been incriminated.
Risk of mucosal metastasis estimated at 5% in the long-term.

First-line treatment

- Meglumine antimoniate 20 mg/kg SbV slow iv od+ pentoxifylline (Torental®) 400 mg po tid for 30 days: cure rate: 90%; grade A in American ML (not studied in Old World ML).

NB: Rather high rate of recurrences (25%). If meglumine antimoniate "alone", cure rate: 75%.

Alternative regimens

- Liposomal amphotericin B: total dose 40 mk/kg (dosage like VL in immunocompromised): cure rate: 85%; grade C).
- Miltefosine 50 mg po tid x 28 days (cure rate: 60-80%; grade B).

Availability and costs
Obtaining adequate drugs for complex CL, MCL and VL in Belgium is an unsolved issue.

Liposomal anphotericin B (AmBisome®/Gilead; vial of 50 mg; 102 euros/vial or Abelcept®/Teva; vial of 100 mg; 115 euros/vial).

- Total cost for 20 mg/kg: 2000-3000 euros + day-clinic/hospital costs.
- Not reimbursed so far in Belgium for this indication.
- Obtained (easily) in compassionate use from Gilead after contact with representative.

Miltefosine (Impavido®)

- Not available in Belgium (and not reimbursed).
- About 15000 USD on internet (generic soon?).

Meglumine antimoniate (Glucantime® vial of 5 ml; 85 mg SbV/ml; 7,5 euros)

- Total cost: 500 euros (2 vials/day x 30 days) + day-clinic/hospital costs.

NB: Sodium stibogluconate (Pentostam® vial of 30 ml; 100 mg SbV/ml) is not available in Belgium.
NB: Amphotericin B deoxycholate (0,7-1 mg/kg slow iv od x 15-20 doses) is not available anymore in Belgium (cheaper but much more toxic than L-AmB).

12.4 Visceral leishmaniasis (VL)

Almost exclusively due to
- *L. donovani* (anthroponotic; Indian subcontinent and East Africa)
- *L. infantum/chagasi* (zoonotic; Middle East, Mediterranean Basin and Latin America)

NB: in severely immunocompromised individuals, any *Leishmania* species may cause VL, often with atypical presentations

Selected References

1. https://dx.doi.org/10.1007/s40265-013-0133-0 (Monge-Maillo and López-Vélez 2013)
2. https://dx.doi.org/10.1517/14656566.2015.973850 (Sundar and Chakravarty 2015)
3. WHO, "control of the leishmaniases," World Health Organization, pp. 1-202, 2010 http://apps.who.int/iris/bitstream/handle/10665/44412/WHO_TRS_949_eng.pdf;jsessionid=3F3F3607683DEEB3EA6FD0DE76713B42?sequence=1(WHO 2010)
4. https://dx.doi.org/10.1016/j.lpm.2010.09.023 (Buffet et al. 2011)
5. https://dx.doi.org/10.1371/journal.pntd.0002832 (Hodiamont et al. 2014)
6. https://dx.doi.org/10.1093/cid/ciw742 (Aronson et al. 2016)
7. https://dx.doi.org/10.1086/367843 (Syriopoulou et al. 2003)
8. https://dx.doi.org/10.1111/tmi.12603 (Atia et al. 2015)
9. https://journals.lww.com/co-infectiousdiseases/Abstract/1998/12000/Chemotherapy_of_leishmaniasis__recent_advances_in.9.aspx (Berman 1998)
10. https://dx.doi.org/10.1086/425359 (Sindermann et al. 2004)
11. https://dx.doi.org/10.1371/journal.pntd.0004304 (Morizot et al. 2016)
12. https://dx.doi.org/10.1371/journal.pntd.0004087 (Diro et al. 2015)

12.4.1 Immunocompetent individuals

First-line treatment

Liposomal amphotericin B (L-AmB): total dose 18 - 21 mg/kg.
- In most guidelines: 3 mg/kg iv od on days 1-5 and on days 14 and 21.
- Hodiamont CJ et al. suggest 20 mg/kg iv od divided in 2-7 days, PREFERENTIALLY 10 mg/kg OD iv for 2 days (to strongly consider when hospital cost is an issue).

NB:
- For children infected with *L. infantum* in the Mediterranean region, this short regimen is the first choice (cure rate of 98%).
- For infection with *L. donovani* acquired in the Indian subcontinent, L-AmB 10 mg/kg iv single dose is sufficient (cure rate > 95%): some other combinations are also effective in India (e.g., single-dose L-AmB 5 mg/kg + 7 days miltefosine or 11 mg/kg paromomycin + miltefosine for 10 days) (Goyal et al. 2018).
- Some experts and WHO recommend a total dose of L-AmB of 30 mg/kg in East-Africa because response rate is lower (85%) with standard regimen (but it is likely that HIV infection was not diagnosed in historical studies).

Alternative regimens

For VL acquired in the Indian subcontinent:

Miltefosine
- Adults 50 mg tid (max 150 mg/day) x 28 days.
- Children: 2,5 mg/kg/d for 28 days.

NB1:

- TERATOGENIC (need of pregnancy testing and drastic contraception).
- Well studied in the Indian subcontinent where it is the preferred alternative regimen, but much less in other settings.
- Case reports of treatment failure (in monotherapy) and even resistance in the Indian subcontinent.

- For VL acquired elsewhere.
- Meglumine antimoniate (Glucantime): 20 mg Sb/kg iv od (or im) x 28 days.

NB2: High rates of (cumulative) toxicity (>30% in meta-analysis), since the second week of treatment (bone marrow, kidney, liver, pancreas, and frequent ECG abnormalities, such as QT prolongation, negative T...); need to fully monitor at least once a week or in case of suggestive symptoms, and even more frequently in elderly).
Not recommended for VL acquired in the Indian subcontinent (high rates of resistance) and in HIV-infected individuals (unacceptable rates of toxicity).
In VL acquired in East Africa, the first-line **field** treatment recommended by WHO is the combination of meglumine antimoniate (20 mg Sb/kg iv/im od) combined with injectable paromomycin (15 mg/kg im od) x 17 days.

Cure rates with miltefosine monotherapy is < 80% in East-Africa and not really studied in other "non-Indian" settings.

12.4.2 Immunocompromised individuals

First-line treatment

- Liposomal Amphotericin B: total 40 mg/kg.
- In most guidelines: L-AmB 4 mg/kg iv od at Days 1-5, 10,17,24,31,38 (based on experience with VL-HIV in Southern Europe).

Alternative regimens (expert opinion only)

- Miltefosine (same dosage as here above) for 6 weeks (but efficacy seems rather unsatisfactory).
- Meglumine antimoniate (same dosage as above) for more than 4 weeks, sometimes to repeat (but high rates of toxicity, especially in HIV patients).
- Several combination treatments have been proposed, with little evidence; expert advice is necessary for case-by-case decisions.

Special situations

- VL (*L. infantum*) unresponsive/refractory to L-AmB has been reported (mainly in immunocompromised patients).
- In such cases, clinical cure was obtained with antimonials.
- Maintenance therapy/secondary prophylaxis in immunocompromised individuals.
- There is no established regimen (dosage, frequency and duration).
- To consider for all patients with sustained immunodeficiency and after relapse.

Suggested regimens

- L-AmB 3-5 mg/kg iv od every 3 weeks (based on experience for *L. infantum* in HIV patients of Southern Europe).
- Meglumine antimoniate (850 mg Sb) slow iv every 4 weeks (idem).
- Pentamidine 4 mg/kg iv od every 2-4 weeks (currently investigated in Ethiopia).

Pregnancy:

- L-AmB is likely the safest treatment during pregnancy (according to a systematic review) (Singh-Phulgenda et al. 2021).

- Post-Kala Azar Dermal Leishmaniasis (PKDL): difficult treatment, requiring expert advice.

Current recommendations:

- Indian subcontinent: Well studied: miltefosine (same dose as above) but for 3 months.

- Elsewhere poorly investigated: WHO recommends L-AmB 2.5 mg/kg iv odfor 20 consecutive days or meglumine antimoniate (same dosage as above) for 30-60 days.
  A field prospective study by MSF suggests that a short course L-AmB 15 mg/kg in total, divided in 5 bi-weekly administrations (of 3 mg/kg each), is sufficiently effective (90%) (Den Boer et al. 2018).

Availability and costs

Obtaining adequate drugs for VL in Belgium is an unsolved issue.

Liposomal amphotericin B (AmBisome®/Gilead; vial of 50 mg or Abelcept®/Teva; vial of 100 mg).

- Total cost for 20 mg/kg: 2000 - 3000 euros + day-clinic/hospital costs.
- Not reimbursed so far in Belgium for this indication.
- Obtained in compassionate use from Gilead after contact with representative at

Miltefosine (Impavido®)

- Not available in Belgium (and not reimbursed)
- About 15000 USD on internet (generic soon?)

Meglumine antimoniate (Glucantime® vial of 5 ml; 85 mg SbV/ml; 7,5 euros)

- Total cost: 500 euros (2 vials/day x 30 days) + day-clinic/hospital costs

NB1: Sodium stibogluconate (Pentostam® vial of 30 ml; 100 mg SbV/ml) is not available in Belgium.
NB2: Amphotericin B deoxycholate (0,7-1 mg/kg OD slow iv for 15-20 doses) is not available any more in Belgium (cheaper but much more toxic than L-AmB).

13 Malaria (Severe, Uncomplicated)

13.1 Severe (or complicated) malaria

Almost always due to *Plasmodium falciparum*; sometimes to *P. knowlesi*; rarely to *P. vivax.*

Note that some groups of nonimmune travelers are at highest risk of severe malaria and requires narrow monitoring: elderly, children < 5 years, pregnant women, serious comorbidity (diabetes, cardiopathy,…) immunosuppression,…

Selected References

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2. WHO, "Management of severe malaria – A practical handbook," World Health Organization, pp. 1-83, 2012. http://apps.who.int/iris/bitstream/handle/10665/79317/9789241548526_eng.pdf?sequence=1
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4. https://dx.doi.org/10.1111/j.1365-3156.1996.tb00033.x (Sukontason et al. 2007)
5. https://dx.doi.org/10.1086/421782 (F. Jacobs et al. 2004)
6. https://doi.org/10.1016/j.medmal.2018.08.003 (Bruneel et al. 2020)

Whenever malaria is suspected or confirmed, and whatever the species, it is necessary to immediately evaluate whether clinical or laboratory criteria of complications are present, because severe (or complicated) malaria requires an immediate specific treatment.

Malaria should be considered as severe if any of the following WHO criteria 2000 is present:

- Parasitemia > 5% (and/or schizontemia); in Belgium like in other nonendemic setting, 2% is usually preferred as cutoff.
- Any major organ dysfunction:
  - Brain: prostration, impaired consciousness, convulsions, coma,…
  - Liver: clinical icterus, bilirubinemia > 3 mg/dl; bleeding signs,
  - Lung: dyspnea, ARDS,…
  - Kidney: oligo-anuria; creatinine > 3 mg,
  - Shock: hypotension not responsive to fluid challenge.
- Severe anemia (hemoglobin level < 7 g/dl in adults)
- Blackwater fever/hemoglobinuria
- Metabolic acidosis (pH < 7.25; bicarbonate < 15 mmol/L)
- Hyperlactatemia (> 5 mmol/L)
- Hypoglycemia (< 40 mg%)

First-line treatment

Artesunate (Malacef®) 2.4 mg/kg iv at diagnosis (T0), at 12h, 24h and then once daily.

- Children < 20 kg administer 3 mg/kg following the same schedule.
- Administration for at least 24-48h and until oral therapy is possible.
- Switch to oral therapy (see treatment uncomplicated malaria), for a full 3-day course of an artemisinin-based combination therapy (ACT, whatever the number of days of artesunate administration.
- If switching to oral therapy is not possible, administer artesunate for 7 days and add doxycycline 100 mg iv bid or clindamycin 5 mg/kg iv tid x 7 days.

NB:

- No need for dose adaptation in case of kidney or liver failure.
- No contra-indication to administer to pregnant women at any trimester (WHO 2023); oral switch to artemether-lumefantrine is authorized now even in first trimester (WHO 2023).

- Supportive care for organ failure according to ICU guidelines; no adjunctive therapy has been found useful so far.
- As (partial) resistance of *P. falciparum* against artemisinin is present in South-East Asia and has emerged in East Africa, it is key to systematically control after 3 (to 5) days whether the blood smear has become negative at that moment; a slow parasite decline/clearance (**early treatment failure**) could reflect some decreased susceptibility.
- There is a risk (25%) of delayed hemolysis (day 7-21) mainly in case of hyperparasitemia; need of monitoring after hospital discharge (consultation to plan after one-two weeks maximum, for early detection before anemia could become symptomatic). The optimal management of this post-artesunate delayed hemolysis is still unclear (steroids? blood transfusion if severe,…); please contact the ITM experts for updated guidance.
- All patients treated for severe (or uncomplicated) malaria should be informed to have a new blood smear (and possibly additional investigations) in case fever recurs within 4 weeks after treatment, as **late treatment failure** can reflect reduced susceptibility to artemisinin and/or the partner drug of the ACT. Please contact also the ITM experts, as genomic analysis could be considered at ITM for surveillance purpose (no immediate impact on clinical care).

Major comment**:** Artesunate is expensive (60 euro per vial/about 3 vials per administration for an adult); the drug is reimbursed since 2013 by the RIZIV/INAMI provided that:

- The decision for administration is taken together with an ITM physician (or an infectious diseases specialist/travel physician affiliated to a University Hospital).
- Any of the following criteria is fulfilled:
  - Any sign of cerebral malaria.
  - At least 3 criteria of severity (see above) including at least dysfunction of one major organ.
  - Need of intravenous treatment (vomiting…), and major contra-indication to quinine.
- The treating physician mentions in the file that he has asked for specialized advice prior to administration and engages himself to fill a CRF about indication of, and evolution with, artesunate to be sent to ITM (Emmanuel Bottieau, ebottieau@itg.be). NB: documents and CRF available on the ITM website under information for physicians

Important information: Up to 2019, this procedure was requested to obtain the reimbursement. A 6-year evaluation performed by Dr Jan Clerinx has shown that indications were well respected overall in Belgium. The RIZIV/INAMI is less strict now with the criteria and the whole procedure (as far as an ID specialist has been involved), but the new requirements have not been fully formalized yet. To be followed-up, as it should change rather soon.

Alternative regimens

- Quinine (ONLY if artesunate is not immediately available).
- Always loading dose 20 mg/kg (max 1000 mg in adults) slow iv (over 4-6h in 500 ml Glucose 5%), followed by 10 mg/kg (max 500-600 mg in adults) tid until switch to artesunate iv.

NB:

- Monitoring of glycemia.
- ECG prior to administration is preferable.
- Not contra-indicated during pregnancy.

Current indications of quinine are rather limited nowadays, and artesunate could be conisdered instead, (as the criteria for reimbursement are becoming less strict):

- Severe malaria not fulfilling the CURRENT criteria for artesunate reimbursement.
- Uncomplicated malaria with no oral therapy possible (repeated vomiting, see below).

Specific precautions with quinine:

- In case of renal failure:
- The dose of quinine for the first 48 hours remains the same but it must be reduced two to three times (only one administration of quinine per 24 hours).
- In case of renal dialysis:
- The dose of quinine must be reduced and administered after dialysis *(QT interval to monitor)*.
- In case of "continuous veno-venous hemodiafiltration":
- It is not necessary to adapt the dose and quinine 500 mg TID iv may be further administered.
- In case of liver failure (jaundice):
- From the second perfusion, the dose must be reduced by 50%.

Final comments

Exchange transfusion/erythrocytapheresis: nowadays, no indication any more due to the powerful effect of artesunate.

In case resistance to artemisinin is suspected, urgent contact with the ITM experts, as there is no clear evidence-based management yet (case-by-case approach).

13.2 Uncomplicated malaria

Selected References

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2. https://dx.doi.org/10.1016/S0140-6736(13)60024-0 (Nicholas J. White et al. 2014)
3. https://dx.doi.org/10.1016/B978-0-12-397900-1.00004-9 (Baird, Maguire, and Price 2012)
4. https://doi.org/10.1016/j.medmal.2019.07.011 (Epelboin et al. 2020)

13.2.1 Plasmodium falciparum

First-line treatment

Artemisinin-based combination therapy (ACT): only artemether-lumefantrine is currently available in Belgium, but artenimol-piperaquine can be obtained from some neighboring countries (France,…):

- Artemether + lumefantrine (Riamet®) tablet of 20 mg/120 mg.
  - > 35 kg: 4 tab po bid x 3 days (with food); NB: second dose after 8h.
  - 25-35 kg: 3 tab po bid x 3 days.
  - 15-25 kg: 2 tab po bid x 3 days.
  - 5-15 kg tab po bid x 3 days.

NB: in obese patients > 90 kg, some experts suggest to treating for 4-5 days due to risk of (lumefantrine) underdosing.

Dihydroartemisinin (syn. Artenimol) + piperaquine (Eurartesim®) tablet of 40 mg/320 mg.

- 75 kg: 4 tab po od x 3 days (fasting!).
- 36-75 kg: 3 tab po od x 3 days.
- 24-35 kg: 2 tab po od x 3 days.
- 13-23 kg tab po od x 3 days.
- 7-12 kg: ½ tab po od x 3 days.
- 5-7 kg: ¼ tab po od x 3 days.

NB: An ECG is advised prior to administration only in patients at risk of QTc prolongation (comedication, vomiting with subsequent hypokalemia,…) (Vignier et al. 2021).

- If QTc > 500 msec both ACT are contra-indicated (see alternative regimens).
- If 450-500 msec, consider drug administration under cardiac monitoring.

Check for possible interactions with other QT-prolonging drugs, or anti-arrhythmic drugs.
Both ACTs may be administered during the 2nd and 3rd trimesters of pregnancy; only artemether-lumefantrine can be given during the first trimester (WHO 2023).

Alternative regimens
Atovaquone + proguanil (Malarone®) tablet of 250 mg/100 mg.
- > 40 kg: 4 tab po od x 3 days (with food).
- 1-40 kg: 3 tab po od x 3 days.
- 21-30 kg: 2 tab po od x 3 days.
- 11-20 kg tab po od x 3 days.
- < 11 kg (not indicated).
- (Quinine 10 mg/kg (max 500 mg) po tid x 4-5 days combined with doxycycline 100 mg po od or clindamycin 10 mg/kg po bid x 7 days).

Special situations
Pregnant woman during first trimester:
- Quinine 10 mg/kg (max 500 mg) tid po x 4-5 days combined with clindamycin 10 mg/kg po bid x 7 days; however WHO has just approved in 2023 the use of artemether-lumefantrine for this scenario.

Other important considerations
- Suspicion of (partial) resistance to artemisinin (**early treatment failure**, defined as parasitic clearance lasting more than 3 days): ask for ITM expert advice since no clear-cut recommendations exist (combination quinine and atovaquone + proguanil?); possibility of genomic analysis
- Suspicion of resistance to partner drug (**late treatment failure** defined as recurrence of parasitemia between D7 and 28 post-initial treatment): ask for ITM expert advice since no clear-cut recommendations exist for recurrent malaria in nonendemic settings; possibility of genomic analysis
- Other ACTs may be administered according to WHO, including (1) artesunate + amodiaquine, (2) artesunate + sulfadoxine-pyrimethamin and (3) artesunate + mefloquine (only available in endemic countries); check always whether the full 3-day treatment has been effectively provided/taken (otherwise recrudescence may be expected). A new ACT is also available in endemic countries (artesunate-pyronaridine).
- In endemic countries targeting malaria elimination, treatment is followed by primaquine 0,25 mg/kg po single dose (to reduce the gametocytemia and decrease transmission to mosquitoes).
- In regions (mainly SE Asia) with artemisinin-resistance, there is an increased use of triple ACT, i.e. a combination of artemisinin derivatives with two partner drugs, mainly artemether/lumefrantrine with amodiaquine or dihydroartemisinin/piperaquine with mefloquine, or of combination of classic ACT with atovaquone/proguanil or pyronaridine (van der Pluijm et al. 2021).
- At this moment, two (non-artemisinin) drugs are being evaluated for resistant-(Pf) malaria in phase 2/3 trials, with promising results: a spiroindolone, cipargamin (KAE609) (Schmitt et al. 2021; Bouwman et al. 2020)and an imidazolopiperazine, ganaplacide (KAF106) (Nicholas J. White et al. 2016; Koller, Mombo-Ngoma, and Grobusch 2018).

13.2.2 Plasmodium non-falciparum (P. vivax, P. ovale, P. malariae, P. knowlesi)

First-line treatment
- Either one of the two abovementioned ACTs (artemether-lumefantrine or dihydroartemisinin-piperaquine) at the same dosages. (Or chloroquine total of 25 mg/kg po within three days).

- For an adult: 600 mg + 300 mg 6 hours later on day 1, 300 mg on day 2 and 300 mg on day 3, for a total dose of 1.5 g).

NB: chloroquine is not available any more in Belgium since 2016.

Alternative regimens

- Atovaquone + proguanil is efficacious also against non-falciparum malaria.

Special situations

- In case of *P. vivax* or *P. ovale,* primaquine is required to prevent relapse from liver hypnozoites 0.5 mg/kg po od for 14 days (for a total of 7 mg/kg).

NB:

- If primaquine is not well tolerated (gastro-intestinal side effects), it is better to reduce the daily dosage and to increase the duration (to obtain the same total dose).
- Primaquine is contra-indicated in pregnant women; a secondary prophylaxis (chloroquine 5 mg/kg/ week) may be considered until delivery.
- The activity of the glucose 6-phosphate dehydrogenase (G6PD) enzyme must be measured prior to administrations.
    - If activity < 10%: primaquine contra-indicated (risk of acute hemolysis).
    - If activity 10-50%: primaquine 0.75 mg/kg once a week for 6-8 weeks.

A new drug tafenoquine is available in the USA (FDA approved) as anti-hypnozoite treatment for *P. vivax/ovale* (Krintafel®; single-dose 300 mg at the end of the treatment of blood stage parasites) (Baird, Maguire, and Price 2012)(Baird 2018). Of note, determination of G6PD activity is mandatory also (contra-indicated if activity is below 70%). Better not to combine with dihydroartemisinin/piperaquine (interactions?) but well OK with artemether/lumefantrine.

Availability and costs

Primaquine: see additional and updated information via contact with ITM.

Current management strategy of (*Pf*) malaria at ITM/UZA (richtlijnen 2024), based on flag system

Black flag: high risk of mortality

Criteria:

- At least one criterion of organ failure OR
- At least three other criteria of severity

ALWAYS admission in ICU with artesunate IV (+ low threshold ceftriaxone IV +/- doxycycline)
NB: Parasitemia often > 4% (indicative)

Red flag: high risk of morbidity

Criteria:

- Maximum two criteria of severity and no organ failure OR
- At least two risk factors of complication OR
- Vomiting with impossibility for oral intake OR
- Pregnant woman

ALWAYS hospital admission with artesunate IV and narrow monitoring in ward (+ consider ceftriaxone IV);
TRANSFER to ICU (low threshold) if deterioration
RAPID SWITCH to ACT whenever stabilized
NB: Parasitemia usually 1-4% (indicative)

Orange flag: potential complications

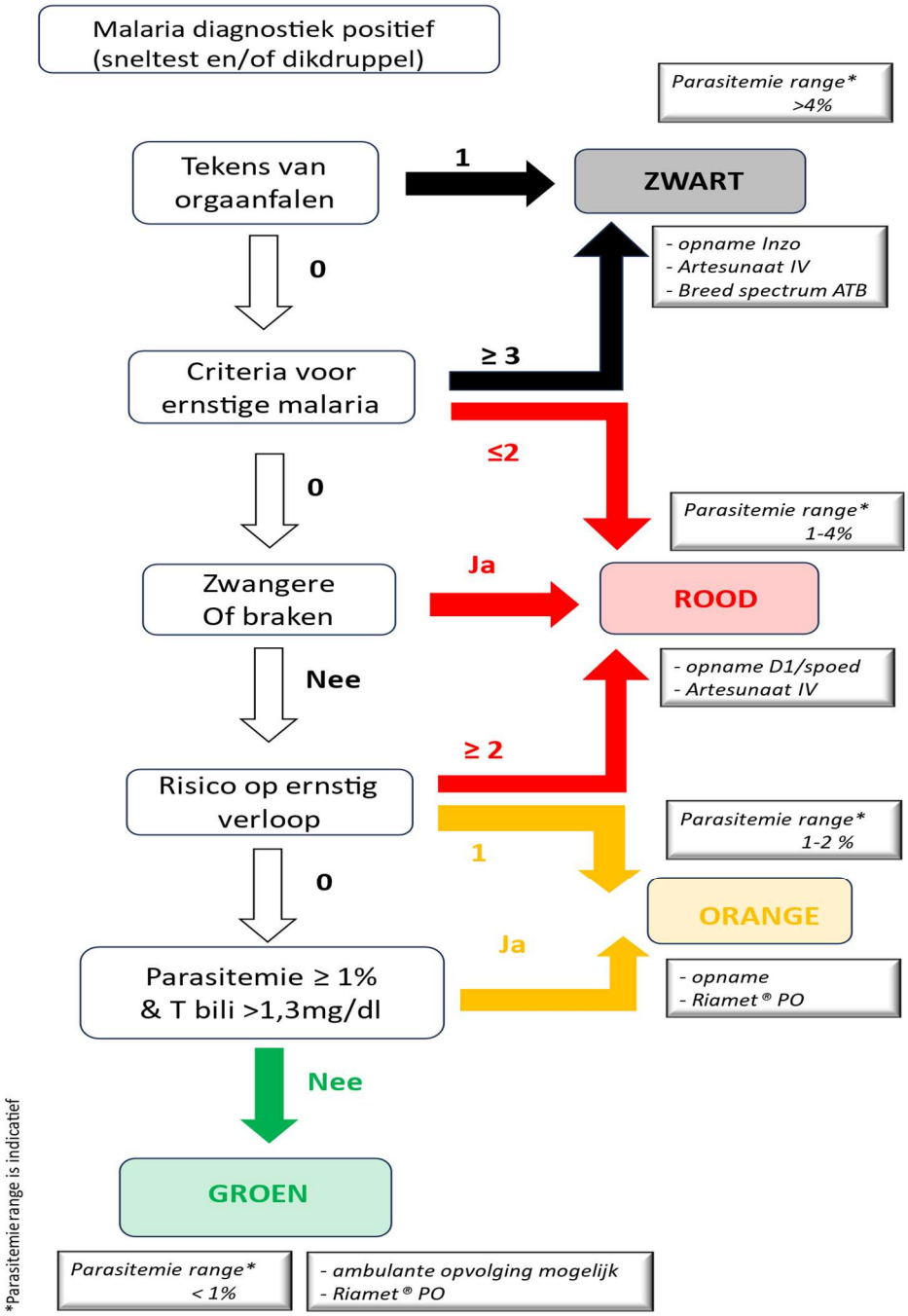
No criteria of severity AND
Maximum one risk factor of complication
ALWAYS (short) hospital admission (ambulatory treatment in exceptional circumstances, to discuss case-by -case) and treatment with oral ACT (artemether-lumefantrine)
NB: Parasitemia usually 1-2% (indicative)

Green flag: minor morbidity

All following criteria must be present!

- Parasitemia < 1%
- Normal bilirubinemia < 1.3 mg/dl
- No risk factor of complication
- No vomiting
- Close follow-up by relatives or friends
- AND no criteria of severity

OUTPATIENT TREATMENT with ACT po with follow-up at D3-5
PROVISION of emergency phone (038213000)
ADMISSION if deterioration or vomiting


Malaria diagnostiek positief
(sneltest en/of dikdruppel)
Parasitemie range*
>4%
Tekens van
orgaanfalen
1
ZWART
- opname Inzo
- Artesunaat IV
- Breed spectrum ATB
0
≥ 3
Criteria voor
ernstige malaria
≤2
0
Parasitemie range*
1-4%
Ja
Zwangere
Of braken
ROOD
Nee
- opname D1/spoed
- Artesunaat IV
≥ 2
Risico op ernstig
verloop
Parasitemie range*
1-2 %
1
0
ORANGE
Ja
Parasitemie ≥ 1%
& T bili >1,3mg/dl
- opname
- Riamet® PO
Nee
GROEN
Parasitemie range*
< 1%
- ambulante opvolging mogelijk
- Riamet® PO
*Parasitemie range is indicatief

14 Microsporidiosis

Selected References

1. https://dx.doi.org/10.3109/08820538.2014.962161 (Thanathanee et al. 2016)
2. https://dx.doi.org/10.1097/QCO.0b013e32834aa152 (Didier and Weiss 2011)
3. https://dx.doi.org/10.1016/j.gcb.2010.07.003 (Anane and Attouchi 2010)
4. https://dx.doi.org/10.1586/14787210.3.3.419 (Didier et al. 2005)
5. https://dx.doi.org/10.1097/01.inf.0000141724.06556.f9 (Tremoulet et al. 2004)
6. https://dx.doi.org/10.1056/NEJMoa012924 (Molina et al. 2002)
7. https://dx.doi.org/10.1111/j.1399-3062.2008.00347.x (Lanternier et al. 2009)
8. https://dx.doi.org/10.1111/j.1469-0691.1995.tb00450.x (Van Gool and Dankert 1995)
9. https://dx.doi.org/10.1056/NEJMoa032655 (C. M. Coyle et al. 2004)

14.1 Intestinal microsporidiosis in immunocompetent individuals

Mainly due to *Encephalitozoon intestinalis* and *Enterocytozoon bieneusi.*
Usually, unapparent infection or self-limiting diarrhea.

Treatment in case of persistent symptoms:

- Albendazole 400 mg po bid x 7 days.
- Fumagillin 20 mg po tid x 14 days: (expensive/not available in Belgium).

14.2 Intestinal and/or disseminated microsporidiosis in immunosuppressed individuals

Due to *Enterocytoon spp.* (*E. hellum, E. cuniculi*…) *Encephalitozoon bieneusi*, *Pleistophora spp.*, *Anacaliia spp.*, *Trachipleistophora spp*…

First restore immunity, whenever possible, (antiretroviral therapy for HIV/AIDS…).
Albendazole

- Adults: albendazole 400 mg po bid x 2-4 weeks, consider treating for 6 months after CD4-count > 200/mm³.
- Children: albendazole 7.5 mg/kg po bid x 2-4 weeks, consider treating for 6 months after CD4-count > 200/mm³.

Add itraconazole if infection due to *Acanaliia spp*. or *Trachipleistophora spp*.
Consider Fumagillin 20 mg po tid x 14 days (not available in Belgium): parasitological cure rate of 94% in a prospective of 166 patients at the cost of a high frequency of hematological toxicity.
Fumagillin 20 mg po tid x 14 days unavailable in Belgium.

14.3 Ocular microsporidiosis

Due to *Enterocytozoon spp* (*E. hellum, cuniculi…*), *Encephalitozoon bieneusi*, *Vittaforma/Nosema spp*. (*V./N. corneae, V./N. ocularum...*).
Collyrium fumagillin bicylohexylammonium (Fumidil B) 3 mg/ml in saline (fumagillin 70 µg/ml).
Albendazole (dose as above) in case of signs of disseminated infection.
Case reports of success with moxifloxacin 0.5% collyrium or voriconazole 1% collyrium (Agarwal, Coc, and Navon 2019).

15 Sarcocystosis

Selected References

1. https://dx.doi.org/10.1128/CMR.00113-14 (Fayer, Esposito, and Dubey 2015)
2. https://dx.doi.org/10.1007/s11908-015-0495-4 (Harris et al. 2015)
3. https://dx.doi.org/10.4269/ajtmh.1999.61.548 (Arness et al. 1999)

15.1 Intestinal sarcocystosis (*S. hominis, S. suihominis*)

No treatment studied; self-clearance is probably frequent. In case of persistent symptoms and no other etiology found, the TMX/SMX can be considered (see dosing below).

15.2 Muscular sarcocystosis (*S. nesbitti*)

The optimal approach to treat muscular sarcocystosis is uncertain. In the absence of robust clinical data, the following regimen can be used:

- Adults: Trimethoprim/sulfamethoxazole 160/800 mg po bid x 14 days.
- Children: Trimethoprim/sulfamethoxazole 5/25 mg/kg po bid x 14 days.
- Corticosteroids 1 mg/kg po od with duration and tapering according to response have been used with reported favorable response in a few cases. However, the lack of inflammation on muscular biopsies suggests limited effectiveness of corticosteroids.

16 Toxoplasmosis (Toxoplasma gondii)

Selected References

1. https://dx.doi.org/10.1016/S0140-6736(04)16412-X (Montoya and Liesenfeld 2004)
2. https://dx.doi.org/10.1155/2014/273506 (Harrell and Carvounis 2014)
3. https://dx.doi.org/10.1093/cid/cis234 (Hotop, Hlobil, and Groß 2012)
4. https://dx.doi.org/10.1016/S1701-2163(15)31053-7 (Paquet et al. 2013)
5. https://dx.doi.org/10.1016/B978-0-444-52910-7.00028-3 (Kieffer and Wallon 2013)

Immunocompetent patients

Usually no need for treatment (self-limiting illness).
In case of severe symptoms (such as pneumonitis, myocarditis, prolonged symptoms, myositis):

First-line treatment

- Pyrimethamine (Daraprim® tablet of 25 mg) 100-200 mg po single dose on day 1 (children 2 mg/kg od x 2 days) followed by 50 mg (children 1 mg/kg) po od.
    - + Sulfadiazine (magistral) 1-1.5 g (children 25-50 mg/kg) po qid.
    - + Folinic acid (e.g., Elvorin® tablet of 7.5 mg) 15 mg po od x 2 to 6 weeks (treat 1-2 weeks beyond resolution of symptoms).

Alternative regimens

- (Mainly due to sulfa-allergy) Pyrimethamine + folinic acid (as above) + clindamycin (300 mg po/iv bid) or azithromycin (500 mg po od).

NB1: atovaquone 750 mg po bid (Wellvone® suspension 750 mg/5 ml) is another option, but very expensive (350 euros for one bottle) and not reimbursed.

NB2: some experts propose one of the 3 alternative drugs (clindamycin, azithromycin or atovaquone) also in monotherapy.

Special situations

Active chorioretinitis:

- Same treatment as here above + prednisolone 1 mg/kg po or iv od until inflammation subsides (in CSF or at fundoscopy).

Infection in pregnancy:

- If diagnosis before 16 weeks of gestation: fetal prophylaxis with spiramycin (rovamycine® tablet of 1,500,000 IU) 1g (=3,000,000 IU) po tid.
    - Either until the end of the pregnancy if the PCR toxoplasma in amniotic fluid remains negative.
    - Or switched to a full fetal treatment (see below) if the PCR at 16-18 weeks in amniotic fluid has been found positive.
- If documented infection (by PCR amniotic fluid) > 16-18 weeks), treatment with:
    - pyrimethamine (50 mg po bid x 2 days followed by 50 mg od.
        - + sulfadiazine 75 mg/kg single dose po on day 1 followed by 50 mg/kg bid (max 4g/day)
        - + folinic acid 10-20 mg po od.

For at least 4 weeks, or during the whole pregnancy if US evidence of fetal infection.

NB: pyrimethamine is teratogenic during the first trimester of pregnancy! Later on, folinic acid is necessary to avoid fetal bone marrow depression.

Fetal/congenital infection

- Complex management relying also on pyrimethamine/sulfadiazine/folinic acid.

Immunocompromised patients

First-line treatment

- Pyrimethamine (Daraprim® tablet of 25 mg) 200 mg single dose po on day 1, followed by 50 (< 60 kg) - 75 mg (>60 kg) po od.
    - + Sulfadiazine (magistral) 1g (< 60 kg)-1.5 g (> 60 kg) po qid.
    - + Folinic acid (e.g., Elvorin® tablet of 7.5 mg) 15 mg po od.

- OR Trimethoprim/sulfamethoxazole (TMP/SMX) 5/25 mg/kg iv or po bid. For at least 6 weeks followed by secondary prophylaxis (see below, special situations)

Alternative regimens

- Pyrimethamine (Daraprim® tablet of 25 mg) 200 mg single dose po on day 1, followed by 50 (< 60 kg)-75 mg (>60 kg) po od.
    - + Folinic acid (e.g., Elvorin® tablet of 7.5 mg) 15 mg po od.
    - + one of the following: clindamycin 600 mg iv or po tid
- OR azithromycin 900 -1200 mg po od.
- OR **a**tovaquone 750 mg po qid.
- For at least 6 weeks followed by secondary prophylaxis (see below, special situations).

Special situations

Primary prophylaxis:

- Trimethoprim/sulfamethoxazole (TMP/SMX) 160/800 mg po od (NB: prevents also PjP)
- OR dapsone 200 mg + pyrimethamine 75 mg + folinic acid 25 mg po once a week.
- (OR atovaquone 1500 mg po od).

Secondary prophylaxis (until restoration of immune function):

- Pyrimethamine 25 mg od + Sulfadiazine 500 mg qid + folinic acid 10 mg po od (NB: protects also against PjP).
- OR pyrimethamine 25 mg od + clindamyc in 300 mg tid + folinic acid 10 mg po od.
- (OR atovaquone 750 mg po od).

17 Trypanosomiasis

Selected References

1. https://dx.doi.org/10.1016/S1474-4422(12)70296-X (Kennedy 2013)
2. WHO, "Control and surveillance of human African trypanosomiasis," World Health Organization technical report series, no. 984, pp. 1-237, 2013. http://www.ncbi.nlm.nih.gov/pubmed/24552089 (WHO 2013)
3. https://dx.doi.org/10.1016/S0140-6736(09)61117-X (Priotto et al. 2009)
4. https://dx.doi.org/10.1093/cid/cis886 (Alirol et al. 2013)
5. https://dx.doi.org/10.1586/14787210.2014.959496 (Eperon et al. 2014)
6. https://dx.doi.org/10.1086/649917 (Mumba Ngoyi et al. 2010)
7. https://dx.doi.org/10.1371/journal.pntd.0001695 (Kuepfer et al. 2012)
8. https://doi.org/10.1016/j.idc.2018.10.003 (Bottieau and Clerinx 2019)

17.1 *Trypanosoma brucei gambiense* (or West African trypanosomiasis)

In any patient with confirmed (by microscopy) or suspected (by serology) *T. b. gambiense* human African trypanosomiasis (HAT), perform a lumbar puncture (LP) to stage disease. A meningo-encephalitic stage is diagnosed if:

- Trypanosomes are found in CSF (at direct examination) OR
- There are > 5 white blood cells (WBC)/µl in CSF

NB: the role of PCR in CSF to diagnose second stage HAT is still unclear, and therapeutic decisions should not be based on this

First-line treatment

Hemo-lymphatic stage (or first stage, or early stage):

- Pentamidine (Pentacarinat® vial of 300 mg/ 21 euro per vial) 4 mg/kg (max. 300 mg) im od (in the field) or slow iv (here) x 7 days.
- Caution: risk of hypoglycemia and hypotension: need of iv line and hospital observation.

Meningo-encephalitic stage (or second stage, or late stage):

- Eflornithine (Ornidyl® 20 g/100 ml) 200 mg/kg slow iv bid x 7 days + nifurtimox (Lampit® tablet of 120 mg) 5 mg/kg po tid x 10 days (= NECT, nifurtimox-eflornithine combination therapy)
- Not inferior but much less cumbersome than eflornithine 100 mg/kg slow iv qid x 14 days (the previous standard of care).
- Low risk of convulsion and hematotoxicity.

Alternative regimens

- Suramin (see dose and schedule here below) is also effective against *T.b. gambiense* FIRST STAGE but the regimen is more complex and less well tolerated (so second-line use only).

- Eflornithine 100 mg/kg slow iv qid x 14 days is as effective as NECT for *T. b. gambiense* SECOND STAGE but longer and more cumbersome (so second-line use only).

Important new developments:

- Melarsoprol should not be used any more for *T. b. gambiense* (much too toxic), except in very rare cases of treatment failure/relapse after expert discussion only!
- Fexinidazole **is** a new oral therapy (od x 10 days, WITH FOOD; 1800 mg/day D1-4 and 1200 mg/day D5-10) that has been demonstrated in a large phase 3 RCT to be as effective as pentamidine in first stage *T.b.g.* HAT and as NECT for second stage *T.b.g*. HAT (if not “too advanced” or if the WBC count in CSF is < 100/µL) (Lindner et al. 2020). A phase 4 trial has confirmed recently the safety and efficacy of

fexinidazole for first- and early second-stage HAT (Kande Betu Ku Mesu et al. 2021). The drug is now recommended in first line by WHO for these indications in tropical fields (much simpler). Of note for children < 6 years or < 20kg and for HAT patients with advanced neurological disease, NECT remain the FIRST CHOICE!!

- Acoziborole (SCYX-7158) is a single-dose oral therapy which appears effective for both stages of *T.b.g.* HAT (but trial results not published yet); ongoing trials in children and in HAT "seropositive only" individuals. Probably a major game changer soon!

The laboratory follow-up of *T.b.g.* second stage has recently been simplified.
LP 6 months after treatment (earlier LP is not indicated, except if relapse of clinical symptoms).

- If CSF WBC count < 5/µl and no detectable trypanosomes: CURED (stop further follow-up).
- If CSF WBC count 6-49/µl, new LP 6 months later (at month 12).
- if CSF WBC count < 20/µl and no trypanosomes: CURED (no further follow-up).
- if CSF WBC count > 20/µl: "RELAPSE" (retreatment).
- If CSF WBC count > or = 50/µl or if trypanosomes are detected: "RELAPSE" (retreatment).

Special situations
Pregnancy and infancy
All above-mentioned regimens may be administered (risk-benefit balance in favor of treatment)
Treatment failure or "relapse"
Very unusual with eflornithine: need of expert discussion for individualized treatment, but usually a new course of the initial treatment is offered again (since no resistance has been demonstrated so far)

17.2 *Trypanosoma brucei rhodesiense* (or East African trypanosomiasis)

First-line treatment
Hemo-lymphatic stage (or first-stage, or early stage).

- Suramin (Germanin® vial of 1 g) 5 mg/kg (children 2 mg/kg) as test dose on Day 1 under close monitoring for a few hours (risk of allergy/anaphylaxis), and the rest (15 mg/kg; max. 1 g) on Day 1 or Day 2: administer 20 mg/kg single dose on Day 3, 10, 17, 24 and 35.

Meningoencephalitic stage (or second-stage, or late stage).

- Melarsoprol (Arsobal® 180 mg/5 ml) 2,2 mg/kg slow iv od x 10 consecutive days + steroids (0,5-1 mg/kg methyl prednisolone iv od).

NB: It is increasingly recommended in clinical practice not to sample CSF immediately after diagnosis of *T. b. rhodesiense* trypanosomiasis, but to wait 2-3 days (in fact until trypanosomes are not detected in blood any more), to avoid contaminating the CSF with blood and get a "false positive" diagnosis of second-stage HAT (with the risk of exposing the patient unnecessarily to a very toxic drug); neuro-invasion is unlikely to begin before 7 days after symptom/fever onset.

Melarsoprol causes a wide variety of toxicities, but the most feared is the post-treatment reactive encephalopathic syndrome (fatality rate of about 10%). Some studies suggest that the concomitant administration of steroids decreases the incidence and severity of this complication, but this is debated. In case reactive encephalopathy occurs, dexamethasone (3 x 15 mg iv per day is usually given).

Alternative regimens
Although considered less effective, pentamidine has been used sometimes successfully when suramin was not immediately available for *T. b. rhodesiense* FIRST STAGE. A case report has shown that a single dose of pentamidine substantially decreases the load and mobility of tryps (confirming that it could be used while waiting for suramin) (van Genderen et al. 2021).

There is so far no alternative regimen to melarsoprol for *T. b. rhodesiens* SECOND STAGE (effectiveness of eflornithine was below 50% in old studies).
NB: A trial evaluating the efficacy of **fexinidazole** for *T. b. rhodesiense* has been completed with promising results (publication pending). Possibly a game changer !

Availability and costs
Eflornithine, nifurtimox, suramin and melarsoprol are available at (ITM)/UZA and are provided for free by WHO Geneva. Pentamidine is available in Belgium (for other indications). Availability not yet clear for fexinidazole, since low-resource countries are prioritized.

17.3 *Trypanosoma cruzi* (or American trypanosomiasis)

See Chagas Disease

Chapter 2: Helminthes

18 Ancylostomiasis (Hookworm)

Most infections with intestinal hookworms are due to *Ancylostoma duodenale* or *Necator americanus.* Other less frequent intestinal hookworms are *Ancylostoma ceylanicum* and *A. caninum* (hookworms of dogs).

Selected References

1. https://dx.doi.org/10.1016/S0065-308X(04)58004-1 (Brooker, Bethony, and Hotez 2004)
2. https://dx.doi.org/10.1056/NEJMra032492 (Hotez et al. 2004)
3. https://dx.doi.org/10.1016/0140-6736(90)91186-E (Prociv and Croese 1990)
4. https://dx.doi.org/10.1371/journal.pntd.0003204 (Levecke et al. 2014)
5. https://dx.doi.org/10.4269/ajtmh.1996.55.477 (Marti et al. 1996a)
6. https://dx.doi:10.1128/AAC.01317-13 (Adegnika et al. 2014a; 2014b)
7. https://dx.doi.org/10.1001/jama.299.16.1937 (Keiser, Duthaler, and Utzinger 2010)
8. https://doi.org/10.1136/bmj.j4307 (Moser, Schindler, and Keiser 2017)
9. https://doi.org/10.1016/bs.apar.2018.08.002 (Moser, Schindler, and Keiser 2019a)

First-line treatment

- Adults and children > 2 years: albendazole 400 mg po od (one to) 3 days.

Alternative regimens

- Adults and children > 1 year: mebendazole 100 mg po bid x 3 days (equivalent to albendazole 400 mg od).
- (Adults and children > 6 months: pyrantel pamoate (10 mg/kg (maximum 1 g) po od x 3 days; not available in Belgium).
- (Adults and children > 6 months: tribendimidine (200 mg children; 400 mg adults od); new drug not yet available in clinical practice; cure rate equivalent to that of albendazole in single dose administration.

NB: In tropical countries the cure rate of a single dose albendazole is 72%; a two-day treatment reaches a cure rate of 90%; a three-day treatment achieves a cure rate of 98%. Although infection is usually less heavy in travel medicine, the same 3-day schedule should be best applied since suppressive therapy only is not satisfactory. Another proposed therapeutic option (only for adults) is albendazole 800 mg single dose.
Ivermectin is not effective on hookworms.

Single high dose of mebendazole (500 mg to 1 gr.), previously reported as moderately effective, is not sufficient anymore (cure rate 30% in recent surveys).
In the tropics, many studies are being conducted with different combined treatments or even triple therapies, to explore effective alternative single dose regimens (Moser et al. 2017).

Ancylostoma ceylanicum causes a disease comparable to *A. duodenale*, particularly in Southeast Asia. It appears to be highly sensitive to albendazole at standard dosage.
Ancylostoma caninum is increasingly recognized as a cause of eosinophilic enteritis/aphthous ileitis.

Special situations

- Albendazole is allowed by WHO in the 2nd and 3rd trimesters; (pyrantel pamoate is safe during pregnancy). Albendazole (and mebendazole) should be avoided during the first trimester, except if clinical benefits are expected to surpass the risk (embryotoxicity/ teratogenicity in animals).
- If diagnosis during the larval migration (Löffler's syndrome), consider inhaled or oral steroids and treat with antiparasitic agents after about 2 months (prepatent period); antiparasitic drugs are not active against larvae.

Availability and costs

Albendazole: see additional and updated information via contact with ITM.

19 Angiostrongyliasis

19.1 Cerebral angiostrongyliasis (*Angiostrongylus cantonensis*)

Selected References

1. http://www.ncbi.nlm.nih.gov/pubmed/25776582 (Eamsobhana 2014)
2. https://dx.doi.org/10.1007/s10096-011-1328-5 (Q.-P. Wang et al. 2012)
3. https://dx.doi.org/10.1086/595852 (Ramirez-Avila et al. 2009)
4. https://dx.doi.org/10.1016/S1473-3099(08)70229-9 (Q. P. Wang et al. 2008)
5. https://dx.doi.org/10.1111/j.1708-8305.2009.00305.x (Diaz 2009)
6. http://www.ncbi.nlm.nih.gov/pubmed/19706911 (Chotmongkol et al. 2009)
7. https://dx.doi.org/10.1002/14651858.CD009088.pub3 (Thanaviratananich, Thanaviratananich, and Ngamjarus 2015)

First-line treatment

Mainly symptomatic: analgesics, corticosteroids, and/or iterative lumbar punctures (if elevated open pressure).

- The only intervention having demonstrated clinical benefit (reduction of severity and duration of headache and of the need of repeated punctures) is the administration of corticosteroids: prednisolone 60 mg/day (1 mg/kg) or dexamethasone (10 to 20 mg) for 2 weeks at least, to taper down slowly.
- No definitive demonstration that adjunction of albendazole is of any clinical benefit (only borderline significance found so far). If albendazole is still considered, administer 400 mg (or 7.5 mg/kg) bid for 14-21 days. There has been for long a theoretical risk of exacerbation of neurological symptoms with albendazole, but recent data are reassuring on this issue (J. L. Jacobs and Mellors 2020). However, the systematic adjunction of steroids (to albendazole) remains recommended.
- The 2020 guideline of the Hawaii Governor's Joint Task Force on Rat Lungworm Disease recommends "to combine steroids and albendazole on a case-by-case basis but considers that in most cases the risk/benefit balance is in favor of the combination, until definitive safety data are available"(Ansdell et al. 2021).

NB: Albendazole, mebendazole, ivermectin have all proven effective in rats but never in humans so far.
An in vitro study on L3 larvae (the pathogenic stage) showed that albendazole, pyrantel pamoate, DEC and praziquantel have killing activity, while ivermectin and moxidectin just reduce the larval mobility (Jacob et al. 2021).

Special situations

Ocular larva migrans:

- Surgical removal of larva.

Pregnancy:
WHO allows use of albendazole in 2nd and 3rd trimesters (but here the risk likely outweighs the inconsistent benefit).

Availability and costs

Albendazole: see additional and updated information via contact with ITM.

19.2 Abdominal angiostrongyliasis (*Angiostrongylus costaricensis*)

Selected References

1. https://doi.org/10.1186/s13071-021-04875-3 (Rojas et al. 2021)

First-line treatment

Conservative/symptomatic treatment or surgery if complications.

NB: Use of albendazole, mebendazole, ivermectin, diethylcarbamazine and pyrantel pamoate has been occasionally reported, but efficacy remains unclear. Most experts consider that anti-helminthic drugs are not recommended and might be even deleterious (erratic effect).

20 Anisakiasis

Anisakis simplex and A physeteris – Pseudoterrnova decipiens and Contracaecum spp.

Selected References

1. https://dx.doi.org/10.1086/496920 (Nawa, Hatz, and Blum 2005)
2. https://dx.doi.org/10.1016/S1473-3099(04)01005-9 (Butt, Aldridge, and Sanders 2004)
3. https://dx.doi.org/10.1086/498309 (Pacios et al. 2005)
4. https://dx.doi.org/10.1128/CMR.00012-07 (Audicana and Kennedy 2008)
5. https://dx.doi.org/10.1086/656238 (Hochberg and Hamer 2010)
6. http://www.ncbi.nlm.nih.gov/pubmed/23092000 (Pravettoni, Primavesi, and Piantanida 2012)
7. https://dx.doi.org/10.1016/S0140-6736(02)09333-9 (Moore, Girdwood, and Chiodini 2002)
8. https://dx.doi.org/10.1645/0022-3395(2002)088[0395:EOIAAA]2.0.CO;2 (Dziekońska-Rynko, Rokicki, and Jablonowski 2002)
9. https://doi.org/10.4269/ajtmh.18-0586 (Carlin et al. 2018)

First-line treatment

- There is no specific treatment, except the early removal (< 12h after symptom onset) of larvae by gastroscopy.
- Spontaneous resolution of symptoms is the rule.
- Anaphylactic/allergic symptoms should be treated accordingly.

Alternative regimens

In vitro and animal models and animal models suggest that albendazole and ivermectin could also be useful in humans.

Limited evidence (case reports, small series) suggests that albendazole 400 mg orally twice daily x 3 to 21 days may be beneficial. Shorter treatment is suggested for acute gastric anisakiasis and longer treatment for the more chronic (and rarer) intestinal anisakiasis.
Co-supplementation of 6-methylprednisolone (1 mg/kg/24 hours) alleviated intestinal obstruction and prevented bowel segment resection in a series from Spain. The addition of corticosteroids can therefore be considered.

NB: Humans are accidental hosts for nematodes that cause anisakiasis. The nematodes cannot progress their life cycles in humans but can nevertheless cause debilitating illness, either directly or by inducing immune hypersensitivity states of variable severity.

Special situations

Pregnancy:
WHO allows use of albendazole in 2nd and 3rd trimesters (but here risk probably outweighs benefit).

Availability and costs

Albendazole: see additional and updated information via contact with ITM.

21 Ascariasis (Ascaris lumbricoides - A. suum)

Selected References

1. https://dx.doi.org/10.1016/j.micinf.2010.09.013 (Dold and Holland 2011)
2. https://dx.doi.org/10.1517/14656566.5.3.529 (Massara and Enk 2004)
3. https://dx.doi.org/10.1517/14656566.2.2.223 (St Georgiev 2001)
4. https://doi.org/10.1016/bs.apar.2018.08.002 (Moser, Schindler, and Keiser 2019b)
5. https://doi.org/10.1002/14651858.CD010599.pub2 (Conterno et al. 2020)

Firstline treatment

- Adults and children > 1 year: mebendazole 100 mg po bid x 3 days; cure rate > 95%.

Alternative regimens

- Mebendazole 500 mg po single dose (no tablet of 500 mg available anymore); cure rate > 90%.
- Albendazole 400 mg po single dose (adults and children > 2 years); 200 mg po single dose (children 1-2 years); cure rate: 97%.
- Ivermectin 200 µg/kg po single dose (adults and children > 15 kg); cure rate: 95%.
- (Pyrantel pamoate 10 mg/kg po (maximum 1gr), single dose (adults and children > 6 months); cure rate: 95%; not available in Belgium.
- (Other "new" drugs, not yet available, such as tribendimidine and moxidectin are highly effective as well, with cure rate > 90%, but not oxantel pamoate, which has a cure rate of 20%).

Special situations

Pregnancy:

- Albendazole is allowed by WHO in the 2nd and 3rd trimesters.
- Pyrantel pamoate is safe during pregnancy, including first trimester (not available in Belgium).

Loeffler's syndrome:
If diagnosis during the larval migration, consider inhaled or oral steroids and treat with antiparasitic agents after about 2 months (prepatent period); antiparasitic drugs are not active against larvae.

Availability and costs

Mebendazole is available in Belgium without prescription.
Albendazole: see additional and updated information via contact with ITM.
Ivermectin: see additional and updated information via contact with ITM.

22 Bayliascariasis (*Baylisascaris procyonis*; raccoon roundworm)

Selected References

1. https://dx.doi.org/10.1128/CMR.00044-15 (Graeff-Teixeira, Morassutti, and Kazacos 2016)
2. https://dx.doi.org/10.1016/B978-0-444-53490-3.00020-0 (Kazacos, Jelicks, and Tanowitz 2013)
3. https://dx.doi.org/10.1086/425364 (Murray and Kazacos 2004)
4. https://dx.doi.org/10.1038/sj.eye.6700742 (de A Garcia et al. 2004)

First-line treatment

Aggressive treatment combining steroids and albendazole should be started as early as possible, on clinical suspicion, and even before any confirmation (high rate of fatalities or neurological damage).

Eosinophilic meningitis: Albendazole

- Adults: 400 mg po bid x 10-28 days (with fatty meal, for absorption).
- Children 5-25 mg/kg po bid x 10-28 days (with fatty meal, for absorption).
  + steroids at "cerebral" dosage!

Ocular Larva Migrans (OLM) or Diffuse Unilateral Subacute Neuroretinitis (DUSN):

- If larvae visible: laser photocoagulation + steroids.
- If larvae not visible: albendazole (as above) + steroids.

Special situations

Post-exposure prophylactic treatment:

- Albendazole as above but x 10 days.
- To strongly consider if exposure since this may avoid symptom development.

Availability and costs

Albendazole see additional and updated information via contact with ITM.

23 Capillariasis

23.1 Hepatic capillariasis *(Capillaria hepatica)*

Selected References

1. https://dx.doi.org/10.3748/wjg.v16.i6.698 (Li, Yang, and Wang 2010)
2. https://dx.doi.org/10.1007/s00436-011-2494-1 (Fuehrer, Igel, and Auer 2011)

Less than 100 cases have been described so far, with 50% mortality!
Optimal treatment not well established.

First-line treatment

- Albendazole: 400 mg po bid for 20-100 days, with fatty meal.
  - + steroids (0,5 mg/kg prednisone) if severe inflammatory reaction.
  - + surgery (partial hepatectomy on some occasions).
- Repeated albendazole courses are sometimes needed. (C. Liu et al. 2019)

NB: No clear data on efficacy of mebendazole or ivermectin in humans.

23.2 Intestinal capillariasis (*Capillaria philippinensis*)

Selected References

1. https://dx.doi.org/10.1016/0169-4758(90)90389-L (Cross 1992)
2. https://dx.doi.org/10.1186/s12876-014-0207-9 (Limsrivilai et al. 2014)

Since this parasite can multiply in humans, untreated patients may develop persistent and/or overwhelming infections that can be fatal.

First-line treatment

Albendazole:

- Adults: 400 mg po bid x 10 (-30) days.
- Children < 2 years: 200 mg od, > 2 years: 400 mg po od x at least 10 days.

The dose and duration are not well established; below 10 days high risk of recurrence, but this duration appeared sufficient in a large observational retrospective study. (Sadaow et al. 2018)

Alternative regimens

Mebendazole: adult and children > 1 year: 200 mg po bid x 21 days (less effective).
Ivermectin 12 mg po od x 3-10 days (has been anecdotally used with good effect).

Availability and costs

Albendazole: see additional and updated information via contact with ITM.
Ivermectin: see additional and updated information via contact with ITM.

24 Clonorchiasis - Opisthorchiasis - (*Metorchiasis*)

Diseases caused by *Opisthorchis spp* (*O. felineus* in East-Europa/Central Asia; *O. viverrini* in Central/East Asia), *Clonorchis sinensis* in Southeast Asia and *Metorchis bilis* in Central Asia.
Eggs are indistinguishable. Try to obtain the adult worm in feces after anti-parasitic treatment for definitive diagnosis.
Clear epidemiological link between chronic *Clonorchis/Opisthorchis* infection and cholangiocarcinoma (to assess during workup).

Selected References

1. https://dx.doi.org/10.1016/S1473-3099(04)01252-6 (Lun et al. 2005)
2. https://dx.doi.org/10.1016/j.actatropica.2003.03.001 (Upatham and Viyanant 2003)
3. https://dx.doi.org/10.1371/journal.pmed.0040201 (Mairiang and Mairiang 2003)
4. https://dx.doi.org/10.1128/CMR.00012-09 (Keiser and Utzinger 2009)
5. https://dx.doi.org/10.1097/QCO.0b013e32833de06a (Keiser, Duthaler, and Utzinger 2010)
6. https://dx.doi.org/10.1016/S0140-6736(15)60313-0 (M. B. Qian et al. 2016)
7. http://www.ncbi.nlm.nih.gov/pubmed/6377514 (Pungpark, Bunnag, and Harinasuta 1984)
8. https://dx.doi.org/10.1093/cid/cix278 (Barda et al. 2017)
9. https://dx.doi.org/10.1016/S1473-3099(16)30198-0 (Sayasone et al. 2016)
10. https://dx.doi.org/10.1093/cid/cis1011 (Sayasone et al. 2016)

First-line treatment

- Praziquantel (Biltricide® 600 mg) 25 mg/kg/ po tid x 2 days (97-100% cure rate).

Alternative regimens

- Albendazole (Zentel® 400 mg) 400 mg/kg po bid x 7 days (cure rate: 63%) (shorter durations have unacceptably low cure rates).

NB: Low efficacy of ivermectin and moxidectin.
Tribendimidine was safe and efficacious in phase 2 trials against for *O. viverrini* (98% cure rate in children at 100 mg and 90% in adults at 400 mg; cure rate was lower (but equivalent to that of praziquantel) for *C. sinensis* (60%). Another phase 2 RCT confirmed the high efficacy of tribendimidine against *O. viverrini* (cure rate 93%) slightly lower than that of praziquantel (97%) (Sayasone et al. 2018).

Special situations

Consider excluding (reasonably) neurocysticercosis before administering praziquantel or albendazole (since "shared" risks of acquisition).

Availability and costs

Praziquantel and albendazole: see additional and updated information via contact with ITM.
Tribendimidine: not available in clinical practice.

25 Cutaneous larva migrans

This syndrome usually corresponds to the cutaneous symptoms related to infection with zoonotic hookworms (ancylostomas), such as mostly *Ancylostoma braziliense*, and to a much lesser extent *Ancylostoma caninum*, *Uncinaria stenocephala*, *Bunostomum phlebotomum*, … Of note, many other helmnthiases can occasionally cause a CLM syndrome, including *Loa loa*, *Gnathostoma spp.*, *Dirofilaria spp.*, *Strongyloides stercoralis*, *Toxocara spp.*, *Fasciola spp.*, *Paragonimus spp.*, *Anisakis simplex*, *Dracunculus medinensis*, *Sparganum proliferum*, *Spirometra spp.*, …

Selected References

1. https://dx.doi.org/10.1056/NEJM199810223391714 (Hepburn and Nicholls 2009)
2. https://dx.doi.org/10.1086/313942 (Bouchaud et al. 2000)
3. https://dx.doi.org/10.1086/313787 (Caumes 2000)
4. https://doi.org/10.2174/1872213X11666170110162344 (Michael W. Simon 2003)
5. https://dx.doi.org/10.1111/j.1708-8305.2007.00148.x (Hochedez and Caumes 2007)
6. https://dx.doi.org/10.1016/S1473-3099(08)70098-7 (Jörg Heukelbach and Feldmeier 2008)
7. https://dx.doi.org/10.1016/S1473-3099(04)01178-8 (Caumes and Danis 2004)
8. https://dx.doi.org/10.1093/cid/cit440 (A. Schuster et al. 2013)
9. https://dx.doi.org/10.1111/jdv.12097 (Vanhaecke et al. 2014)

First-line treatment

Ivermectin 200 µg/kg po single dose; cure rate of 80-100%.
Usually pruritus disappears within 3 days (max: 20 days) and creeping dermatitis within 7 days (max: 30 days).
Ivermectin for two successive days is advised in case of treatment failure or relapse or in case of hookworm-related folliculitis (since a single dose is only 66% effective).

Alternative regimens

Albendazole 400 mg (or 7,5 mg/kg) po bid x 5 days: cure rate of 90-100% (NB: low efficacy of single dose albendazole).

NB1: Topical treatments are only effective for cases with lesions limited in number and size. Ointment containing thiabendazole is not produced any more; ointment with albendazole (10 % = 3 tablets of 400 mg dissolved in 12 gr of vaseline tid x 10 days); ointment with ivermectin has recently emerged as well.

NB2: Cryotherapy is obsolete as larvae are located several centimeters ahead of the lesion and survive very low temperature.

NB3: Secondary bacterial infections are frequent and should be treated with topical/systemic antibiotics.

26 Cysticercosis (*Taenia solium*, pig tapeworm)

Disease caused by the larval stage of *Taenia solium* (pig tapeworm) only, after accidental ingestion of eggs. Diagnosis of neurocysticercosis (NCC) should rely on a combination of epidemiological, laboratory and radiological criteria as updated in 2017 by Del Brutto et al.
(O. H. del Brutto et al. 2017)

Revised diagnostic criteria and degrees of diagnostic certainty for neurocysticercosis.

Diagnostic criteria
Absolute criteria:
• Histological demonstration of the parasite from biopsy of a brain or spinal cord lesion. • Visualization of subretinal cysticercus. • Conclusive demonstration of a scolex within a cystic lesion on neuroimaging studies.
Neuroimaging criteria:
Major neuroimaging criteria:
• Cystic lesions without a discernible scolex. • Enhancing lesions.[a] • Multilobulated cystic lesions in the subarachnoid space. • Typical parenchymal brain calcifications.[a]
Confirmative neuroimaging criteria:
• Resolution of cystic lesions after cysticidal drug therapy. • Spontaneous resolution of single small enhancing lesions.[b] • Migration of ventricular cysts documented on sequential neuroimaging studies.[a]
Minor neuroimaging criteria:
• Obstructive hydrocephalus (symmetric or asymmetric) or abnormal enhancement of basal leptomeninges.
Clinical/exposure criteria:
Major clinical/exposure:
• Detection of specific anticysticercal antibodies or cysticercal antigens by well-standardized immunodiagnostic tests.[a] • Cysticercosis outside the central nervous system.[a] • Evidence of a household contact with *T. solium* infection.
Minor clinical/exposure:
• Clinical manifestations suggestive of neurocysticercosis.[a] • Individuals coming from or living in an area where cysticercosis is endemic.[a]
Degrees of diagnostic certainty
Definitive diagnosis:
• One absolute criterion. • Two major neuroimaging criteria plus any clinical/exposure criteria. • One major and one confirmative neuroimaging criteria plus any clinical/exposure criteria. • One major neuroimaging criteria plus two clinical/exposure criteria (including at least one major clinical/exposure criterion), together with the exclusion of other pathologies producing similar neuroimaging findings.
Probable diagnosis:
• One major neuroimaging criteria plus any two clinical/exposure criteria. • One minor neuroimaging criteria plus at least one major clinical/exposure criteria.

Source: Del Brutto O *et al*. Revised diagnostic criteria for neurocysticercosis. *J Neurol Sci.* 2017.

Treatment needs to be individually tailored and antiparasitic treatment relies completely on neuroimaging (location, stage and number of cysticerci). A multidisciplinary approach with a neurologist, and sometimes a neurosurgeon, is key.

Selected References

1. https://dx.doi.org/10.1016/j.jns.2016.11.045 (H. H. Garcia, Nash, and Del Brutto 2014)
2. https://dx.doi.org/10.1016/S1474-4422(14)70094-8 (O. H. Del Brutto et al. 2017)
3. https://dx.doi.org/10.1371/journal.pntd.0001851 (Gabriël et al. 2012)
4. https://dx.doi.org/10.7326/0003-4819-145-1-200607040-00009 (Oscar H. del Brutto et al. 2006)
5. http://www.ncbi.nlm.nih.gov/pubmed/15728858 (H. H. Garcia et al. 2005)
6. https://dx.doi.org/10.1016/S0140-6736(03)14117-7 (Oscar H. Del Brutto et al. 2006)
7. https://dx.doi.org/10.1128/CMR.15.4.747-756.2002 (García et al. 2003)
8. https://dx.doi.org/10.1093/cid/ciw134 (H. H. Garcia et al. 2016)

9. https://dx.doi.org/10.1056/NEJM199601113340216 (Corona et al. 1996)
10. https://dx.doi.org/10.1086/511040 (Mitre et al. 2007)
11. https://dx.doi.org/10.1212/WNL.0b013e318253d641 (Callacondo et al. 2012)
12. https://pubmed.ncbi.nlm.nih.gov/32461308/ (H. Garcia, Gonzalez, and Gilman 2020)
13. https://pubmed.ncbi.nlm.nih.gov/30712759 (C. Coyle 2019)

26.1 Cysticercosis of the skeletal muscles or subcutaneous tissues

No need for antiparasitic treatment if no CNS involvement; no treatment necessary if no intestinal tapeworm present.

26.2 Neurocysticercosis

26.2.1 Cystic (= viable, vesicular) or degenerating (= enhancing, colloidal or granuloma) lesions

One or two lesions:
Albendazole 7,5 mg/kg po bid x 10-14 days (slightly higher efficacy through better CSF penetration).
OR praziquantel 25 mg/kg po bid x 10-14 days (according to a recent Cochrane review, the evidence with this drug is very weak). (Monk, Abba, and Ranganathan 2021).

- ALWAYS under hospital supervision (risk of exacerbation/worsening mainly between the 2nd and 5th day post-antiparasitic treatment).
- ALWAYS after excluding any occult ocular cysticercosis.
- ALWAYS associated with dexamethasone (0,1 mg/kg po od starting 1 day prior to antiparasitic treatment, for 1-2 weeks, and followed by slow tapering).
- OFTEN associated with antiepileptic drugs (up to 2 years after the last seizure; shorter course could be considered if perilesional edema is associated with 1-3 degenerating cysts).

Three or more lesions:
Albendazole 7,5 mg/kg po bid x 10-14 days AND praziquantel 25 mg/kg po bid x 10-14 days (more efficacious than each drug in monotherapy).

- ALWAYS under hospital supervision.
- ALWAYS after excluding any occult ocular cysticercosis.
- ALWAYS associated with dexamethasone (0,1mg/kg po od starting 1 day prior to antiparasitic treatment, for 1-2 weeks, and followed by slow tapering).
- OFTEN associated with antiepileptic drugs (up to 2 years after the last seizure).

Antiparasitic treatment destroys 60-80% of cysts, with complete resolution of all cysts in less than 40% of the cases. Favorable clinical outcome as reflected by a 45% decrease of epileptic seizures. A recent Cochrane review challenges, however, the quality of evidence for praziquantel and even for albendazole when there are multiple cysts. (Monk, Abba, and Ranganathan 2021).
Albendazole absorption is fat dependent. Its concentration is increased by 50% with concomitant administration of praziquantel.
Praziquantel concentration is lowered by concomitant use of steroids (but no evidence that it has a clinical impact).

Special situations
Single (enhancing) lesion:

- Albendazole for 3 days or praziquantel for 1 day are probably sufficient.
- Surgery (often for diagnostic purposes) with complete cyst removal is therapeutic.
- Also, it is unclear whether antiparasitic treatment is necessary in case of single lesion.

Numerous cystic/degenerating lesions:

- Longer courses of antiparasitic treatment and/or repeated treatments are sometimes needed on a case-by-case basis (according to imaging response).

Cysticercal encephalitis (countless cysticerci associated with signs/symptoms of intracranial hypertension)
Antiparasitic treatment ABSOLUTELY CONTRA-INDICATED.

- Control edema and intracranial hypertension with high and prolonged dose steroids (up to 16 mg/kg dexamethasone) and if needed osmotic diuretics and/or decompressive craniotomy.

Calcified lesions:

- Epileptic seizures remain possible due to inflammatory reaction on remnants or on gliosis scars.
- No need for antiparasitic treatment. Antiepileptic drugs and steroids in case of symptoms (and depending on reactive edema).
- No (preventive) treatment at all in case of incidental finding in asymptomatic individuals.

26.2.2 Extra-parenchymal neurocysticercosis (NCC)

Treatment is based on case series and low level of evidence.

26.2.3 Intraventricular NCC

- If possible, neurosurgical (endoscopic) removal of cysticerci (or fenestration) for the lateral and third ventricles; open surgery sometimes necessary for the fourth ventricle
- If not possible, ventriculoperitoneal shunt
  - + combination of albendazole and praziquantel as above (but often longer course, up to 3 months or sometimes longer, based on imaging response).
  - + dexamethasone (high dose as above) for at least 1-3 months

NB: methotrexate at < 20 mg/week may allow steroids reduction if prolonged treatment is necessary.

26.2.4 Subarachnoid (racemose) NCC

Basal cisterns or Sylvian fissure:

- Prioritize control of intracranial hypertension by ventriculoperitoneal shunt (prior to antiparasitic treatment),
  - + combination of albendazole and praziquantel as above (but often longer course, up to 3 months or sometimes longer, based on imaging response).
  - + dexamethasone (high dose as above) for at least 2-3 months; in case of associated arachnoiditis/ependymitis, up to 16 mg/kg!

Small cysts in the convexity of the subarachnoid space:

- Treat as intraparenchymal NCC.
- ALWAYS perform spinal MRI in case of subarachnoid NCC since in up to 60% of the cases clinically inapparent cysticerci may be present.

26.2.5 Ocular cysticercosis

ALWAYS surgery.

26.2.6 Spinal neurocysticercosis

Intramedullary or subarachnoid spinal cysts are usually treated with surgery, and adjunction of steroids and anti-helminthic drugs seems to improve the outcome (Barrie et al. 2020).

27 Dicrocoeliasis (Dicrocoelium dendriticum, D. hospes)

Selected References

1. https://dx.doi.org/10.1179/1364859411Y.0000000029 (Cabeza-Barrera et al. 2011)
2. https://dx.doi.org/10.1016/j.actatropica.2010.03.004 (Le Bailly and Bouchet 2010)

First-line treatment

- Praziquantel 25 mg/kg po tid x 1-2 days (+ mechanical removal of fluke in case of biliary obstruction).

Alternative regimens

- Triclabendazole 10 mg/kg po od x 1-2 days.

Special situations

The presence of eggs in feces often reflects a "spurious" infection (through intestinal passage of eggs after ingestion of infected animal liver). True infection with presence of adult fluke in the biliary tract is very rare and can only be ascertained by persistence of egg detection in repeated feces exams with a liver-free diet (or by imaging).

28 Diphyllobothriasis (D. latum, D. pacificum, D. nihonkaiense)

Selected References

1. https://dx.doi.org/10.1128/CMR.00033-08 (Scholz et al., 2009)
2. https://dx.doi.org/10.1016/S0140-6736(86)90532-5 (Waki et al. 1986)
3. https://dx.doi.org/10.1159/000067695 (Ignjatovic et al., 2003)

First–line treatment

- Praziquantel: usually 25-50 mg/kg po single dose (in fact 25 mg/kg for *D. latum*; 10 mg/kg is sufficient for *D. pacificum* and *D. nihonkaiense*); cure rate > 90%.
- Niclosamide 2 gr po single dose in adults; 1 gr po single dose in children ≥ 6 years; cure rate > 90%.

Alternative regimens

- Paromomycin 35-50 mg/kg po single dose; cure rate 96% in a small series (n=24).
- Gastrografin (400 ml): successful in some case reports, to restrict to refractory cases.

Special situations

Dipylidium caninum

- Very rare; same treatment as above.

Diplogonoporus grandis

- About 250 cases reported; same treatment as above but praziquantel and paromomycin maybe less effective; gastrografin 90% cure rate (expelled worm).

Dioctophyma renale

- < 20 cases reported
- Review: Ignjatovic I et al. Infestation of the human kidney with *Dioctophyma renale* ((Ignjatovic et al., 2003aUrol Int 2003; 70:70)
- Treatment of choice: nephrectomy; one case report of successful treatment with ivermectin.

29 Dirofilariasis

Selected References

1. https://dx.doi.org/10.1089/vbz.2010.0247 (Genchi, Kramer, and Rivasi 2011)
2. https://dx.doi.org/10.1128/CMR.00012-12 (Simón et al. 2012)
3. https://dx.doi.org/10.2478/s11686-013-0187-x (Sałamatin et al. 2013)
4. https://dx.doi.org/10.1111/jtm.12174 (Diaz 2015b)

29.1 *Dirofilaria immitis* (also called heartworm)

First-line treatment

- No treatment necessary or surgical removal (pulmonary coin lesion).

NB: surgery is almost always required for diagnosis (serology is not sensitive enough).

29.2 *Dirofilaria repens* (*D. tenuis, D. ursi, D. subdermata, D. striata*)

First-line treatment

- Surgical removal of subcutaneous nodule or ocular lesion.
- No further medical treatment.

NB: Case reports of anti-helminthic trial: diethylcarbamazine (DEC) (2 mg/kg po tid for 4 weeks) or ivermectin (150 µg/kg single dose).

30 Dracunculiasis (*D. medinensis*)

Selected References

1. https://dx.doi.org/10.1016/j.idc.2012.02.005 (Knopp, Steinmann, Keiser, et al. 2012)
2. https://dx.doi.org/10.1128/CMR.15.2.223-246.2002 (Cairncross, Muller, and Zagaria 2002)
3. https://dx.doi.org/10.1093/trstmh/tru039 (Al-awadi et al. 2014)
4. https://dx.doi.org/10.4269/ajtmh.1994.51.797 (Magnussen, Yakubu, and Bloch 1994)
5. https://dx.doi.org/10.4269/ajtmh.13-0638 (Eberhard and Ruiz-Tiben 2014)

First-line treatment

The only treatment with proven efficacy is the manual progressive extraction of the worm by winding it around a stick (within at least a period of two weeks). Massaging the skin around and cooling it down with ice can accelerate the extraction/mitigate the pain (*S. Knopp, personal observation in Togo*).
Consider systemic broad-spectrum antibiotics if bacterial superinfection is suspected; consider antibiotics in ointment for prevention of.

Controversially, the administration of Metronidazole (Flagyl®) 250 mg po tid x 10 days may facilitate the extraction of the worm (by decreasing the surrounding inflammation).
None of the anti-helminthic or anti-protozoan drugs is effective.
NB: Human infection with *Eustrongylides* can mimic dracunculiasis.

31 Echinococcosis

31.1 Alveolar echinococcosis (*Echinococcus multilocularis*)

Selected References

1. https://dx.doi.org/10.1097/QCO.0b013e32833d7516 (Kern 2010)
2. https://dx.doi.org/10.1016/j.actatropica.2009.11.001 (Brunetti, Kern, and Vuitton 2010)
3. https://dx.doi.org/10.1016/j.ijid.2008.03.037 (Moro and Schantz 2009)
4. https://dx.doi.org/10.1586/14787210.7.2.145 (Vuitton 2009)
5. https://dx.doi.org/10.1016/S0140-6736(03)14573-4 (McManus et al. 2003)
6. https://www.ncbi.nlm.nih.gov/pubmed/8789923(WHO 1996)
7. https://dx.doi.org/10.2967/jnumed.112.109942 (Caoduro et al. 2013)
8. https://doi.org/10.1128/cmr.00075-18 (H. Wen et al. 2019a)

Treatment is increasingly based on the PNM staging of the disease (see below).

TABLE 2 WHO Informal Working Group on Echinococcosis PNM classification and staging of alveolar echinococcosis[a]

Classification	Description
P	Hepatic localization of the parasite
PX	Primary AE lesion cannot be assessed
P0	No detectable AE lesion in the liver
P1	Peripheral lesion(s) without proximal vascular and/or biliary involvement
P2	Central AE lesion(s) with proximal vascular and/or biliary involvement of one lobe[b]
P3	Central lesion(s) with hilum vascular or biliary involvement of both lobes and/or with involvement of two hepatic veins
P4	Any liver lesion with extension along the vessels[c] and the biliary tree
N	Extrahepatic involvement of neighboring organs (diaphragm, lung, pleura, pericardium, heart, gastric and duodenal wall, adrenal glands, peritoneum, retroperitoneum, parietal wall [muscles, skin, bone], pancreas, regional lymph nodes, liver ligaments, kidney)
NX	Not evaluable
N0	No regional involvement[d]
N1	Regional involvement of contiguous organs or tissues
M	Absence or presence of distant metastases (lung, distant lymph nodes, spleen, central nervous system, orbital, bone, skin, muscle, kidney, distant peritoneum, and retroperitoneum)
MX	Not completely evaluated
M0	No metastasis[e]
M1	Metastasis
PNM stages	
I	P1 N0 M0
II	P2 N0 M0
IIIa	P3 N0 M0
IIIb	P1–P3 N1 M0, P4 N0 M0
IV	P4 N1 M0, any P any N and/or M1

[a]According to reference 88.
[b]For classification, the plane projecting between the bed of the gall bladder and the inferior vena cava divides the liver in two lobes.
[c]Vessels mean inferior vena cava, portal vein, and arteries.
[d]Including a negative chest X ray or thoracic CT result.
[e]Including a negative chest X ray or thoracic CT result as well as a negative brain CT result.

Source: Wen H *et al*. Echinococcosis: Advances in the 21st Century. *Clin Microbiol Rev.* 2019

First-line treatment

- Radical surgery with excision of lesion(s), with safety margin >2 cm, is the only curative treatment.
- + Albendazole 5-7,5 mg/kg po bid x 2 years.
- In case of non-radical surgery or stage P3, N1 and/or M1: albendazole 5-7,5 mg/kg po bid for several years/lifelong.

NB: Absorption of albendazole is fat dependent (to take with fatty meal). The optimal duration of albendazole treatment remains undetermined.

Monitor once/2 weeks the blood cell count (leucopenia <1%) and liver enzymes (elevation of transaminases 15%); some experts recommend blood controls every 3 months or based on (hepatic) symptoms.

Consider (if unfavorable evolution) to determine/monitor the albendazole-sulfoxide (metabolite) plasma level (target: 2-5 µmol/l; reduce dose if > 10 µmol/l); see with the WHO reference center of Besancon, France.

Follow-up with ultrasound every 6 months, and 18 FDG PET-CT/MRI + serology every 2 years; anti-infective treatment discontinuation is only recommended after a negative FDG-PET.
In immunosuppressed patients, all efforts should be made to reduce the level of immunosuppression; also, usually the medical treatment is poorly tolerated.

Alternative regimens (suboptimal)

- Palliative surgery, endoscopic stenting of biliary tract or liver transplantation.
- Albendazole for < 2 years, in case of toxicity or cost.
- Mebendazole 15 mg/kg po tid indefinitely (but usually considered as inferior to albendazole, because of poorer absorption).

Availability and costs

Albendazole: reimbursed at a maximum daily dose of 800 mg and for at least one year in this indication, following a medical report by an internist or ID specialist to the "medical advisor of the mutuality"; see additional and updated information via contact with ITM.

31.2 Cystic echinococcosis (*Echinococcus granulosus*)

Selected References

1. https://dx.doi.org/10.1371/journal.pntd.0001880 (Stojkovic et al. 2012)
2. https://dx.doi.org/10.1016/j.actatropica.2009.11.001 (Brunetti, Kern, and Vuitton 2010)
3. https://dx.doi.org/10.1371/journal.pntd.0000524 (Stojkovic et al. 2009)
4. https://dx.doi.org/10.1016/j.actatropica.2009.04.006 (Bygott and Chiodini 2009)
5. https://dx.doi.org/10.1016/S0140-6736(03)14573-4 (McManus et al. 2003)
6. https://dx.doi.org/10.1016/S0001-706X(02)00223-1 (Macpherson et al. 2003)
7. https://dx.doi.org/10.1056/NEJM199709253371303 (Khuroo et al. 1997)
8. https://doi.org/10.1128/cmr.00075-18 (H. Wen et al. 2019b)

Treatment of cystic echinococcosis (CE) depends on the cyst size, stage, location and presence of complications. Imaging (ultrasound, CT scan, MRI) is key for diagnosis and treatment.

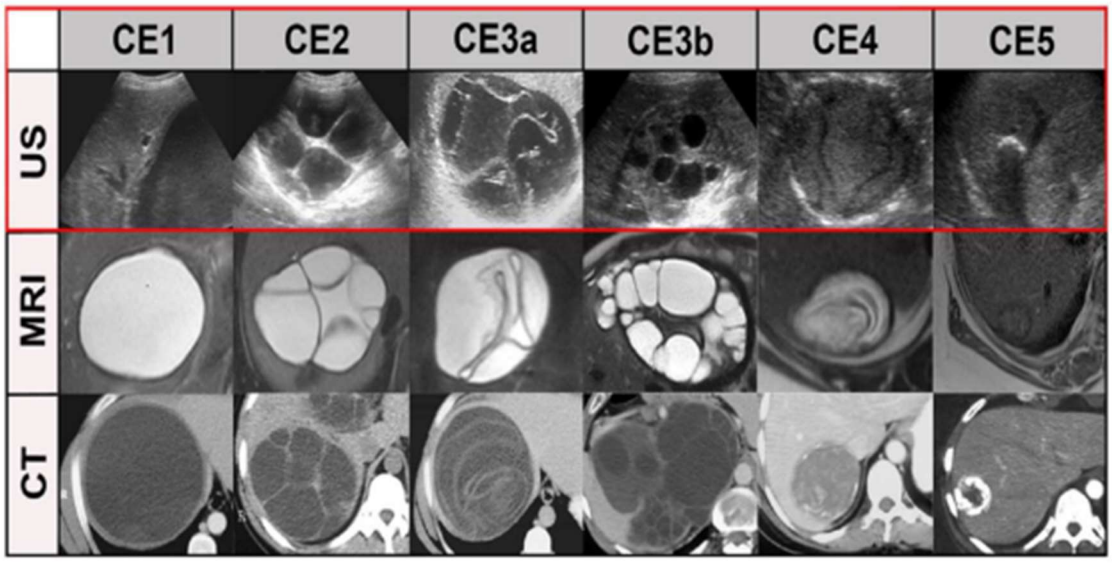


Figure 4. "Best case" of CT/MR imaging. CE1: unilocular, simple cysts with liquid content and often with the CE1-specific "double line sign", CE2: multivesicular, multiseptated cysts, CE3a: cysts with liquid content and the CE3a-specific detached endocyst, CE3b: unilocular cysts with daughter cysts inside a mucinous or solid cyst matrix, CE4: heterogenous solid cysts with degenerative, CE4-specific canalicular structure of the cyst content, and CE5: cysts with degenerative content and heavily calcified wall.

Source Figure: Stojkovic M *et al*. Diagnosing and Staging of Cystic Echinococcosis: How Do CT and MRI Perform in Comparison to Ultrasound? *PLoS Negl Trop Dis.* 2012

Preliminary remarks

- There are three types of treatment: medical, percutaneous or surgical.
- A "watch and wait" approach should always be considered (see indications below).
- If a treatment is necessary (big size, activity, location, complication...), consider always surgery first (in expert hands), since it is the only radical treatment with 100% efficacy.
- If percutaneous or surgical treatment is chosen, peri-interventional chemoprophylaxis combining albendazole and praziquantel is necessary to reduce the spillage-related risk of systemic seeding and secondary echinococcosis.
- Some experts and a meta-analysis (Velasco-Tirado et al. 2018) suggest that combining praziquantel to albendazole would have a higher scolicidal effect than albendazole alone in complex cases of CE. The evidence remains however very weak, and the dose and schedule of praziquantel administration (daily, weekly, monthly…) has not been determined. Also, such long administration would represent an important cost for the patient, with no certainty of clinical utility.
- WHO recommendations have been designed to offer also therapeutic options in low-resource settings

I. Active lesions (CE1 & CE2)

WHO Stage CE1 (unilocular non-echoic cystic lesion)

- < 5 cm: Albendazole 5-7,5 mg/kg po bid x 3-6 months (OR "wait and watch" if no risky location/no complication).

NB: Absorption of albendazole is fat dependent (to take with fatty meal). The optimal duration of albendazole treatment remains undetermined. When the medical treatment is started, there is a small risk (10%) of cyst leakage with worsening of symptoms, that often requires urgent surgery (better to inform the surgeon each time a medical treatment is initiated).
Monitor once/2 weeks the blood cell count (leucopenia <1%) and liver enzymes (elevation of transaminases 15%).
Mebendazole 15 mg/kg po tid x 3-6 months is a second-line option since its tissue penetration is less good than that of albendazole.

- 5 cm: Albendazole (5-7,5 mg/kg po bid) starting at dinner on the day before intervention and continued for at least 1 month (up to 3 months if overt spillage) + praziquantel (60-75 mg/kg po od) starting at dinner on the day before intervention for 1 day (if no apparent spillage), for 3-5 days (if unclear spillage), and for > 14 days (if overt spillage).

Percutaneous treatment
PAIR technique (puncture-aspirate-instillate [a scolicidal agent]-reaspirate) OR permanent catheterization (drain left in place until drainage > 10 ml/day; increasingly used for very large cysts > 10 cm) + peri-interventional chemoprophylaxis/drug therapy:

NB: Percutaneous treatment is only indicated for hepatic CE (70% of the cases).
PAIR has been developed for settings without advanced surgical facilities, but is also widely used in developed countries as it is minimally invasive, allows very short hospital stay and has a success rate > 80%; there exist some variations in the technical procedure (mini-laparotomy, laparoscopy...).

PAIR is contra-indicated if there is (on imaging) suspicion of biliary-cyst fistulae (risk of sclerosing cholangitis after injection of the scolicidal agent).
The scolicidal agents recommended by WHO are 0,5 % cetrimide solution or 70-95 % ethanol or 15-20 % hypertonic saline solution (less toxic in case of fistulae).
Praziquantel has an excellent protoscolicidal activity but has almost no effect on metacestodes.

WHO Stage CE2 (multiseptated, "rosette-like", "honeycomb" cyst)

First-line treatment
- Surgery (+ peri-interventional chemoprophylaxis as above).

Alternative regimen
- Albendazole (as above), but poor response.

NB: PAIR should be considered as contra-indicated: almost unfeasible and little effective (< 40% of response).

II. Transitional lesions

WHO Stage CE3A (cyst with detached membrane; "water-lily sign")

- < 5 cm: albendazole (as above for CE1 < 5 cm).
- > 5 cm: percutaneous treatment + peri-interventional chemoprophylaxis (as above for CE1 > 5 cm).

WHO Stage CE3B (cyst with daughter cysts in solid matrix)

First-line treatment
- Surgery (+ per-interventional chemoprophylaxis); see CE2.

Alternative regimen
- Albendazole (as above), but poor response.

III. Inactive lesions

WHO Stage CE4 (cyst with heterogeneous hypo-/hyperechoic contents, no daughter cysts)

Usually "wait and watch" attitude.

WHO Stage CE5 (solid cyst plus calcified wall)

Usually "wait and watch" attitude.

Availability and costs
Since 2019, albendazole (800 mg daily maximum for adults, and by periods of 6 months) is reimbursed by the INAMI/RIZIV provided that a request (short medical report) is elaborated and submitted to the mutuality by an internist or ID specialist; see additional and updated information through this link.

31.3 Other echinococcosis

Echinococcus vogeli and *E. oligarthrus* have been involved in a rare form of echinococcosis (polycystic echinococcosis); radical surgery is difficult, and treatment is similar to that of *E. multilocularis.* No human cases have been reported so far for *E. felidis* and *E. shiquicus*.

32 Enterobiasis/Oxyuriasis (*Enterobius vermicularis*, pinworm)

Selected References

1. https://dx.doi.org/10.1016/j.actatropica.2008.03.007 (L. Y. Wen et al. 2008)

First-line treatment

- Mebendazole: 100 mg po single dose, to repeat after 10-14 days.

NB: no effect on larvae and eggs!

Other important measures (eggs extremely resistant in environment, remaining infective for more than 5 weeks.

- Wash hands with soap after using the toilet
- Bath or shower the children once a day
- Change underpants
- Change bedclothes daily
- Cut fingernails short
- Consider cleaning regularly all toys
- ALWAYS treat the whole family at once with mebendazole

Alternative regimens

- Albendazole: 400 mg po single dose (> 2 years); 200 mg po single dose (1-2 years), to repeat after 10-14 days.
- Ivermectin: 200 µg/kg po single dose, to repeat after 10-14 days; less effective: cure rate 50%.
- (Pyrantel pamoate0 mg/kg (maximum 1 g) po single dose, to repeat after 10-14 days; not available in Belgium).

Special situations

In some exceptional refractory cases (after reinfection from close contact has been excluded), consider mebendazole 100 mg (or more effective albendazole 400 mg) po single doses every other week for at least 6 weeks (and even longer), in addition to all maximized other measures.
Safety of benzimidazoles and ivermectin in children < 1 year and < 15 kg, respectively, has not been studied.

Availability and costs

Albendazole: see additional and updated information via contact with ITM.
Ivermectin: see additional and updated information via contact with ITM.

33 Fascioliasis (Fasciola hepatica and F. gigantica)

Selected References

1. https://dx.doi.org/10.1097/QCO.0b013e3283567b7e (Cabada and White 2012)
2. https://dx.doi.org/10.1097/QCO.0b013e32830f9818 (Marcos, Terashima, and Gotuzzo 2008)
3. https://dx.doi.org/10.1002/hep.1840140620 (Bacq et al. 1991)
4. https://dx.doi.org/10.1371/journal.pntd.0004361 (Cabada et al. 2016)
5. https://dx.doi.org/10.1111/j.1469-0691.2004.00820.x (Saba et al. 2004)
6. https://doi.org/10.2147/rrtm.s237461 (Caravedo and Cabada 2020)

First-line treatment

- Triclabendazole (Egaten® 250 mg tablets) 10 mg/kg po od x 2 days (> 80% cure rate) (Gandhi et al. 2019)

NB: To take with a high fat meal. In case of severe and/or chronic infections, or if treatment failure: triclabendazole 20 mg/kg po od x 2 days (not in children < 6 years).
Add steroids in case of acute fascioliasis; consider endoscopic removal of flukes and antibiotics in case of biliary obstruction.

High rates of treatment failure are increasingly reported from endemic countries (Peru...), in relation probably with massive use of triclabendazole in cattle (Morales et al. 2021).
Retrospective case series suggest a limited additional therapeutic yield with higher dosage or repeated treatment rounds (up to four), but no increased toxicity (Angélica Terashima et al. 2021).

Alternative regimens

- Nitazoxanide 1-3 years 100 mg; 4-11 years 200 mg; > 12 years 500 mg po bid x 7 days. Cure rate 50-100%; does not seem very effective in case of fascioliasis refractory to triclabendazole and is therefore not really an alternative is such cases.(Ramadan et al. 2019).

NB: Very expensive and not available in Belgium.

- Bithionol 15 mg/kg po tid on alternate days x 10-15 days. Cure rate 100%.

NB: Not available in Belgium; unsecure production. Very low cure rate with praziquantel.

Special situations

Pregnancy:

- Little data on triclabendazole; need of benefit/risk balance case by case.

Second-line treatment failure:

- In case of failure of second-line therapy (triclabendazole 20 mg/kg x 2 days), consider combination of triclabendazole with ivermectin, or ketoconazole or an artemisinin (case reports), or with nitazoxanide (7 cases); consider also albendazole for 14 days.

Availability and costs

Triclabendazole: see additional and updated information via contact with ITM.

34 Filariasis

34.1 Loiasis (*Loa loa*)

Selected References

1. https://dx.doi.org/10.1016/j.idc.2012.02.005 (Knopp, Steinmann, Hatz, et al. 2012)
2. https://dx.doi.org/10.1111/j.1708-8305.2012.00605.x (Boussinesq 2012)
3. https://dx.doi.org/10.1179/136485906X112194 (M. Boussinesq 2006)
4. https://dx.doi.org/10.1016/S0140-6736(96)11094-1 (Jacques Gardon et al. 1997)
5. https://dx.doi.org/10.1086/598654 (Horton and Nutman 1999)
6. https://dx.doi.org/10.1056/NEJM198809223191204 (Nutman et al. 1988)

Treatment of *loiasis* relies on the initial quantification of the microfilaremia, since DEC (and to a lesser extent ivermectin) may cause encephalitis by abrupt lysis of the blood microfilaria.
Low microfilaremia is usually expressed in microfilaria/ml of blood after a Knott concentration test. High parasitemia, for which the Knott test is not necessary, is expressed in microfilaria/20 µl of blood after observing a calibrated thick blood smear. As an example, 1 microfilaria/20 µl blood corresponds to 50 microfilaria per ml.

Absence of microfilaremia or microfilaremia below 1000/ml:
DEC should not cause any severe reaction: 200 mg (or 3-4 mg/kg) po bid x 21 days.
However, it is safer to increase progressively the dose

- D1 x 25 mg (adults) – 1 x 0,5 mg/kg (children).
- D2 x 50 mg (adults) – 1 x 1 mg/kg (children).
- D3: 2 x 50 mg (adults) – 2 x 1 mg/kg (children.)
- D4 x 200 mg (adults) – 1 x 4 mg/kg (children).
- From D5 and up to D21: 2 x 200 mg/day (adults) – 2 x 4 mg/kg/day (children).

It is common practice to administer systematically antihistaminic and prescribe steroids in case of need.
It is important to first rule out concomitant onchocerciasis if there is any suspicion (risk of severe eye damage with DEC).

Often (20-60% of the cases), the treatment will be repeated after a one month until complete disappearance of symptoms or normalization of eosinophil count.
There is no *Wolbachia* endosymbiots in *Loa loa* (and therefore no utility of doxycycline treatment).

Microfilaremia between 1000 and 8000 microfilaria/ml:
About 30% of patients will have moderate adverse events.

- Either DEC with gradual increasing dose, together with systematic antihistaminic AND steroids; consider short initial admission
- Or first ivermectin 200 µg/kg po single dose (reduction to 10% of the initial load, persisting up to one year), and administration of DEC after one month (when the microfilaremia is < 1000/ml) (Pion et al. 2019)
- Or first albendazole 200 mg po bid x 21 days, and administration of DEC about 6 months later (much slower microfilaria clearance, and absence of adverse event).
- Levamisole (2,5 mg/kg single dose) can produce a fast and moderate decrease of the microfilaremia (within a few days, and with no adverse events) prior DEC administration, but this drug is not available anymore in Belgium (Campillo et al. 2021).

Microfilaremia > 8000/ml:

- DEC absolutely contra-indicated (high risk of encephalitis and death).
- The risk of encephalitis with ivermectin is also at about 1% and is therefore contra-indicated for most experts.
- Discuss the option of plasmapheresis/apheresis (UZA), followed by DEC (as above)
- Consider administration of albendazole for 21 days (or more), possibly followed by ivermectin and ultimately DEC (as above).
- Discuss abstention and observation (if no/mild symptom).

NB: a pilot RCT using reslizumab (an anti- IL5 antibody) in loiasis patients did not show any effect on post-DEC adverse events despite good control of the post-DEC eosinophil count rise (Legrand et al. 2021).

Special situations

Prevention for travelers

- Very rarely indicated (long stay in high-risk rural area).
- DEC: 300 mg/week.

Non-availability of DEC:

In such situation, which is increasingly frequent in European countries, the only alternative is a course of albendazole 400 mg bid x 21 or 28 days (based on a small RCT in Cameroon and a retrospective case series in Italy) (Gobbi et al. 2018; 2019). Because this option has been poorly studied among travelers/migrants, it is important to carefully follow-up for possible relapse of symptoms or persistence of microfilaremia or eosinophilia. It is possible that additional courses of albendazole are needed since the efficacy is notoriously lower than that of DEC

Availability and costs

Diethylcarbamazine (DEC, Notezine): frequent stockouts; possibility of importation with a medical attestation; see additional and updated information via contact with ITM.
Ivermectin: see additional and updated information via contact with ITM.
Albendazole: see additional and updated information via contact with ITM.

34.2 Lymphatic filariasis (*Wuchereria bancrofti, Brugia malayi, Brugia timori*)

Selected References

1. https://doi.org/10.1016/j.idc.2012.02.005 (Knopp, Steinmann, Keiser, et al. 2012)
2. https://doi.org/10.1016/S0140-6736(10)60586-7 (Taylor, Hoerauf, and Bockarie 2010)
3. https://doi.org/10.1007/s00430-007-0062-1 (Hoerauf et al. 2008a)
4. https://doi.org/10.1016/S0140-6736(05)66591-9 (Taylor et al. 2005)
5. https://doi.org/10.1086/501351 (Turner et al. 2006)

First-line treatment

Doxycycline 100 mg po bid for 4-6 weeks.

- Anti-*Wolbachia* chemotherapy, with a macrofilaricidal effect.
- More effective than diethylcarbamazine (DEC) against adult worms (cure rate 85% in endemic settings).
- Less adverse events due to the slower die-off of the parasites (compared to DEC).

Followed by albendazole 400 mg po single dose.

- Some effect on adult worms and microfilaria.

And diethylcarbamazine 6 mg/kg po single dose.

- Rapid microfilaricidal effect.

- Some effect on adult worms.

NB: Administering these 3 drugs sequentially should minimize the risk of adverse event (due to parasite clearance) and maximize the macrofilaricidal effect. In case side effects occur, add steroids.
Much research is ongoing to identify short-course anti-*Wolbachia* therapy (tylosine A...).

Alternative regimens
Diethylcarbamazine (DEC; Notezine®) 3 - 4 mg/kg po bid x 2 weeks with an initial gradual increase:
- D1 x 25 mg (adults) – 1 x 0,5 mg/kg (children).
- D2 x 50 mg (adults) – 1 x 1 mg/kg (children).
- D3: 2 x 50 mg (adults) – 2 x 1 mg/kg (children).
- D4 x 200 mg (adults) – 1 x 4 mg/kg (children).
- Since D5: 2 x 200 mg/day (adults) – 2 x 4 mg/kg/day (children); followed by po a single dose of albendazole 400 mg.

Repeat po single doses of albendazole 400 mg and DEC 6 mg/kg po after 3, 6, 12 months (not clearly defined) because these two drugs are not macrofilaricidal.

NB:
- Exclude concomitant onchocerciasis before administering DEC (risk of severe eye damage).
- Avoid administering DEC during the acute lymphangitic phase since symptoms may severely worsen.
- Administer antihistaminic and steroids in case of DEC-related symptom exacerbation.
- Treatment of an episode of acute adeno-lymphangitis consists of rest (hospital admission), hydration and local/systemic antibiotic therapy since bacterial superinfection is almost always present (in 97 % of cases, when lymphoedema has been present for a long time).
- Treatment of lymphedema/elephantiasis requires strict local hygiene, elevation of the legs and aggressive therapy of any bacterial/mycotic superinfection. Surgery is often disappointing.

Special situations
Lymphatic filariasis in children < 8 years and pregnant women:
- DEC (see alternative regimen) remains the first choice

Tropical pulmonary eosinophilia:
- First-line treatment: DEC 2 mg/kg po tid x 12-21 days + steroids
- Alternative regimen: ivermectin 200 µg/kg single dose + steroids (followed by doxycycline/DEC/albendazole, as first-line here above)

NB: in this condition, which is related to allergic reaction on microfilaria, DEC is the first choice to obtain a rapid clearance of the microfilaria (exclude first concomitant onchocerciasis).

Prevention for travelers:
- Very rarely indicated (only for long stays in high-risk rural areas).
- DEC 6 mg/kg po single dose every 6 months OR DEC 400 mg/day x 2 days once a month.
- Control and prevention of transmission in endemic countries.

WHO has recommended since about 20 years annual or semiannual administration of single dose of albendazole combined with either DEC (outside Africa) or ivermectin (in Africa) to decrease the proportion of carriers of microfilaremia, and therefore decrease the transmission in the community. This has led to improved control in most endemic areas, although not sufficient everywhere. Since the demonstration by a large RCT in Papua New Guinea that a single-dose triple-therapy (ivermectin, DEC, albendazole) was superior to the two-drug regimens in the long-term suppression of blood microfilaria, this has become the preferred "preventive" chemotherapy in endemic countries outside Africa (King et al. 2018).

34.3 Mansonellosis

Selected References

1. https://dx.doi.org/10.1016/j.actatropica.2010.01.014 (Simonsen, Onapa, and Asio 2011)
2. http://ajol.info/index.php/ajid/article/view/55085 (Downes and Jacobsen 2010)
3. https://dx.doi.org/10.1056/NEJMoa0900863 (Coulibaly et al. 2009a)
4. https://dx.doi.org/10.1016/j.trstmh.2005.07.009 (Bregani et al. 2006)
5. https://dx.doi.org/10.1016/S0035-9203(02)90112-4 (J. Gardon et al. 2002)
6. https://dx.doi.org/10.1016/J.NMNI.2018.08.016 (Mediannikov and Ranque 2018)
7. https://dx.doi.org/10.2147/RRTM.S125750 (Ta-Tang et al. 2018)

34.3.1 Mansonella perstans

A treatment is not always necessary except in case of associated allergic manifestations and/ or severe eosinophilia.

First-line treatment

- Doxycycline 100 mg po bid for 6 weeks.

NB: Some *M. perstans* strains harbor *Wolbachia* but other not; doxycycline has been efficacious in several RCTs in Mali (Coulibaly et al. 2009b), Ghana (Weiskopf et al. 1987),…. Even if activity seems inconsistent, most experts consider this treatment is worth a try.

Alternative regimens

(If no clinical response or contra-indications of doxycycline).

- DEC 200 mg + mebendazole 100 mg po bid x 21 days.

NB:

- DEC in monotherapy is only partially effective, even if administered for 21 days.
- DEC and mebendazole in monotherapy are inferior to the combination of both drugs.
- Albendazole, ivermectin and even the combination of both are largely insufficient (although repeated doses of ivermectin (200 µg/kg) every 3 months seemed effective in one retrospective study).
- Levamisole (Ergamisol®) was previously used in combination with mebendazole (based on old small studies in DR Congo), but is not produced anymore since 2010.

For information, treatment schedule used previously at ITM:

- *Day 1:* Ergamisol® three 50 mg tablets od 11 PM
- *Day 2*: Vermox® one 500 mg tablet tid
- *Day 3:* Vermox® one 500 mg tablet tid
- Ergamisol® three 50 mg tablets of around 11 PM
- *Day 4:* Vermox® one 500 mg tablet tid
- *Day 5:* Vermox® one 500 mg tablet tid
- Ergamisol® three 50 mg tablets od around 11 PM
- *Day 6 to 16 included:* Vermox® one 500 mg tablet tid
- *Day 35:* (5 weeks after the beginning of the treatment): blood test (eosinophilia, IgE, microfilaria concentration)

34.3.2 Mansonella streptocerca

First-line treatment

- DEC 200 mg po bid x 21 days + ivermectin 200 µg/kg po single dose (if symptomatic, since symptoms are due to microfilaria).

NB: it is worth a try with doxycycline, although the presence of *Wolbachia* and efficacy of doxycycline have not been explored.

34.3.3 Mansonella ozzardi

First-line treatment

- Doxycycline 100 mg po bid x 6 weeks (*M. ozzardi* harbors *Wolbachia,* but doxycycline has never been tested) + ivermectin 200 µg/kg po single dose (if symptomatic, since symptoms are due to microfilaria)

NB: DEC is ineffective; ivermectin is very effective in reducing microfilaremia (De Almeida Basano et al. 2018).

Availability and costs

Diethylcarbamazine (DEC, Notezine): frequent stockouts; possibility of importation with a medical attestation; see additional and updated information via contact with ITM.
Ivermectin: see additional and updated information via contact with ITM.

34.4 Onchocerciasis (*Onchocerca volvulus*)

Selected References

1. https://dx.doi.org/10.1016/S0140-6736(10)60586-7 (Taylor, Hoerauf, and Bockarie 2010)
2. https://dx.doi.org/10.1007/s00430-007-0062-1 (Hoerauf et al. 2008b)
3. https://dx.doi.org/10.1128/CMR.00057-10 (Tamarozzi et al. 2011)
4. https://dx.doi.org/10.1086/509325 (Udall 2007)
5. https://dx.doi.org/10.1016/S0140-6736(00)02095-X (Hoerauf et al. 2000)
6. https://dx.doi.org/10.1016/S0140-6736(00)04581-5 (Hoerauf et al. 2001)
7. https://dx.doi.org/10.1016/S0140-6736(02)09456-4 (Jacques Gardon et al. 2002)
8. https://doi.org/10.1016/j.actatropica.2020.105677 (Brattig, Cheke, and Garms 2021)

First-line treatment

- Doxycycline 100 mg po bid x 6 weeks (about 60% of macrofilaricidal effect in endemic countries in various large RCTs).
- + ivermectin 200 µg/kg po single dose (microfilaricidal, either in the beginning of the treatment if low microfilaria load, or after 4 months if high microfilaria load).

Alternative regimens

- Ivermectin 200 µg/kg po single dose once or twice a year for several years (up to 10 - 15 years, depending on recurrence of symptoms or eosinophilia).

NB1:

- DEC is absolutely contra-indicated
- Perform an eye examination (only if high microfilaria load), and consider adding steroids (prednisone 1 mg/kg/day) if microfilaria are present in the anterior chamber
- Surgical removal of cosmetically or mechanically disturbing skin nodules may be considered
- Rule out concomitant *loiasis*

NB2: Adjunction of single dose albendazole to ivermectin did not reduce the load of macro- and microfilaria compared to ivermectin alone (Debrah et al. 2020).

Special situations

Control and prevention of transmission in endemic countries:

- Annual or semiannual administration of single dose of ivermectin (microfilaricidal) is used since > 20 years to treat/prevent morbidity and interrupt transmission in endemic areas, with undeniable success.
- A new drug moxidectin (not yet available in clinical practice) has recently demonstrated higher activity than ivermectin in reducing the skin microfilaria load in a large phase 3 RCT (Opoku et al. 2018), bringing much hope to accelerate the elimination of onchocerciasis in endemic countries (Milton et al. 2020).

Availability and costs

Diethylcarbamazine (DEC, Notezine): frequent stockouts; possibility of importation with a medical attestation; see additional and updated information via contact with ITM.

Ivermectin: see additional and updated information via contact with ITM.

35 Gnathostomiasis (Gnathostoma spinigerum, G. binucleatum, ...)

Selected References

1. https://dx.doi.org/10.1111/jtm.12212 (Diaz 2015a)
2. https://dx.doi.org/10.1128/CMR.00003-09 (Herman and Chiodini 2009)
3. https://dx.doi.org/10.3201/eid1707.101433 (Katchanov et al. 2011)
4. https://dx.doi.org/10.1016/0035-9203(92)90248-B (P. Kraivichian et al. 1992)
5. https://dx.doi.org/10.4269/ajtmh.2009.80.33 (Strady et al. 2009)
6. http://www.ncbi.nlm.nih.gov/pubmed/16124432 (Nontasut et al. 2005)
7. http://www.ncbi.nlm.nih.gov/pubmed/15569795 (K. Kraivichian et al. 2004)
8. http://www.ncbi.nlm.nih.gov/pubmed/17120960 (Bussaratid et al. 2006)
9. https://dx.doi.org/10.1086/322625 (Chappuis, Farinelli, and Loutan 2001)
10. https://dx.doi.org/10.4269/ajtmh.2003.69.67 (Chai et al. 2003)
11. https://dx.doi.org/10.1016/0022-510X(90)90136-B (Punyagupta, Bunnag, and Juttijudata 1990)

First-line treatment

Single superficial lesion, or ocular lesion:

- Surgical excision.

Multiple/deep/systemic lesions:

- Either albendazole 400 mg po bid x 21 days (or 7,5 mg/kg po bid x 21 days).
  Cure rate in endemic regions: 80-95%.
  Relapses are frequently observed in travelers (up to 60% in 13 travelers); at least 12 months follow-up is advised.
- Or ivermectin 200 µg/kg po od x two consecutive days.
  Cure rate of 90% is achieved with ivermectin for two consecutive days.
  One-day ivermectin does not seem sufficient (cure rate < 75%).

NB1: some experts recommend combining immediately both first-line treatments in case of cutaneous/visceral larva migrans "close to the CNS" (head, neck, proximity of spine)

NB2: Latin American experts have observed that *Gnathostoma* larvae tend to emerge through the skin within 7 - 14 days after albendazole administration (diagnostic method). In fact, there are very few publications on post-treatment percutaneous larval emergence, but this seems to also occur after exposure to ivermectin or even praziquantel. Of note spontaneous emergence is extremely rare (Sapp et al. 2019).

Special situations

In case of relapse:
Give the alternative first-line treatment which has not been administered; some experts recommend combining both.

In case of neurological involvement (neurognathostomiasis):
It is common practice to add steroids (1 mg/kg/day prednisolone) to albendazole (400 mg po bid x 21 days), although no study could demonstrate any clear benefit, including the largest one.

Availability and costs

Ivermectin: see additional and updated information via contact with ITM.
Albendazole: see additional and updated information via contact with ITM.

36 Hymenolepiasis: *Hymenolepis nana* (dwarf tapeworm), *H. diminuta* (rat tapeworm)

Hymenolepis nana is the most frequent tapeworm infection in the world. *H. diminuta* is very rare in humans.

Selected References

1. https://dx.doi.org/10.1016/j.cmi.2015.01.004 (R. C. A. Thompson 2015)
2. https://dx.doi.org/10.1371/journal.pntd.0002321 (Soares Magalhães et al. 2013)
3. https://dx.doi.org/10.1016/S0035-9203(02)90301-9 (Ortiz et al. 2002)

First-line treatment

- Praziquantel (Biltricide®): 25 mg/kg po single dose (cure rate: 95%).
  Treat the whole family systematically.
  Consider repeating the same treatment 10-14 days after the first course (possibility of reinfection/autoinfection).

- Niclosamide (Yomesan®)
  - Adults: 2 gr po od x 7 days (to chew or crush at intake!).
  - Children1 - 34 kg: 500 mg po od x 7 days; 34-50 kg gr po od x 7 days.

ALWAYS repeat treatment after 10-14 days.

NB: longer and repeated treatments are needed because niclosamide is little effective against the cysticerci present in the intestinal wall (in contrast with praziquantel).

Alternative regimens

- (Nitazoxanide-3 years 00 mg; 4 - 11 years: 200 mg; > 12 years 500 mg po bidfor 3 days; cure rate 75-90%; not available in Belgium, and very expensive).

Availability and costs

Praziquantel: see additional and updated information via contact with ITM.

37 Intestinal flukes (Fasciolopsis buski, Echinostoma spp., Haplorchis spp., Gastrodiscoides hominis, Heterophyes heterophyes, Metagonimus yokogawai, Nanophetus salmincola, ...)

Selected References

1. https://dx.doi.org/10.1007/978-1-4939-0915-5 (Toledo et al. 2016)
2. https://dx.doi.org/10.1136/bmj.e4093 (Fürst et al. 2012)
3. https://dx.doi.org/10.1128/CMR.00012-09 (Keiser and Utzinger 2009)

First-line treatment

- Praziquantel 25 mg/kg po single dose.

NB: efficacy varies between 10 and 25 mg/kg depending on the species; however accurate identification of species is very difficult.

Alternative regimens

- Other drugs that may be active, but have been hardly studied: triclabendazole, albendazole, niclosamide, artemisinin derivates, ...

Special situations

- In case of treatment failure, give praziquantel 25 mg/kg po tid x 1 day. No resistance has been described.

Availability and costs

Praziquantel: see additional and updated information via contact with ITM.

38 Oesophagostomiasis

May be due to *Oesophagostomum bifurcum, O. stephanostomum, O. apiostomum, O. aculeatum*.
Eggs in feces are similar at microscopy to those of *Ancylostoma spp*.

Selected References

1. https://dx.doi.org/10.1016/S0035-9203(00)90267-0 (Storey et al. 2000)

First-line treatment

- Albendazole 200 mg (children 1-2 years) or 400 mg (adults and children > 2 years) po single dose.
- Surgery may be necessary in the case of complications.

Alternative regimen

- Pyrantel pamoate 10 mg/kg (max 1g) po od x 3 days (not available in Belgium).

Availability and costs

Albendazole: see additional and updated information via contact with ITM.

39 Paragonimiasis (Lung fluke)

Due to many different species of *Paragominus spp*., including (not exhaustive) *P. westermani* (Asia), *P. siamensis* (Thailand), *P. heterotremus* (China), *P. africanus* and *P. uterobilateralis* (West Africa), and *P. kellicotti* and *P. mexicanus* (North/Central/South America).

Selected References

1. https://dx.doi.org/10.1016/B978-0-444-53490-3.00023-6 (Chai 2013)
2. https://dx.doi.org/10.1016/S0035-9203(98)90919-1 (Calvopiña et al. 1998)

First-line treatment

- Praziquantel: 25 mg/kg po tid x 2 - 3 days; cure rate 90-100%.

NB: a recent retrospective case series of 11 pediatric cases from China showed a high rate of failure (63%) with one 3-day course of praziquantel, with frequent need to repeat the praziquantel courses (up to 3 times) or to switch to triclabendazole (M. Qian et al. 2021).

Alternative regimens

- Triclabendazole**:** 10 mg/kg po bid x 1 day (with a fat rich meal); cure rate: 90-100%.
- (Bithionol: 30-50 mg/kg/day po on alternate days for 10-15 doses; not available in Belgium).

Special situations

- Cerebral paragonimiasis/eosinophilic meningitis
- Praziquantel 25 mg/kg po tid x 14 days + steroids (at "cerebral" dosage), and sometimes neurosurgery.

Availability and costs

Praziquantel: see additional and updated information via contact with ITM.
Triclabendazole see additional and updated information via contact with ITM (remains the second choice because of the higher cost).

40 Schistosomiasis

Main causative species: *Schistosoma haematobium* (genitourinary schistosomiasis) and *S. mansoni* (hepatointestinal schistosomiasis). Other geographic-specific species: *S. japonicum, S. mekongi, S. intercalatum, S. mattheei, S. malayensis, S. guineensis, …* (all of them causing hepato-intestinal schistosomiasis). In recent years, molecular techniques have allowed increasingly identifying hybrid infections (*S. bovis/S. haematobium*, *S. mattheei/S. haematobium*), with less classic clinical presentations

Selected References

1. https://dx.doi.org/10.1016/S0140-6736(13)61949-2 (Colley et al. 2014)
2. https://dx.doi.org/10.1097/NRL.0b013e3182704d1e (Vale, De Sousa-Pereira, et al., 2012)
3. https://dx.doi.org/10.1007/s11910-012-0305-4 (Carod Artal, 2012a)
4. https://dx.doi.org/10.1016/S0140-6736(06)69440-3 (Gryseels et al. 2006)
5. https://dx.doi.org/10.1111/j.1469-0691.2009.03131.x (Jauréguiberry, Paris, and Caumes 2010)
6. https://dx.doi.org/10.1016/j.jinf.2005.07.022 (Bottieau et al. 2006)
7. https://dx.doi.org/10.3201/eid1209.060113 (Clerinx et al. 2006)
8. https://dx.doi.org/10.1016/0924-8579(94)90032-9 (V. Kumar and Gryseels 1994)
9. https://dx.doi.org/10.1016/0140-6736(93)91743-6 (Flisser et al. 1993)
10. https://dx.doi.org/10.1016/S1473-3099(15)00345-X (Olveda et al. 2016)
11. https://dx.doi.org/10.1080/00034983.1989.11812373 (Richards Jr. et al. 1989)
12. https://dx.doi.org/10.1128/AAC.47.5.1487-1495.2003 (Utzinger et al. 2003)
13. https://doi.org/10.1016/j.pt.2020.05.009 (Gobbi et al. 2020)

40.1 Acute schistosomiasis (Katayama syndrome)

First-line treatment

Praziquantel (Biltricide®, tablet of 600 mg at ITM): 20-30 mg/kg po bid x 2 days.

- To associate (in case of symptoms) systematically with methylprednisolone (Medrol®) 0.5-1 mg/kg po odfor 7 days (rapid tapering).

NB1: Methylprednisolone 0,5 mg/kg od x 3 days is probably sufficient in most cases (*Clerinx J, personal observation, not yet published*).

NB2: Since steroids substantially decrease the praziquantel blood concentration, the administration of the two doses of praziquantel could be given with 2 hours apart, followed 2 hours later by the administration of steroids (*Clerinx J, personal observation, not yet published*).

- Repeat a single dose praziquantel 40 mg/kg po 3 months after suspected moment of infection (or 6-8 weeks after onset of Katayama symptoms).

NB3:Treatment of acute schistosomiasis remains controversial and there is no well-established therapeutic protocol; some groups consider praziquantel as useless (no activity against young [7-28 days] schistosomulae) or even dangerous (risk of clinical exacerbation in up to 50% of the patients).
However, at ITM, we prefer to administer immediately praziquantel at least if the diagnosis is made 4-6 weeks after infection (and not to wait until 3 months), for three reasons:

- At diagnosis (after 6 weeks), some adult worms are already present (on which praziquantel is active).
- Activity is limited against schistosomulae, but may help control the parasitic load.
- There is a small but existing risk of early neuroschistomosiais due to embolization of emerging adults or eggs.

There is demonstrated activity of artemisinin derivates and mefloquine against schistosomulae, but no study has been conducted so far in non-immune travelers, so that no recommendation about their use can be made.

Consider adding ivermectin 200 µg/kg single dose if steroids are administered, in case concomitant strongyloidiasis is suspected or confirmed.

40.2 Chronic schistosomiasis (early and late)

First-line treatment

- Praziquantel (Biltricide®, tablet of 600 mg at ITM): 40 mg/kg po single dose.

NB1: This dosage is recommended by WHO as suppressive treatment in endemic areas. It is probably sufficient in most (light) chronic infections (only serologically positive) seen in non-endemic countries, but this has not been evaluated as such in the post-travel setting, leading here again to varied treatment protocols (with higher dosage/multiple day praziquantel regimens) (Cucchetto et al. 2019).
Indeed, since the cure rate is not 100% with the WHO-recommended dosage, some National Societies of Tropical Medicine recommend higher doses, i.e., 60 mg/kg od x 2 days (Swiss) or 40 mg/kg od x 3 days (German). At ITM, the single-dose 40 mg/kg may be repeated every 1 to 3 months until normalization of the eosinophilia and disappearance (or complete calcification) of the eggs.

NB2: Moderate systemic and gastro-intestinal side effects are often reported, probably somehow related to parasite lysis (better to administer during a day-off).

NB3: Consider ruling out concomitant neurocysticercosis (by serology) in patients from endemic regions before giving praziquantel as this may provoke seizures (although this risk appears extremely limited in endemic areas).

NB4: In migrants with detectable eggs in feces/urines, consider assessing the presence of organ-specific damages by ultrasound examination (either liver or urinary tract).

Alternative regimens

- (Metrifonate: active only against *S. haematobium*: not produced anymore).
- (Oxamniquine: active only against *S. mansoni* (cure rate > 80% at 15 mg/kg single dose, but resistance has emerged in Brazil…): not available in Belgium.

Special situations

Pregnancy

- To date, no mutagenic, teratogenic or embryotoxic effects have been observed with praziquantel. Although human data are limited, WHO concluded that there is no contra-indication after the first trimester. Risks of treatment during the first trimester should be balanced with the risks of schistosomiasis (which are not negligible!). A recent phase 2 trial (n=370) in pregnant women did not detect any safety signal.
- Infection due to *S. japonicum* (or *S. mekongi*).
- The most studied (and therefore recommended) regimen for these zoonotic Asian species) is praziquantel 25 mg/kg po tid x 1 or 2 days.

Neuroschistosomiasis (*cerebral or myeloradiculopathy*):

- Methylprednisolone 1 mg/kg od for 1-2 months, followed by tapering for up to 6 months (or shorter in case of earlier full recovery).

  - Consider an initial attack dose of 15 mg/kg/day prednisolone (max. 1 gr) for 5 days in case of myeloradiculopathy.
  - Neurosurgery and removal of lesions in case of intracranial hypertension.
- Combined with praziquantel
  - Either 30 mg/kg bid /day x 14 days (based "only" on animal experiments or
  - 30 mg/kg bid on days 0 (controversial), 30, 60 and 90 (based on expert opinion only).

In fact, there is no consensus on the schedule, dose and length of the praziquantel treatment for neuroschistosomiasis. Evidence obtained through multiple case reports is extremely variable (see recommended reviews here above: Vale TC et al. and Carod Artal FJ). (Carod Artal, 2012b; Vale, de Sousa-Pereira, et al., 2012)

(Post-exposure prophylaxis)
Since artemisinin compounds are active on young schistosomes, this could be an option in the future. However, it would need to be administered "immediately" (to kill the cercaria, just after bathing), or after one week (no activity before 7 days). No study with clinical outcome has been published so far. No specific measure has been proven effective after a "risky" bathing.

Availability and costs
Praziquantel: see additional and updated information via contact with ITM.

41 Sparganosis

Proliferative (*Sparganum proliferum*) or non-proliferative (*Spirometra mansoni, S. mansonoides, S. ranarum, S. theileri,…*)

Selected References

1. https://dx.doi.org/10.1016/S1473-3099(15)00133-4 (Q. Liu et al. 2015)
2. https://dx.doi.org/10.1016/B978-0-444-53490-3.00027-3 (Lescano and Zunt 2013)

First-line treatment

For localized cutaneous lesion:

- Surgical removal or local injection of ethanol procaine 40%.

For visceral form:

- Praziquantel 30-40 mg/kg (adults) or 50 mg/kg (children) po bid for 2 to 7 days (sometimes to repeat), or sometimes surgery.

For neurosparganosis:

- Classically, either radical surgery (followed by a 4-day administration of praziquantel as here above, or praziquantel associated with corticosteroids were recommended, but with no clear dosage and duration schedule (to taper according to clinical/radiological response)

A retrospective multicentric case series on neurosparganosis in China (n>100) suggests that high dose praziquantel (either 50 mg/kg/day for 10 days or 75 mg/kg/day for 7 days) is “as effective” as neurosurgery in selected cases (and should be considered for inoperable cases(Hong et al. 2018)). There was no systematic use of corticosteroids in those centers (only if allergy/deterioration). The course of praziquantel was repeated monthly till complete disappearance of lesions at imaging (max 8 cycles). Cure rate was 90% for both the medical and surgical treatment groups.

Availability and costs

Praziquantel: see additional and updated information via contact with ITM.

42 Strongyloidiasis

Selected References

1. https://dx.doi.org/10.1136/bmj.f4610 (Greaves et al. 2013)
2. https://dx.doi.org/10.1371/journal.pntd.0002002 (Requena-Méndez et al. 2013)
3. https://dx.doi.org/10.1517/14656566.5.12.2615 (Igual-Adell et al. 2004)
4. https://dx.doi.org/10.4269/ajtmh.1989.40.304 (Naquira et al. 1989)
5. https://dx.doi.org/10.4269/ajtmh.2002.66.749(Loutfy et al. 2002)
6. https://dx.doi.org/10.4269/ajtmh.2009.80.788(Leydon et al. 2009)
7. https://dx.doi.org/10.1371/journal.pntd.0001044(Suputtamongkol et al. 2011)
8. https://dx.doi.org/10.1002/14651858.CD007745.pub3(Henriquez-Camacho et al. 2016)
9. https://dx.doi.org/10.1016/S1201-9712(02)90132-3(Angelica Terashima et al. 2002)
10. https://dx.doi.org/10.1093/cid/cit656(van Westerloo et al. 2014)
11. https://dx.doi.org/10.3109/00365540903443165(Grein et al. 2010)
12. https://dx.doi.org/10.1097/QCO.0b013e3283551dbd(Mejia and Nutman 2012)
13. https://doi.org/10.1016/j.cmi.2021.07.016 (Buonfrate et al. 2021)

First-line treatment

Ivermectin (ITM 3 mg tablets).

- Adults and children > 15 kg: 200 µg/kg po single dose (NB: > 85 kg 250 µg/kg single dose).

NB:

- A pivotal phase 3 RCT in Europe has demonstrated that a single dose of ivermectin was as effective as four doses (2 successive days with 2 weeks apart), with a cure rate of 85% in both arms (as assessed by a significant decrease of antibody titres at 12 months) (Buonfrate et al. 2019).
- The previous recommendation of administering a second dose of ivermectin after 14 days (because of low efficacy on circulating larvae) is not supported any more by the evidence.
- In case of treatment failure or relapse (when reinfection is excluded), check for HTLV-1 infection (and for HIV).

Alternative regimens

Albendazole (ITM tablet of 200 mg)

- Adults: 400 mg po bid x 7-14 days.
- Children 2-15 years: 400 mg po od x 7-14 days.
- Children 1-2 years: 200 mg po od x 7-14 days.

Lower cure rate than ivermectin single dose (about 65%):

- (Thiabendazole 25 mg/kg BID po for 3 days: as effective as ivermectin but more side effects; not available in Belgium)

(Moxidectin: cure rate of 85-95% at a single dose of 8 mg in an exploratory trial (Barda et al. 2017) and a more recent phase 2 dose-finding RCT in Laos (Hofmann et al. 2021). Larger trials are planned to look for non-inferiority compared to ivermectin.

Special situations

Hyperinfection syndrome/disseminated strongyloidiasis (almost exclusively in immunosuppressed patients):

- Ivermectin 200 µg/kg po od (or nasogastric tube) until 2 weeks after the last positive stool sample (very weak evidence, based on case reports and on one Japanese retrospective case series, n=70) (Mukaigawara et al. 2020).
- Always cover simultaneously bacterial enteropathogens (translocation) if there are septic signs.
- Consider ivermectin 200 µg/kg OD sc (veterinary preparation) in case oral therapy is unsuitable, BUT serum levels and drug-drug interactions should be monitored, since toxic encephalopathy may develop.

- Rectal administration is not recommended any more since serum levels remain very/too low.
- Consider maintenance/intermittent suppressive treatment with ivermectin (i.e., 200 µg/kg po once a month) in case immunosuppression persists.

NB: there are some cases reports (mainly from Asia) where ivermectin and albendazole are combined (in various schedules) in hyperinfection syndromes.

Availability and costs
Ivermectin: see additional and updated information via contact with ITM.
Albendazole: see additional and updated information via contact with ITM.

43 Taeniasis (Taenia solium, T. saginata & T. asiatica)

Selected References

1. https://dx.doi.org/10.1128/CMR.00033-08 (Scholz et al. 2009)
2. https://dx.doi.org/10.1016/S0889-8553(05)70267-3 (Schantz 1996)
3. https://dx.doi.org/10.4269/ajtmh.1984.33.511 (J. F. Rossignol and Maisonneuve 1984)
4. https://www.ncbi.nlm.nih.gov/pubmed/11273175 (Koul et al. 2000)
5. https://dx.doi.org/10.1016/0140-6736(90)92388-X (Ohnishi and Murata 1990)
6. https://doi.org/10.1371/journal.pntd.0007873 (Haby et al. 2020)

First-line treatment

Niclosamide:

- Adults: 2 g po single dose.
- Children: 50 mg/kg po single dose.

Tablets need to be thoroughly chewed or crushed at intake (available in pharmacy with prescription: 4 tablets of 500 mg).
No intestinal absorption, so no risk in case of concomitant neurocysticercosis.
Efficacy > 95%.

NB: ideally the scolex should be expelled in feces to confirm cure, otherwise the tapeworm will regenerate (in some countries, an osmotic purgative is administered before and after anti-parasitic treatment to improve this expulsion.

Alternative regimens

- Praziquantel 10-20 mg/kg as single dose (available only at ITM); cure rate > 95%; consider ruling out neurocysticercosis (by serology) in patients from endemic regions before giving praziquantel, as treatment (even low doses) may induce seizures.
- Nitazoxanide (adults: 500 mg BID po for 3 days; children 10-12,5 mg/kg BID for 3 days); cure rate of 98%; not available in Belgium, and extremely expensive.
- Albendazole 400 mg/day for 3 days (cure rate of 85% in a meta-analysis)
- Mepacrine 1 g po single dose; cure rate > 90 %, but in only one study.

Special situations

For refractory cases, use of the endoluminal radiocontrast medium Gastrografin (amidotrizoic acid) in some case reports.

44 Thelaziasis

A few hundreds of cases have been reported so far mainly in Asia.
Mainly *Thelazia callipaeda* (oriental eyeworm); rarely *T. californiensis*.

Selected Reference

1. https://dx.doi.org/10.1645/GE-823R.1 (Shen et al. 2006)

First-line treatment

Mechanical removal of adult parasites (with a forceps), after local anesthesia
Rinsing the conjunctival sac with sterile physiological saline solution (to remove immature larvae).

NB: no anti-parasitic treatment.

45 Toxocariasis (Toxocara canis, T. cati)

Selected References

1. https://dx.doi.org/10.1016/j.pt.2014.07.003 (Moreira et al. 2014)
2. https://dx.doi.org/10.1371/journal.pntd.0002938 (Ahn et al. 2014)
3. https://dx.doi.org/10.1093/jpids/pit066 (Woodhall and Fiore 2014)
4. https://dx.doi.org/10.1179/136485910X12607012373957 (Rubinsky-Elefant et al. 2010)
5. https://dx.doi.org/10.1016/j.actatropica.2012.08.003 (Othman 2012)
6. https://dx.doi.org/10.1128/CMR.16.2.265-272.2003 (Despommier 2003)
7. https://dx.doi.org/10.1371/journal.pntd.0003559 (Van Den Broucke et al. 2015)
8. https://dx.doi.org/10.1017/S0031182000065240 (Magnaval 1995)
9. https://dx.doi.org/10.7326/0003-4819-100-3-463_3 (Bekhti 1984)
   : *1*
10. https://doi.org/10.1016/bs.apar.2020.01.007 (Nicoletti 2020)
11. https://doi.org/10.1016/bs.apar.2020.01.005 (Auer and Walochnik 2020)
12. https://doi.org/10.1016/s1473-3099(17)30331-6 (Ma et al. 2018)

Preliminary comments

- Asymptomatic infection (eosinophilia and positive serology) does not require therapy.
- In case of moderate symptoms, symptomatic treatment is often sufficient since the disease is self-limiting (according to a large observational study) (Yoon et al. 2018).
- For (symptomatic) visceral larva migrans (VLM).

Use of anti-parasitic drugs is controversial. However, in most cases anti-helmintic treatment is helpful to shorten the duration of symptoms.

First-line treatment

Albendazole (ITM = 200 mg tablets):

- Adults: 400 mg po bid x 5 days.
- Children 2-15 years: 400 mg po od x 5 days.
- Children 1-2 years: 200 mg po od x 5 days.

+ methylprednisolone 0.5-1 mg/kg po for 1-2 weeks (to taper down thereafter).

Alternative regimens

- Diethylcarbamazine = DEC (50 mg tablets, only at ITM): 3-6 mg/kg po od x 3 weeks; maybe more effective but also more side effects; to use in second line.
- Mebendazole (Vermox®) (100 mg tablets) 00-200 mg po bid x 5-21 days.

NB: ivermectin and thiabendazole appear less effective.

Special situations

Neurotoxocariasis:

Very limited data: no certainty about benefit of anti-helminthic drugs or corticosteroids. Usually both albendazole 400 mg po bid x 10 days and DEC 200 mg po bid x 21 days are administered together, in combination with methylprednisolone 1 mg/kg x 4 weeks..

Ocular toxocariasis:
Administration of anti-helminthic drug (albendazole 400 mg BID po for 2 weeks) is associated with less recurrences at 6 months, but the administration of steroids (topical: prednisone acetate 1%, or systemic: prednisolone 1 mg/kg/day for 2 to 4 weeks), is the mainstay of treatment.

See also specialized ophthalmologic literature; vitro-retinal surgery.

Availability and costs
Albendazole: see additional and updated information via contact with ITM.
DEC: see additional and updated information via contact with ITM.

46 Trichinellosis (*Trichinella spiralis* and subspecies)

Asymptomatic patients with "incidental" positive serology do not need to be treated. Most infections are mild, requiring only symptomatic treatment (analgesics and antipyretics)

Selected References

1. https://dx.doi.org/10.1586/14787210.2015.1075394 (Shimoni and Froom 2015)
2. https://dx.doi.org/10.1128/CMR.00026-08 (Gottstein, Pozio, and Nöckler 2009)
3. https://dx.doi.org/10.2807/1560-7917.ES.2016.21.37.30341 (Messiaen et al. 2016)
4. https://dx.doi.org/10.1093/cid/civ199 (Faber et al. 2015)

First-line treatment

Enteric phase

Only adult intestinal worms and new-born larvae are susceptible to anti-helminthic drugs; anti-helminthic treatment is more likely to be beneficial if given within 7-10 days after onset of (gastro-intestinal) symptoms.

- Albendazole (ITM: 200 mg tablets): 400 mg po bid x 10-14 days.
- + Methylprednisolone 40-60 mg/day x 10-15 days then taper progressively following the International Commission on Trichinellosis guidelines.

Invasive phase

No clear effect of anti-helminthic drugs on encapsulated larvae that may survive and cause symptoms for years. The necessity of anti-helminthics beyond 10-14 days after infection has never been proven.

- Methylprednisolone 40-60 mg/day x 10-15 days then taper progressively following the International Commission on Trichinellosis guidelines.

Alternative regimens

- Mebendazole (Vermox®): 200-400 mg po tid x 3 days followed by 400-500 mg tid x 10-15 days, or 5-10 mg/kg po tid x 14 days.

There is little evidence about the dose that must be used; it has been estimated that 77 g (!) would be necessary for a larvicidal effect.

Special situations

Pregnancy:

WHO allows the use of albendazole in the 2nd and 3rd trimester of pregnancy
Pyrantel pamoate (10-20 mg/kg OD po for 3 days has been proposed but efficacy is doubtful (active only against adult worms during the enteric phase).

Post-exposure prophylaxis:

Strongly consider in outbreaks, for patients (even if still asymptomatic) within 7 days following ingestion: mebendazole 5 mg/kg po bid x 5 days.

47 Trichostrongyliasis (*Trichostrongylus spp*)

Most infections are asymptomatic.
Eggs are almost indistinguishable from those of hookworms.

Selected References

1. https://dx.doi.org/10.3201/eid1707.101519 (Lattès et al. 2011)

First-line treatment

Albendazole:

- Adults and children > 2 years: 400 mg po single dose.
- Children 1-2 years: 200 mg po single dose.

Alternative regimens

Mebendazole:

- Adults and children > 1 year00 mg po bid x 3 days.
  (Pyrantel pamoate)
- Adults and children > 6 months0 mg/kg (max. 1g) po single dose.
  (Levamisole 2.5 mg/kg po single dose).
  (Ivermectin?)

48 Trichuriasis (*Trichuris trichiura*, whipworm)

Overall, cure rates with albendazole and mebendazole are rather low (especially in single dose), and mebendazole seems more effective

Selected References

1. https://dx.doi.org/10.1001/jama.299.16.1937 (Keiser and Utzinger 2008)
2. https://dx.doi.org/10.1016/S0140-6736(06)68653-4 (Bethony et al. 2006)
3. https://dx.doi.org/10.1371/journal.pone.0025003 (P. Steinmann et al. 2011)
4. https://dx.doi.org/10.1056/NEJMoa1301956 (Speich et al. 2015a)
5. https://dx.doi.org/10.1016/S0035-9203(02)90301-9 (Ortiz et al. 2002)
6. https://dx.doi.org/10.1371/journal.pntd.0001685 (Speich et al. 2012)
7. https://dx.doi.org/10.4269/ajtmh.1996.55.477(Marti et al. 1996b)
8. https://dx.doi.org/10.1371/journal.pntd.0003046(Xu et al. 2014)
9. https://dx.doi.org/10.1016/j.trstmh.2011.07.009(Namwanje, Kabatereine, and Olsen 2011)
10. https://dx.doi.org/10.1086/657310(Knopp et al. 2010)
11. https://dx.doi.org/10.1016/S1473-3099(14)71050-3(Speich et al. 2015b)
12. https://doi.org/10.1093/cid/ciy423 (Clarke et al. 2019)

First-line treatment

- Mebendazole (Vermox®) (100 mg tablets, available in pharmacy without prescription):
  - Adults and children > 1 year: 500 mg po od x 3 days.

NB: mebendazole 100 mg po bid x 3 days: cure rate of 70%.

Alternative regimens

- Albendazole:
  - Adults and children > 2 years: 400 mg po od x 3 days.
  - Children 1-2 years: 200 mg po od x 3 days.

NB: cure rate for a single dose treatment (whatever dosage: 25%; for a 3-day course: 55%) (Patel et al. 2020).

- Nitazoxanide: initially promising (89% cure rate in a small Peruvian study; but very little effective in more recent studies.
- Ivermectin 200 µg/kg (up to 600 µg/kg) single dose: cure rate of 20% maximum! (Wimmersberger et al. 2018)
- Oxantel pamoate: cure rate of about 30%, with egg reduction rate of 95%; up to 80% when associated with albendazole (Barda et al. 2018).
- Tribendimidine?: disappointing also
- Moxidectin single dose 8 mg (like for onchocerciasis): cure rate of 45%; (up to 65% when associated with albendazole) (Keller et al. 2020).

Special situations

Treatment failure:

- Either albendazole or mebendazole in monotherapy for longer period.
- Or combination therapies: (1) mebendazole + albendazole performed better than each drug separately; (2) mebendazole + ivermectin: cure rate 50%; (3) albendazole + ivermectin: 30-60% cure rate.
- Much research is being conducted in tropical fields to evaluate new single-dose combinations (e.g., moxidectin + albendazole).

Chapter 3: Bacteria

49 Anthrax

Disease caused by *Bacillus anthracis*. All patients with (suspicion of) systemic anthrax (bioterrorism) should undergo lumbar puncture to evaluate for meningitis. "Natural" anthrax is usually cutaneous (rarely digestive). In case of exposure by inhalation, a PEP should be considered.

49.1 Anthrax PEP

PEP can be given to patients exposed to aerosolized *Bacillus anthracis*.

Selected References

1. https://dx.doi.org/10.1056/NEJMra1409755) (Adalja, Toner, and Inglesby 2015b)
2. https://wwwnc.cdc.gov/eid/article/20/2/13-0687 (Hendricks et al. 2014; Moser, Schindler, and Keiser 2019b)

First-line treatment

- Ciprofloxacin 500 mg po bid x 60 days (children 15 mg/kg bid) AND Anthrax vaccine: 3 injections of 0,5 ml on W0, W2 and W4.

Alternative regimens

- Doxycycline 100 mg po bid for 60 days (< 45 kg: 2.2 mg/kg bid).
- Antitoxin therapy (Raxibacumab, see below) can be used when alternative preventive therapies are not available or are not appropriate.

Availability and costs

Anthrax vaccine not available in Belgium. Please mail to ITM for contact information.
Raxibacumab is not registered outside the USA. Please mail to ITM for contact information.

49.2 Cutaneous anthrax

First-line treatment

- Ciprofloxacin 500 mg po bid (children 15 mg/kg bid).
- For bioterrorism-associated cases and cases in which aerosol exposure is suspected, the duration of therapy is 60 days. For naturally acquired infection (e.g., animals with anthrax, hides from animals with anthrax), the duration of therapy is 7 to 10 days.

Alternative regimens

- Doxycycline 100 mg po bid or levofloxacin 750 mg po od or moxifloxacin 400 mg po od or clindamycin 600 mg po tid.

Special situations/additional comments

- Ciprofloxacin is the preferred treatment in pregnancy.
- Glucocorticoids can be added in case of cutaneous anthrax with extensive edema involving the head and neck

49.3 Systemic anthrax with meningitis

First-line treatment

- Antibiotic treatment**:** Ciprofloxacin 400 mg iv tid (children 10 mg/kg tid) + Meropenem 2 gr. iv tid (children 40 mg/kg tid) + Linezolid 600 mg iv bid (children < 12 y 0 mg/kg tid; > 12y 5 mg/kg bid).
- Antitoxin treatment**:** Raxibacumab adults > 50 kg: 40 mg/kg iv single dose (15-50 kg: 60 mg/kg; < 15 kg: 80 mg/kg); premedicate with an anti-histaminic.

NB: There is no conclusive evidence demonstrating that anthrax antitoxin therapy, when combined with a therapeutic course of antibiotics, provides a survival benefit in inhalational anthrax (Vietri 2018).

After improvement on iv treatment (at least 2 weeks), a 60-day treatment should be installed with ciprofloxacin 500 mg po bid or doxycycline 100 mg po bid to prevent relapse from surviving *B. anthracis* spores.

Alternative regimens

- Ciprofloxacine can be replaced with levofloxacine 750 mg/d or moxifloxacine 400 mg/d.
- Meropenem can be replaced with imipenem 1gr. iv 4x/d or doripenem 500 mg tid; if penicillin susceptible penicillin G or amoxicillin can be used.
- Linezolid can be replaced with clindamycin 900 mg iv bid.
- Raxibacumab can be replaced with Obiltoxaximab (Anthim®): patients > 40 kg: 6 mg/kg iv single dose (15-40 kg: 24 mg/kg, < 15 kg: 32 mg/kg); premedicate with an anti-histaminic.
- Raxibacumab can also be replaced with Anthrax immunoglobulin (Anthrasil®).

Special situations/additional comments

Pregnancy: same treatment.

NB: Glucocorticoids can be added in case of anthrax meningitis, cutaneous anthrax with extensive edema involving the head and neck or anthrax with vasopressor-resistant shock.
Pleural fluid drainage preferably with chest tubes in case of pleural effusion.
Ascites drainage in case of ascites fluid.

Availability and costs

Raxibacumab is not registered outside the USA, contact: Dr Gregg Little Director, Clinical and Medical AffairsEmergent BioSolutions400 Professional Drive, Suite 400 Gaithersburg, MD 20879 Tel +1 240 631 3334 glittle@ebsi.com
Obiltoxaximab: Elusys Therapeutics, Tel-844-808-0222.

49.4 Systemic anthrax without meningitis

First-line treatment

- Antibiotic treatment**:** Ciprofloxacin 400 mg iv tid (children 10 mg/kg tid) + clindamycin 900 mg iv tid (children 13 mg/kg/d tid) or linezolid 600 mg iv bid (in children clindamycin is preferred).
- Antitoxin treatment**:** Raxibacumab: adults > 50 kg: 40 mg/kg iv single dose (15-50 kg: 60 mg/kg; < 15 kg: 80 mg/kg); premedicate with an anti-histaminic.
- After improvement on iv treatment (at least 2 weeks), a 60-day treatment should be installed with ciprofloxacin 500 mg po bid or doxycycline 100 mg po bid to prevent relapse from surviving *B. anthracis* spores.

Alternative regimens

- Ciprofloxacine can be replaced with levofloxacine 750 mg/d or moxifloxacine 400 mg/d or meropenem 2 gr iv tid; if penicillin susceptible Penicillin G or Amoxicillin can be used.
- Raxibacumab can be replaced with Obiltoxaximab (Anthim®) patients > 40 kg6 mg/kg iv single dose (15-40 kg: 24 mg/kg, < 15 kg: 32 mg/kg); premedicate with an anti-histaminic.
- Raxibacumab can also be replaced with Anthrax immunoglobulin (Anthrasil®).

Special situations/additional comments

Pregnancy: Same treatment.

NB: Glucocorticoids can be added in case of anthrax meningitis, cutaneous anthrax with extensive edema involving the head and neck or anthrax with vasopressor-resistant shock.
Pleural fluid drainage preferably with chest tubes in case of pleural effusion.
Ascites drainage in case of ascites fluid.

Availability and costs

Raxibacumab is not registered outside the USA. Please mail to ITM for contact information.
Obiltoxaximab. Please mail to ITM for contact information.

50 Bartonellosis (B. baciliformis, Endocarditis, B. henselae, B. quintana)

50.1 *Bartonella bacilliformis* (Carrion's disease)

Selected References

1. https://dx.doi.org/10.1128/AAC.48.6.1921-1933.2004 (Rolain et al. 2004)
2. https://doi.org/10.1128/CMR.00056-17 (Gomes and Ruiz 2018)

First-line treatment

Oroya Fever *(acute febrile hemolytic disease)*:

- Ciprofloxacin 500 mg po bid x 10 days.
- Severe disease: Ciprofloxacin 500 mg po bid x 10 days (or 400 mg iv bid) + ceftriaxone 1 gr iv od x 7-10 days

Verruga Peruana *(chronic cutaneous manifestations)*:

- Azithromycin 500 mg OD po x 7 days (children 10 mg/kg).

Alternative regimens

Oroya Fever:

- Chloramphenicol 500 mg po qid + beta-lactam antibiotic x 2 weeks

Verruga Peruana:

- Rifampin 600 mg po od (children 10mg/kg) x 14 days or ciprofloxacin 500 mg po bid x 10 days.

Special situations

Oroya Fever:

- Children and pregnancy: amoxi-clav 875/125 mg po tid (children: 22,5/3,2 mg/kg bid); for severe cases use ceftriaxone 1 gr iv od (children 75 mg/kg).

50.2 *Bartonella* Endocarditis

Selected References

1. https://dx.doi.org/10.1128/AAC.48.6.1921-1933.2004 (Rolain et al. 2004)
2. https://dx.doi.org/10.1161/CIRCULATIONAHA.105.165564 (Larry M. Baddour et al. 2015)

First-line treatment

- Doxycycline 100 mg po bid (children 2 mg/kg) or iv for 6 weeks + gentamicin 1 mg/kg iv tid x 2 weeks.
- Discuss valve replacement with cardiac surgeon.

Alternative regimens

Gentamicin can be replaced by rifampicin 300 mg po bid or iv (children 20 mg/kg).

50.3 *Bartonella henselae* (Cat Scratch Disease, CSD)

Selected References

1. https://dx.doi.org/10.1128/AAC.48.6.1921-1933.2004 (Rolain et al. 2004)
2. https://dx.doi.org/10.1086/515197 (Arisoy et al. 1999)
3. https://dx.doi.org/10.1161/CIRCULATIONAHA.105.165564(L. M. Baddour 2005)

4. http://www.scielo.org.pe/scielo.php?script=sci_arttext&pid=S1726-46342006000300009 (Tarazona F et al. 2006)

First-line treatment

- Typical CSD (lymphadenitis): Azithromycin 500 mg (< 45 kg 10 mg/kg) po od on day 1, followed by azithromycin 250 mg (< 45 kg: 5 mg/kg) po od from day 2-day 5.

NB: In mild forms, treatment might not be necessary.
Needle aspiration of lymphadenopathy/other abscesses to considered for symptom. relief: surgical excision rarely needed.

Neuro-retinitis**:**

- Doxycycline 100 mg po bid x 4-6 weeks (< 8y: azithromycin po od 10 mg/kg day 1,5mg/kg po od day 2-day 5) + rifampicin 300 mg po bid x 4-6 weeks.

Hepatosplenic disease and prolonged fever**:**

- Rifampicin 300 mg po bid for 14 days + azithromycin 500mg (< 45kg 0mg/kg) po od on day 1, followed by azithromycin 250mg (< 45kg: 5mg/kg) po od from day 2-day 14 OR gentamycin loading dose 2mg/kg, followed 1,5 mg/kg iv tid x 14 days (adapt dose to serum concentration).

Endocarditis**:**

- Doxycycline 100mg bid + gentamycin loading dose 2 mg/kg, followed 1,5 mg/kg iv tid for 14 days (adapt dose to serum concentration); extend doxycycline up to 6 weeks after valvular surgery or up to 3 months post-replacement.

Alternative regimens

- Typical CSD**:** Clarithromycin 500mg po bid (< 45 kg 0 mg/kg bid) x 7-10 days or rifampicin 300mg po bid (children 10 mg/kg bid) x 7-10 days.

50.4 *Bartonella quintana* (Trench Fever)

Selected References

1. https://dx.doi.org/10.1128/AAC.48.6.1921-1933.2004 (Rolain et al. 2004)

First-line treatment

- Doxycycline 200 mg po od for 4 weeks + gentamicin 3mg/kg iv od x 2 weeks.
- Delousing the body and delousing of all clothing and bedding sheets is important to avoid re-infection (cfr. chapter *Pediculosis corporis*).

Alternative regimens

If gentamycin is not available, it can be replaced with rifampicin 300mg po bid x 14 days.

51 Borreliosis (relapsing fever)

Selected References

1. http://www.ncbi.nlm.nih.gov/pubmed/9455525 (Cadavid and Barbour 1998)
2. https://dx.doi.org/10.1111/j.1469-0691.2009.02819.x (S. J. Cutler, Abdissa, and Trape 2009)
3. https://dx.doi.org/10.1016/j.trstmh.2011.04.004 (Guerrier and Doherty 2011)
4. https://dx.doi.org/10.1016/j.cll.2015.07.001 (Sally J. Cutler 2015)
5. https://dx.doi.org/10.1056/NEJMoa053884 (Hasin et al. 2006)
6. https://dx.doi.org/10.1016/0035-9203(77)90207-3 (Salih 1977)
7. https://dx.doi.org/10.1016/j.micinf.2006.04.007 (Larsson et al. 2006)

51.1 *Borrelia duttoni, crocidurae, persica*… (tick-borne)

First-line treatment

It is recommended to admit patients with relapsing fever for a few hours to administer the first drug dose under medical observation (cardiac monitoring and iv line): risk of (potentially lethal) Jarish-Herxheimer reaction (risk 20 to 80% according to the series, higher with louse-borne borreliosis).

- Doxycycline 100 mg/d po bid x 10-14 days OR Penicillin G 5 MU iv qid or ceftriaxone 2 gr iv od x 10-14 days, switch to oral medication when the patient is clinically stable.

Alternative regimens

- Erythromycin 500 mg po qid x 7 - 10 days (treatment failures have been described), azithromycin should work also but has not been studied.

Special situations

CNS involvement:

- Ceftriaxone 2 gr iv od x 14 days is the first choice currently.

Pregnancy and children < 8 years:

- Erythromycin: 500 mg (12,5 mg/kg) po qid x 7 days or penicillin G 5 MU iv qid or ceftriaxone 2 gr iv od x 10-14 days.

NB: Doxycycline single dose is allowed during pregnancy (CDC).

Post-exposure treatment:

- In case of intense exposure (soldiers…), a post-exposure treatment (doxycycline 200 mg/d for 4 days) resulted in 100% protective effect.

51.2 *Borrelia recurrentis* (louse-borne)

First-line treatment

- Procaine Penicillin G 400.000-800.000 U (children 200.000-400.000 U) im single dose or doxycycline 200 mg po/iv single dose (children 5 mg/kg, max. 200 mg).

Alternative regimens

- Erythromycin 500 mg po/iv single dose.

52 Borreliosis (Lyme disease)

Selected References

1. L. Belkhir, "Lyme-borreliose (infectie met Borrelia)," pp. 1-27, 2016. http://overlegorganen.gezondheid.belgie.be/sites/default/files/documents/gids_lyme_borreliose_nl_march2017.pdf (Belkhir et al., 2016a)
2. IGGI guidelines, http://www.bvikm.org/(Belgische Vereniging voor Infectiologie en Klinische Microbiologie 2019)

53 Brucellosis

Selected References

1. https://dx.doi.org/10.1371/journal.pmed.0040317 (Ariza et al. 2007)
2. https://dx.doi.org/10.1016/j.ijid.2008.03.014 (Alp and Doganay 2008)
3. https://dx.doi.org/10.1086/525266 (Colmenero et al. 2008)
4. https://dx.doi.org/10.1128/AAC.05974-11 (Erdem et al. 2012)
5. https://dx.doi.org/10.2169/internalmedicine.47.0866 (Gul et al. 2008)

First-line treatment

Uncomplicated**:**

- Doxycycline 100 mg po bid x 6 weeks + gentamycin 5 mg/kg od im/iv x 2-3 weeks.

Osteo-articular brucellosis:

- Doxycycline 100 mg po bid x 12 weeks + streptomycin 15 mg/kg od im for 2-3 weeks (Unuvar, Kilic, and Doganay 2019).

NB: very few clinical studies with gentamycin, but good in vitro activity and better tolerated (see endocarditis here under).

Discuss with a neurosurgeon in case of spinal instability, cord compression, radiculopathy, cauda equina syndrome, and severe weakness of the muscles due to extradural inflammatory mass or progressive collapse.

Neurobrucellosis:

- Doxycycline 100 mg po bid + rifampicin 600-900 mg (15 mg/kg) po od + ceftriaxone 2 gr iv bid.After initial improvement this regimen can be switched to Doxycycline 100 mg po bid+ rifampicin 600-900 mg (15 mg/kg) po od + cotrimoxazole 800/160 mg po bid.

NB: Treatment to be continued till normalization of CSF fluid; this might take several months.

Endocarditis:

- Streptomycin 15 mg/kg im od or Gentamycin 3 mg/kg im/iv od + Doxycycline 100 mg po bid or 200 mg po od + Rifampicin 600-900 mg (15 mg/kg) po od or cotrimoxazole 800/160 mg po bid; duration can vary from 6 weeks till 6 months. (Koruk et al. 2012; Turhan et al. 2013).

Most cases need a combination of surgery and antibiotics. (Turhan et al. 2013 ; Koruk et al. 2012)

Alternative regimens

Uncomplicated**:**

- Doxycycline 100 mg po bid+ rifampicin 600-900 mg (15 mg/kg) po od, both for 6 weeks or Doxycycline 100 mg po bid x 6 weeks + gentamycin 5 mg/kg im/iv od x 7 day.

Osteo-articular brucellosis:

- Doxycycline 100 mg BID po + rifampicin 600-900 mg (15 mg/kg) OD po, both for 12 weeks or Doxycycline 100 mg BID po + ciprofloxacin 500 mg BID po, both x 12 weeks.

Special situations

Pregnancy:

- Rifampicin 600-900 mg (15 mg/kg) po od x 12 weeks +/- cotrimoxazole 800/160 mg po bid (if possible, avoid cotrimoxazole in the last week of pregnancy to avoid kernicterus).

Children:

- 8y uncomplicated: Doxycycline 1-2 mg/kg po bid + rifampicin 15-20 mg/kg po od, both x 6 weeks.
- < 8y uncomplicated: Cotrimoxazole (5 mg/kg trimethoprim + 25 mg/kg sulfamethoxazole) po bid + rifampicin 15-20 mg/kg po od, both x 6 weeks.

- > 8y spondylitis/neuro/endocarditis: Doxycycline 1-2 mg/kg po bid for at least 6 weeks + streptomycin 10-20 mg/kg/d im bid for 2 weeks (or gentamycin 2,5 mg/kg im/iv bid).
- < 8y spondylitis/neuro/endocarditis: Cotrimoxazole (5 mg/kg trimethoprim + 25 mg/kg sulfamethoxazole) po bid for 6 weeks + streptomycin 10-20 mg/kg im bid for 2 weeks (or gentamycin 2,5 mg/kg im/iv bid).

54 Campylobacter species

Selected References

1. https://dx.doi.org/10.1128/CMR.00006-15 (Kaakoush et al. 2015)
2. https://dx.doi.org/10.1093/jtm/taw090 (Tribble 2017)
3. https://dx.doi.org/10.1111/j.1708-8305.2008.00236.x (Vlieghe et al. 2008)
4. https://dx.doi.org/10.1007/s10096-017-3032-6 (Post et al. 2017)
5. https://dx.doi.org/10.1016/j.diagmicrobio.2017.05.015 (O'Hara, Fitchett, and Klein 2017)
6. https://dx.doi.org/10.1093/cid/cir509 (Feodoroff et al. 2011)
7. https://dx.doi.org/10.1086/591530 (Pacanowski et al. 2008)
8. https://dx.doi.org/10.1097/MD.0000000000002858 (van Samkar et al. 2016)
9. https://dx.doi.org/10.1128/JCM.00631-13 (Suy et al. 2013)

General principles

- Important food-borne pathogen and cause of travelers' diarrhea, particularly in Asia travelers. May be self-limiting or may cause more severe disease, with or without extra-intestinal complications. Impact of (appropriate) AB treatment on recovery not consistent between studies and countries.
- Antibiotic resistance, especially for fluoroquinolones, has been observed over the past decades, see e.g.:
- Invasive infections (bacteremia, meningitis, pericarditis, aortitis...) occur in < 1%, particularly but not exclusively in immune depressed and debilitated populations.
- Evidence on effective antibiotic treatment is scarce and has been derived so far from case series and expert opinion.
    - First choice products are *fluoroquinolones* and *macrolides.* Given widespread fluoroquinolone resistance, macrolides are preferred for empirical use. Azithromycin is the macrolide of choice because of effectiveness/tolerance balance. However, an increasing resistance rate to macrolides is reported, especially in children and in non-jejuni-isolates (Schiaffino et al. 2019; Bolinger and Kathariou 2017).
    - Among beta-lactams, *only amoxicillin-clavulanic acid and carbapenems* seem to have sufficient in vivo activity. The use of cephalosporins has been associated with worse outcomes in bloodstream infections
    - *Gentamicin* is an effective choice for bloodstream infection and endovascular infections.

Recommendations:

(Travelers) diarrhea:

Will be mainly empirical treatment. Only severe diarrhea with fever, and/or dysenteric presentation requires antibiotic treatment.

See: http://www.itg.be/Files/docs/Reisgeneeskunde/nreizigersdiarree.pdf)

- Adults: azithromycin 1000 mg po single dose.
- Children: azithromycin 10 mg/kg/d po od x 3 days.

Invasive infection (no meningitis):

Treatment as much as possible to be tailored to susceptibility pattern.

Bacteremia:

Patients have been successfully treated with at least 14-day courses of carbapenems (e.g., meropenem 1 gr iv tid),

- or gentamicin 5 mg/kg/d iv/im od (endovascular infections),
- or macrolides (mild cases): e.g.: azithromycin 1000 mg Day 1 then 500 mg po od day 2-day 14,
- or ciprofloxacin 500 mg po bid (if proven susceptibility).

AVOID ceftriaxone:

- Meningitis: prolonged course with combination therapy ampicillin + gentamycin; chloramphenicol; cefotaxime and carbapenems (e.g., meropenem 1-2 gr tid) x 2-5 weeks have been successful. (Kusulja et al. 2020).

55 Ehrlichiosis & anaplasmosis

Ehrlichia chaffeensis, agent of human monocytic ehrlichiosis.
Anaplasma phagocytophilum, agent of human granulocytic anaplasmosis.

Selected References

1. https://dx.doi.org/10.1086/508667 (Wormser et al. 2006)
2. https://dx.doi.org/10.1086/518146 (Dumler et al. 2007)
3. https://dx.doi.org/10.1086/520659 (Dhand et al. 2007)

First-line treatment

- Doxycycline 100 mg po bid or iv (children 2 mg/kg bid) x 10 days or till 3 days after defervescence; in children.
- < 8 years a shorter course of 4-5 days can be considered to diminish the risk of dental staining, with close follow-up to ascertain resolution of the infection; in severe disease doxycycline should still be given to children even for longer periods.

Alternative regimens

- Rifampicin 300 mg po bid x 7-10 days.

Special situations

Pregnancy:

- Rifampicin 300 mg po bid x 7-10 days; in severe disease in pregnancy the recommended treatment is doxycycline 100 mg po bid or iv.

56 Furunculosis (recurrent > 4/year)

Selected References

1. https://dx.doi.org/10.1093/cid/ciu444 (Stevens et al. 2014)
2. https://dx.doi.org/10.1111/j.1365-2133.2012.11151.x (Demos, McLeod, and Nouri 2012)
3. https://www.ntvg.nl/system/files/publications/a5548.pdf (Engelhard, Spanjaard, and Stijnis 2013)
4. https://dx.doi.org/10.2147/CCID.S35302 (Ibler and Kromann 2014)
5. https://dx.doi.org/10.3109/00365548.2013.810815 (Davido et al. 2013)
6. https://www.ntvg.nl/system/files/publications/2008126670001a.pdf (Wertheim et al. 2012)

General considerations

- To be differentiated from hidradenitis suppurativa.
- Rule out underlying immune suppression (rare) and/or systemic involvement (blood stream infection, endocarditis, device infection…)
- Different guidelines exist with many different treatment suggestions.

Treatment recommendations

Acute episode of skin abscess:

- Incision and drainage.
- (empiric) antibiotics are only required in case of systemic involvement:
  - po flucloxacillin 500 mg q6 x 7 d or
  - po clindamycin 600 mg q6 x 7 d, or
  - po trimethoprim-sulfamethoxazole 160/800 mg q12 x 7 d.

Recurrent episodes (> 3-4 episodes/year):
Look for nasal carriership, colonization of the living environment or of close contacts or pets, chronic wounds, underlying immune problems, specific virulence factors (e.g., PVL).
'3 steps approach':

1. Nasal mupirocin ointment q8 & daily chlorhexidine body wash for 5 days.
2. If persisting: screening and treating carriership close contacts/environmental disinfection with culture. Focus on personal, interpersonal, and environmental hygiene issues is crucial to reduce the risk of contamination and recurrences.
3. If still persisting: eradication treatment with antibiotics based on susceptibility testing e.g., clindamycin 150 mg q24 for 3 months.

- Or: 'CMC regimen': skin disinfection with chlorhexidine for 21 days + nasal mupirocin ointment for 5 days + oral clindamycin 600 mg q6-8 for 21 days.

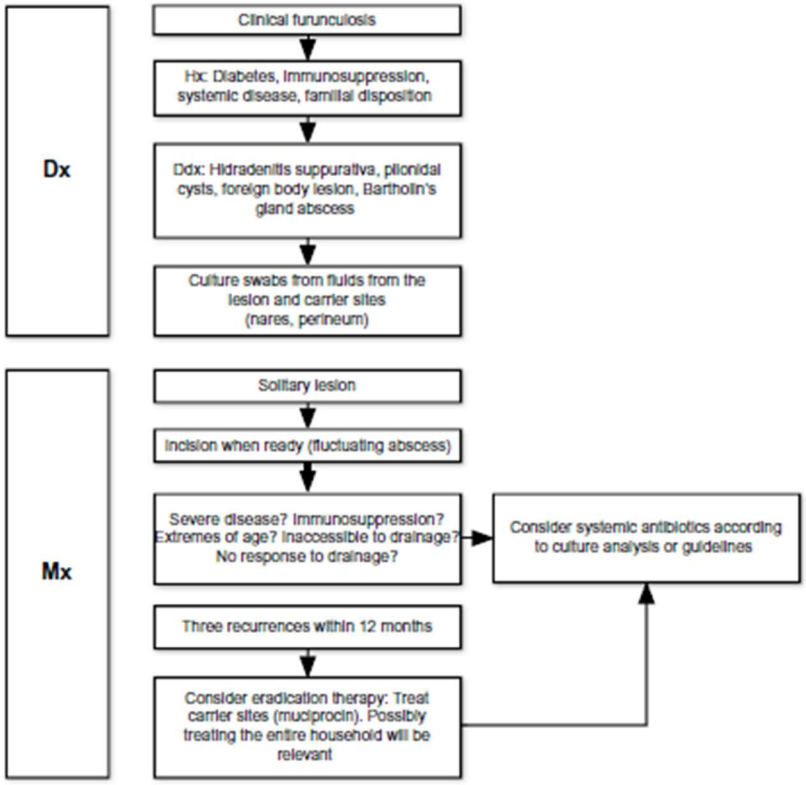


Figure 1 Flowchart of diagnosis and treatment of furunculosis.
Abbreviations: Ddx, differential diagnosis; Dx, diagnosis; Hx, history; Mx, management.

Source: Ibler KS & Kromann CB. Recurrent furunculosis – challenges and management: a review. *Clin Cosmet Investig Dermatol*. 2014

57 Leprosy (Hansen's disease; *Mycobacterium leprae*)

Selected references

1. WHO. WHOTreatmentGuide.pdf. Published online 1998:28.
2. Cooreman E, Gillini L, Pemmaraju V, et al. Guidelines for the diagnosis, Treatment and Prevention of Leprosy. World Heal Organ. 2018;1:106
3. Marlowe, S. N. S., Leekassa, R., Bizuneh, E., Response to ciclosporin treatment in Ethiopian and Nepali patients with severe leprosy Type 1 reactions. *Transactions of the Royal Society of Tropical Medicine and Hygiene*, *101*(10), 1004–1012. https://doi.org/10.1016/j.trstmh.2006.11.010 (Marlowe et al. 2007b)

First-line treatment

Paucibacillary (PB) and multibacillary (MB) Leprosy (WHO guideline 2018).

- Rifampicin 600 mg once monthly + clofazimine 300 mg once monthly + dapsone 100 mg daily + clofazimine 50 mg daily.
    - Child: 10-14 y: rifampicin 400 mg once monthly + clofazimine 150 mg once monthly + clofazimine 50 mg on alternate days + dapsone 50 mg daily.
    - Child < 10 y: rifampicin 10 mg/kg once monthly + clofazimine 100 mg once monthly + clofazimine 50 mg twice weekly + dapsone 2 mg/kg daily.

Treatment duration: 6 months for PB leprosy and 12 months for MB leprosy.
NB: treatment duration is a compromise between efficacy and costs/logistical constraints/adherence. Some experts (in high income countries) still recommend a 24-month treatment for MB leprosy.
It is good clinical practice to exclude G6PD deficiency before starting the dapsone treatment.

Leprosy reactions
Type I reactions:

- If severe or nerve involvement: prednisolone 30-60 mg/day, reduced dose gradually every week or 2 weeks for a total duration of 4-6 months.
- If mild or moderate: analgesics only.
- Lack of response to steroids: cyclosporine (5-7,5 mg/kg/day) could be used as a 2nd line drug(Marlowe et al. 2007).

Type II reactions:

- Prednisolone 30-60 mg/day, reduced dose gradually every week or 2 weeks; shorter courses than for type I reactions are possible.
- Lack of response to steroids or steroids contra-indicated:
    - Clofazimine 100 mg 3x1 co daily, total duration maximum 12 months.
    - Thalidomide 300-400 mg daily initially, then taper gradually to 100 mg daily; afterwards taper every few months; to control ENL thalidomide might be continued for several years.

57.1 Neuritis

Prednisolone 30-60 mg/day, reduced dose gradually every week or 2 weeks for a total duration of 4-6 months.
If the response is insufficient, urgent surgical decompression is to be considered.

57.2 Iridocyclitis

To be considered as an emergency. Best managed in collaboration with an ophthalmologist. Atropine drops and corticosteroid drops must be started immediately.
NB: Tear substitutes are used in patients with lagophthalmos and/or decreased lacrimation.

Special situations
Drug-resistant leprosy(Cooreman et al. 2018)

Resistance type	**Treatment**	
	First 6 months (daily)	**Next 18 months (daily)**
Rifampicin resistance	Ofloxacin 400 mg* + minocycline 100 mg + clofazimine 50 mg	Ofloxacin 400 mg* OR minocycline 100 mg + clofazimine 50 mg
	Ofloxacin 400 mg* + clarithromycin 500 mg + clofazimine 50 mg	Ofloxacin 400 mg* + clofazimine 50 mg
Rifampicin and ofloxacin resistance	Clarithromycin 500 mg + minocycline 100 mg + clofazimine 50 mg	Clarithromycin 500 mg OR minocycline 100 mg + clofazimine 50 mg

*Ofloxacin 400 mg can be replaced by levofloxacin 500 mg OR moxifloxacin 400 mg.

Pregnancy:
- Same regimen and dosage for first-line treatment and drug-resistant leprosy

Household contacts of MB leprosy patients:
Chemoprophylaxis can be considered, since it reduces the risk of leprosy occurrence by 50%. According to the WHO guideline, single-dose rifampicin (SDR) may be used as leprosy preventive treatment for contacts of leprosy patients (adults and children aged 2 years and above), after excluding leprosy and tuberculosis (TB) disease, and in the absence of other contraindications.

Availability and costs
Leprosy treatment is available in blister format for free at the ITM (now only triple-drug blisters should be used); see updated information via contact with ITM; or direct communication with WHO
Thalidomide can also be obtained at ITM following a special request

58 Leptospirosis

Selected References

1. https://dx.doi.org/10.1016/S1473-3099(03)00830-2 (Bharti et al. 2003)
2. https://dx.doi.org/10.1586/14787210.2.2.293 (Edwards and Levett 2004)
3. https://dx.doi.org/10.1128/CMR.14.2.296-326.2001 (Levett 2001)
4. https://dx.doi.org/10.1097/QCO.0b013e3280106818 (M. E. Griffith, Hospenthal, and Murray 2006)
5. https://www.ntvg.nl/artikelen/leptospirose (van de Weyer, Ramakers, and Pickkers 2015)
6. https://dx.doi.org/10.1002/14651858.CD008264.pub2 (Brett-Major and Coldren 2012)
7. http://www.ncbi.nlm.nih.gov/pubmed/23930159 (Charan et al. 2013)
8. https://dx.doi.org/10.1371/journal.pone.0059266 (Guerrier and D'Ortenzio 2013)
9. https://dx.doi.org/10.1093/trstmh/tru148 (Rodrigo et al. 2014)

General considerations

There is an ongoing debate on effectiveness of antibiotic treatment for leptospirosis:

- Cochrane analysis 2012: insufficient evidence is available to advocate for or against the use of antibiotics in the therapy for leptospirosis. Further clinical research is needed to include broader panels of therapy tested against placebo.
- When electing to treat with an antibiotic, selection of penicillin, doxycycline, or cephalosporin does not seem to impact mortality nor duration of fever.
- Several case series have reported shortened duration of illness when appropriate antibiotic therapy was administered during the initial phase of the illness (within 2–4 days).
- In patients with severe disease, late administration of antibiotics has also shown clinical efficacy and reduction in mortality rates.
- A logical rule whether to treat or not: if the patient is ill enough to seek medical care, antibiotics should be administered to shorten the duration of illness.

Currently recommended regimens and dosages are based on the severity of the disease:

Ambulatory patient, mild:

- Doxycycline 100 mg po bid x 5-7 days.
- Amoxicillin 500 mg po tid x 7 days.
- Azithromycin 500 mg po od x 3 days.
- Penicillin G (1.5 MU q6) and ceftriaxone (1_2 gq24) x 7-10 d are indicated for severe disease.
- Children and pregnant woman: amoxicillin with above doses.

Hospitalized patient, severe:

- Penicillin G 1,5 MU iv qid x 7 days.
- Ceftriaxone 2 gr iv od x 7 days.
- Doxycycline 100 mg iv bid x 7 days.
- Children: Penicillin G 250.000-400.000 U/kg iv per day in 4-6 divided doses x 7 days.

Prophylaxis:

- Chemoprophylaxis may be impractical to administer in highly endemic areas but is likely to be useful.
- For adventure travelers and military personnel who visit endemic areas, and in accidental laboratory infections.
- Doxycycline 200 mg po weekly does not prevent leptospiral infection in an endemic area but may have a significant protective effect in reducing morbidity and mortality, even in an endemic setting.

59 Lyme disease (see Borreliosis)

Selected References

4. L. Belkhir, "Lyme-borreliose (infectie met Borrelia)," pp. 1-27, 2016. http://overlegorganen.gezondheid.belgie.be/sites/default/files/documents/gids_lyme_borreliose_nl_march2017.pdf(Belkhir et al. 2016b)
5. IGGI guidelines, http://www.bvikm.org/

60 Melioidosis

Selected References

1. "Raising awareness of Melioidosis," International Melioidosis Society, 2018. http://www.melioidosis.info
2. https://doi.org/10.3201/eid1812.120638 (Lipsitz et al. 2012)
3. https://dx.doi.org/10.1371/journal.pntd.0003586 (Pitman et al. 2015b)
4. https://dx.doi.org/10.1016/j.ijantimicag.2014.01.005 (Dance 2014)
5. https://dx.doi.org/10.1056/NEJMra1204699 (Wiersinga, Currie, and Peacock 2012)
6. https://dx.doi.org/10.1097/QCO.0b013e32833fb88c (Cheng 2010)

Severe bacterial systemic infection caused by *Burkholderia pseudomallei*, presenting as acute (<2 months), chronic (>2 months), latent or relapsing disease.
Clinical presentation: pneumonia, skin and soft tissue infection, deep tissue abscess, central nervous system (CNS) melioidosis, sepsis and septic shock.

Risk factors for mortality: diabetes mellitus, alcohol abuse and underlying chronic disease (Currie et al. 2021).
Treatment is divided in an intravenous intensive phase and an oral eradication phase, in order to prevent relapse.

60.1 Intravenous intensive phase

Ceftazidime 2 g (50 mg/kg = up to 1-2 g in children < 15 y) iv tid, or 6g/24 h continuous infusion after a loading dose of 2 g or Meropenem 1 g (25 mg/kg = up to 1 g in children < 15 y) iv tid.
(Amoxicillin-clavulanic acid 20/5 mg/kg iv qid may be used as a less-effective, second line drug).
Minimum duration of 10–14 days (except for very mild cases, see below).

Longer intravenous intensive therapy is recommended for:

- Complicated pneumonia (multilobar and/or with bacteremia and/or lymphadenopathies) and deep-seated infection (e.g., deep abscesses): 4 weeks.
- Osteomyelitis: 6 weeks.
- CNS melioidosis and mycotic aneurysm: 8 weeks.

Complex presentations:

- CNS melioidosis: Meropenem is the preferred initial intravenous therapy, and the dose should be doubled.
- Consider adding trimethoprim–sulfamethoxazole (in the doses recommended for eradication therapy) from the start of the initial intensive therapy in cases of neurological melioidosis, osteomyelitis and septic arthritis and deep-seated infections.
- Whenever possible, incision, drainage or debridement of large abscesses, affected bone or joints... should be carried out (repeatedly if required).
- Blood cultures should be repeated after 72h of treatment start, and from then weekly until fever clearance.
- Consider adding G-CSF 263 µg od sc x 3 days.

60.2 Oral eradication phase

Trimethoprim–sulfamethoxazole 6/30 mg/kg po bid.

- Up to 240/1,200 mg bid in children = 1.5 tablets of 160/800 mg bid.
- Up to 240/1,200 mg bid in adults (40-60 kg) = 1.5 tablets of 160/800 mg bid.

- Up to 320/1,600 mg bid in adults (> 60 kg) = 2 tablets of 160/800 mg bid;
- + PO folic acid 5 mg (0,1 mg/kg up to 5 mg in children) po od.

The eradication therapy should last for ≥3 months after the end of the initial intensive therapy.
Longer eradication therapy (≥6 months) is recommended for CNS melioidosis, mycotic aneurysm and osteomyelitis.
Mild cases (*i.e.* non-septic, skin-only, no underlying risk factors, …) may be treated without initial intensive therapy.

Trimethoprim–sulfamethoxazole (eradication dose) for 3 months.
In case of adverse reactions/allergy, trimethoprim-sulfamethoxazole may be replaced by:
Amoxicillin-clavulanic acid 20/5 mg/kg po tid;

- Adult >60 kg: 3 tablets of 50 0mg/125 mg tid.
- Adult <60 kg: 2 tablets of 500 mg/125 mg tid.
- Child: 20 mg/5 mg/kg tid (maximum 1000 mg/250 mg tid).

OR
Doxycycline 200 mg po od (Pitman et al. 2015a; Sullivan, Ward, and Currie 2019).
Both alternatives may be associated with more relapses.

60.3 Post-exposure prophylaxis (after accidental (laboratory) contact with the pathogen, duration 21 days)

Trimethoprim/sulfamethoxazole

- Adult >60 kg: 60 mg/800 mg tablets:2 tablets bid.
- Adult 40–60 kg: 60 mg/800 mg tablets: 5 tablets bid.
- Adult <40 kg: 60 mg/800 mg tablets tablet bid.
- Child: 8 mg/40 mg/kg (maximum dose 320 mg/1600 mg bid).

OR
Amoxicillin/clavulanic acid

- Adult>60kg: 500mg/125mgtablets: 3 tablets tid.
- Adult, <60kg: 500mg/125mgtablets: 2 tablets tid.
- Child: 20mg/5mg/kg q8 (maximum dose1000 mg/250cmg tid).

61 Mycobacteriosis, other than leprosy and tuberculosis

61.1 *Mycobacterium marinum* (fish tank granuloma)

Selected References

1. https://dx.doi.org/10.1517/14656566.8.17.2965 (Rallis and Koumantaki-Mathioudaki 2007)
2. https://dx.doi.org/10.1128/microbiolspec.TNMI7-0038-2016 (Aubry et al. 2016)

First-line treatment

Preliminary notes

- Some (mild) cases may heal spontaneously but it may take years.
- Evidence limited to case reports/small case series; no strong guideline exists.
- Duration of treatment is undefined (from 2 weeks to 2 years depending on individual factors); usually experts recommend to continue the antibiotherapy up to 2 months after the healing of lesions (so an average of 4 months in total, but sometimes much longer).
- In vitro, *M. marinum* is usually resistant to isoniazide, ethambutol, pyrazinamide, and all first-generation quinolones. Rifampicine and rifabutine are the most effective drugs (but no reimbursement for this indication). All other drugs: cyclines, amikacin, clarithromycin, second-generation quinolones, lizenolid, trimethoprim-sulfamethoxazol are considered moderately active.
- Treatment failures have been described with all "recomended" regimens.
- The role of surgery is controversial; topical therapy, whatever the drug used, is ineffective.

Mild disease (few superficial lesions limited in size):

- Doxycycline (200 mg po od) monotherapy may suffice; based on the in vitro data, a bitherapy seems "always" preferable (doxycycline with either clarithromycin 500 mg po bid or cotrimoxazole 160/800 po bid).

Extended disease (more than 3 lesions or deeper infiltration) or non-response to "first-line regimen".

- A rifampicin-containing (600 mg po od) bi or tritherapy (with doxycycline +/- clarithromycin; ethambutol also frequently used) is recommended (special request to obtain the reimbursement).

Alternative regimens

Many drugs listed here above (including those considered as moderally and even non active) have been used occasionally against *M. marinum* infection, most of the time in combination, so that their respective added value is unclear: (azithromycin, ethambutol, ciprofloxacin, moxifloxacin…).

61.2 Mycobacterium ulcerans (Buruli ulcer)

Selected References

1. https://dx.doi.org/10.1016/S1473-3099(06)70464-9 (Sizaire et al. 2006)
2. WHO, "Treatment of Mycobacterium Ulcerans Disease (Buruli Ulcer)," World Health Organization, pp. 1-66, 2012. https://afro.who.int/publications/treatment-mycobacterium-ulcerans-disease-buruli-ulcer(WHO 2012)
3. https://dx.doi.org/10.1586/14787210.2014.910113 (Huang and Johnson 2014)
4. https://dx.doi.org/10.5694/mja13.11331 (O'Brien et al. 2014)
5. https://dx.doi.org/10.1128/AAC.00175-07 (Chauty et al. 2007)
6. https://dx.doi.org/10.1016/S0140-6736(09)61962-0 (Nienhuis et al. 2010)
7. https://dx.doi.org/10.1371/journal.pntd.0000736 (Kibadi et al. 2010)
8. https://dx.doi.org/10.1128/AAC.02165-13 (Phillips et al. 2014)
9. https://dx.doi.org/10.1128/AAC.02853-15 (N. D. Friedman et al. 2016)
10. https://dx.doi.org/10.1371/journal.pntd.0003503 (Cowan et al. 2015)
11. https://dx.doi.org/10.1093/ofid/ofu021 (Christinet et al. 2014)
12. https://dx.doi.org/10.1016/j.jinf.2015.12.007 (Cowman et al. 2016)
13. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6513118/pdf/CD012118.pdf (Yotsu RR 2018)

First-line treatment

Preliminary notes:

- The incubation period is 4 months in average (range 1 to 9 months) in Australia.
- Staging is important to determine the best therapeutic option (see adapted WHO definitions here below).
- Nowadays, treatment relies almost always on the combination of surgery with antibiotic therapy, with excellent outcome (100% cure rate).
- Medical treatment alone is possible with early (nodular/small ulcer) stage 1 lesions; surgical treatment alone is not an option anymore (up to 30% relapse, even for small ulcers).
- Bacterial superinfection is possible but unusual; no need for prophylactic antibiotics (only culture-based).
- A slow healing of the ulcers must be expected without surgery (up to 10 months).
- Paradoxical reaction is possible in 25-30% of the treated patients; sometimes biopsy is needed to distinguish from treatment failure; steroids have been occasionally used for severe cases (by analogy to tuberculosis).

Table 2. Categories of Buruli ulcer and aims of treatment.

Treatment category	Form of disease	Treatment	Primary aim	Secondary aim
Category I	Single small lesion (e.g., nodule, papule, plaque and ulcer <5 cm in diameter)	Complete antibiotics If at or near a joint, maintain same movement as on unaffected side If surgery is needed in non-critical areas, consider this after 8 weeks of antibiotic treatment	Cure without surgery Cure without movement limitations	Reduce or prevent recurrence
Category II	Non-ulcerative and ulcerative plaque and edematous forms Single large ulcerative lesion 5–15 cm in diameter	Complete antibiotics, before surgery (if possible) If at or near a joint, maintain same movement as on unaffected side	Cure without surgery Reduce the extent of surgical debridement when needed Cure without movement limitations	Reduce or prevent recurrence
Category III	Lesions in the head and neck region, particularly face Disseminated and mixed forms such as osteitis, osteomyelitis, joint involvement Multiple lesions and osteomyelitis Extensive lesions >15 cm	Complete antibiotics, before surgery (if possible) If at or near a joint, maintain same movement as on unaffected side	Cure without surgery Cure without movement limitations	Reduce or prevent recurrence

Source: Treatment of Mycobacterium ulcerans disease (Buruli ulcer): guidance for health workers, *WHO* 2012

9789241503402_eng.pdf (5.062Mb)

WHO regimen (for endemic settings)

- Rifampicin 600 mg (10 mg/kg) po od + streptomycin 15 mg/kg im od x 8 weeks (+ surgical debridement/skin grafting for larger ulcers in a second step).
  - With this regimen depending on the size of ulcers, from 50 to 90% of the patients do not require surgery.
  - Medical treatment alone provided > 95% cure rate in early, limited (stage1) lesions.
  - For large ulcers > 10-15 cm and osteomyelitis (stage 3), some groups recommend a 12-week treatment.

NB1: Regimens with a 4-week rifampicin/streptomycin followed by a 4-week rifampicin/clarithromycin (7,5 mg/kg po od) and with a 2-week rifampicin/streptomycin followed by a 6-week rifampicin/clarithromycin (7,5 mg/kg po od) combination were found non-inferior, allowing to substantially decrease the number of injections.
NB2: Full oral therapies (see below) are also accepted by WHO since 2012 (although less evidence).

Australian regimen (more adapted to the non-endemic setting)

- Rifampicin 600 mg (10 mg/kg) po od + ciprofloxacin 500 mg bid (or moxifloxacin 400 mg od) po OR clarithromycin 500 mg (7,5 mg/kg) po bid x 8 weeks (+ limited surgical debridement in a subset of patients).

NB1: in this field study including > 100 patients (80% of them having stage 1 WHO lesions), up to 99% cured, some patients also with a shorter treatment (6 weeks); 25% had a paradoxical reaction after 6 weeks in average.
NB2: A retrospective study suggests that 14 to 42 days of medical treatment (most of the time associated with minor surgery) may provide cure rates up to 90%.

Alternative regimens

- There is no head-to-head RCTs that have compared the "full oral treatments". The combination rifampicin + ciprofloxacin/moxifloxacin should be viewed as second line (much less studied).

Special situations

Pregnancy:

- Streptomycin is contra-indicated; use the combination rifampicin/clarithromycin.

Immunosuppression:

- In case of HIV infection, careful assessment of an underlying TB before treatment.
- Clinical presentation seems more severe in HIV patients.
- Treatment outcome is usually similar using the standard regimens.

61.3 Other non-tuberculosis mycobacteria (NTM)

Main therapeutic principles:

- Monotherapy should be avoided.
- Treatment should be guided by drug susceptibility testing (DST).
- Almost all species are still sensitive to clarithromycin and amikacin, except some strains of *M. abscessus* and *M. simiae,* for which clofazimine, cycloserine and tigecycline could be considered.
- Usually, bitherapy of at least 4 months for limited infections, up to tritherapy for 6-12 months for disseminated/severe infections, with an intensive phase.

- Surgery should be considered.

There are four clinical situations where NTM may be incriminated.

61.3.1 Skin and soft tissue infection

Selected Reference

1. https://dx.doi.org/10.1016/j.det.2015.03.017 (Gonzalez-Santiago and Drage 2015)

Main causative agents
Slow-growing NTM (> 7 days)

- *M. marinum* (see above)
- *M. ulcerans* (see above)
- *M. kansasii* (immunosuppression)
- *M. haemophilum* (immunosuppression)

Fast-growing NTM (< 7 days)

- *M. abscessus* complex (trauma, surgery, injection,…)
- *M. fortuitum* complex (trauma, surgery, injection,…)
- *M. chelonae* (trauma, surgery, injection,…)

First-line treatment

- For *M. marinum* and *ulcerans*: see above.
- For others: no standard regimen: DST-based combination therapy associated with surgery in selected cases

61.3.2 Chronic pulmonary disease

Selected References

1. https://dx.doi.org/10.1586/14787210.2013.830413 (van Ingen 2015)
2. https://dx.doi.org/10.1164/rccm.200604-571ST (D. E. Griffith et al. 2007)
3. https://www.idsociety.org/practice-guideline/nontuberculous-mycobacterial-ntm-diseases/ (Daley et al. 2020)

61.4 Main causative non-tuberculous mycobacteria (NTM)

M. avium/intracellulare complex; *M. kansasii; M. abscessus* complex; *M. xenopi.*

Principles of therapy

It is crucial (but not easy) to distinguish between colonization and infection. Please use the criteria as revised elaborated in the Infectious Diseases Society of America and American Thoracic Society (IDSA/ATS) 2020 guideline (here below).

Table 2. Clinical and Microbiologic Criteria for Diagnosis of Nontuberculous Mycobacterial Pulmonary Disease[a]

Clinical	Pulmonary or Systemic Symptoms	
Radiologic	Nodular or cavitary opacities on chest radiograph, or a high-resolution computed tomography scan that shows bronchiectasis with multiple small nodules	Both Required
and	Appropriate exclusion of other diagnoses	
Microbiologic[b]	1. Positive culture results from at least two separate expectorated sputum samples. If the results are nondiagnostic, consider repeat sputum AFB smears and cultures **or** 2. Positive culture results from at least one bronchial wash or lavage **or** 3. Transbronchial or other lung biopsy with mycobacterial histologic features (granulomatous inflammation or AFB) and positive culture for NTM or biopsy showing mycobacterial histologic features (granulomatous inflammation or AFB) and one or more sputum or bronchial washings that are culture positive for NTM	

Source: Daley CL *et al*. Treatment of Nontuberculous Mycobacterial Pulmonary Disease: An Official ATS/ERS/ESCMID/IDSA Clinical Practice Guideline. *Clin Infect Dis*. 2020

There are 2 major clinical presentations (fibrocavitary disease, more severe, and nodular bronchiectatic disease, more stable).

Watchful waiting is recommended for asymptomatic cases. Treatment relies mainly on the combination of macrolide-based therapy with 2 other (injectable) drugs for up to 12 months after culture negativation (see recommendations here below for each species) with surgery in selected cases.

Current recommendations (2020)

Organism	No. of Drugs	Preferred Drug Regimen[a]	Dosing Frequency
M. avium complex			
Nodular-bronchiectatic	3	Azithromycin (clarithromycin) Rifampicin (rifabutin) Ethambutol	3 times weekly
Cavitary	≥3	Azithromycin (clarithromycin) Rifampicin (rifabutin) Ethambutol Amikacin IV (streptomycin)[b]	Daily (3 times weekly may be used with aminoglycosides)
Refractory[c]	≥4	Azithromycin (clarithromycin) Rifampicin (rifabutin) Ethambutol Amikacin liposome inhalation suspension or amikacin IV (streptomycin)[b]	Daily (3 times weekly may be used with aminoglycosides)
M. kansasii			
	3	Azithromycin (clarithromycin) Rifampicin (rifabutin) Ethambutol	Daily
	3	Azithromycin (clarithromycin) Rifampicin (rifabutin) Ethambutol	3 times weekly
	3	Isoniazid Rifampicin (rifabutin) Ethambutol	Daily
M. xenopi			
	≥3	Azithromycin (clarithromycin) and/or moxifloxacin Rifampicin (rifabutin) Ethambutol Amikacin[b]	Daily (3 times weekly may be used with aminoglycosides)

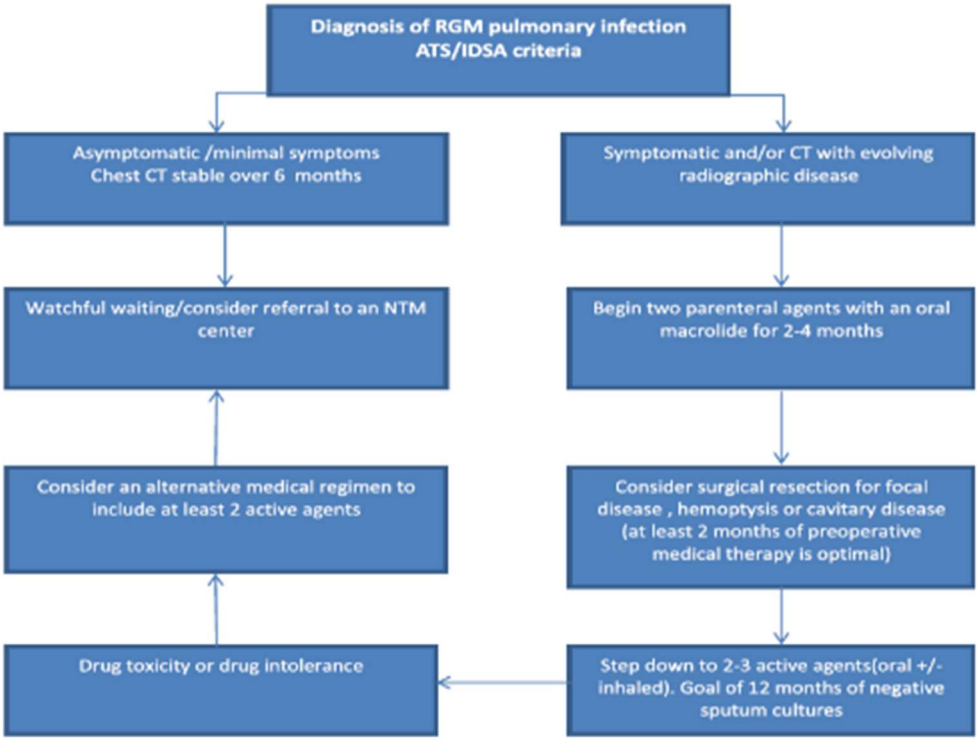
Source: Daley CL *et al*. Treatment of Nontuberculous Mycobacterial Pulmonary Disease: An Official ATS/ERS/ESCMID/IDSA Clinical Practice Guideline. *Clin Infect Dis*. 2020

Table 5. Treatment Regimens for *Mycobacterium abscessus* by Macrolide Susceptibility (Mutational and Inducible Resistance)

Macrolide Susceptibility Pattern				
Mutational[a]	Inducible[b]	No. of Drugs[c]	Preferred Drugs	Frequency of Dosing
Susceptible	Susceptible	Initial phase ≥ 3	*Parenteral (choose 1–2)* Amikacin Imipenem (or Cefoxitin) Tigecycline *Oral (choose 2)* Azithromycin (clarithromycin)[d] Clofazimine Linezolid	Daily (3 times weekly may be used for aminoglycosides)
		Continuation phase ≥ 2	*Oral/inhaled (choose 2–3)* Azithromycin (clarithromycin)[d] Clofazimine Linezolid Inhaled amikacin	
Susceptible	Resistant	Initial phase ≥ 4	*Parenteral (choose 2–3)* Amikacin Imipenem (or Cefoxitin) Tigecycline *Oral (choose 2–3)* Azithromycin (clarithromycin)[e] Clofazimine Linezolid	Daily (3 times weekly may be used for aminoglycosides)
		Continuation phase ≥ 2	*Oral/inhaled (choose 2–3)* Azithromycin (clarithromycin)[e] Clofazimine Linezolid Inhaled amikacin	
Resistant	Susceptible or resistant	Initial phase ≥ 4	*Parenteral (choose 2–3)* Amikacin Imipenem (or Cefoxitin) Tigecycline *Oral (choose 2–3)* Azithromycin (clarithromycin)[e] Clofazimine Linezolid	Daily (3 times weekly may be used for aminoglycosides)
		Continuation Phase ≥ 2	*Oral/inhaled (choose 2–3)* Azithromycin (clarithromycin)[e] Clofazimine Linezolid Inhaled amikacin	

Source: Daley CL *et al*. Treatment of Nontuberculous Mycobacterial Pulmonary Disease: An Official ATS/ERS/ESCMID/IDSA Clinical Practice Guideline. *Clin Infect Dis*. 2020

The algorithm here below can also be helpful:



Source: Daley CL *et al*. Treatment of Nontuberculous Mycobacterial Pulmonary Disease: An Official ATS/ERS/ESCMID/IDSA Clinical Practice Guideline. *Clin Infect Dis*. 2020

Disseminated infection in immunosuppressed individuals.
Case by case treatment decision based on identification and DST.

61.5 Lymphadenitis (mostly cervical, in children)

Selected References

1. https://dx.doi.org/10.1016/j.jinf.2015.02.010 (Zimmermann et al. 2015)

Main causative NTM (most are slow-growing):

- *M. avium* complex; *M. Intracellulare* complex; *M. Scrofulaceum* complex; (*M. haemophium, M. malmoense….*)

First-line treatment

- Spontaneous cure occurs in up to 70% of cases within 6 months and almost 100% within 1 year.
- Cure rate with antimicrobial therapy is not much higher (60-75%); the main reported treatment is clarithromycin (15 to 30 mg/kg/day), most of the time combined with rifampicin or rifabutin or ethambutol, for an average duration of 12 weeks
- The best outcome is obtained with complete lymph node resection (90-95% cure rate), but with some risk of facial palsy. Puncture-aspiration provided low cure rate 30%)

62 Plague (Yersinia pestis)

Selected References

1. https://dx.doi.org/10.1586/14787210.2013.814432 (Oyston and Williamson 2013)
2. https://dx.doi.org/10.1016/S0140-6736(07)60566-2 (Prentice and Rahalison 2007)
3. https://dx.doi.org/10.1128/AAC.04548-14 (Heine et al. 2015)
4. https://dx.doi.org/10.1086/500137 (Mwengee et al. 2006)
5. https://dx.doi.org/10.3201/eid2303.161212 (Apangu et al. 2017)
6. https://doi.org/10.1093/cid/ciz1226 (C. A. Nelson et al. 2020)
7. https://www.cdc.gov/mmwr/volumes/70/rr/rr7003a1.htm?s_cid=rr7003a1_w (C. A. Nelson et al. 2021)

First-line treatment

Bubonic and pharyngeal plague

- Doxycycline 200 mg loading dose, then 100 mg (2.2 mg/kg) bid iv or po or ciprofloxacin 400 mg tid iv /750 mg po bid or gentamicin 2.5 mg/kg im or iv bid x 10-14 days.
- Surgical incision and drainage might be necessary if the bubo becomes suppurative
- Dual therapy with two distinct classes of antimicrobials should be used for initial treatment of patients with large buboes or infected after intentional release of *Yersinia pestis*.

Pneumonic and septicemic plague

- Mild to moderate disease
  - Ciprofloxacin 400 mg tid iv/750 mg po bid or gentamicin 2.5 mg/kg im or iv bid x 10-14 days.
- Severe disease or infection following intentional release of *Y pestis.*
  - Dual therapy with first (or second)-line antimicrobials (of two distinct classes) for 10-14 days.

Plague meningitis

- Chloramphenicol 25 mg/kg iv qid (maximum 1 g/dose) + levofloxacin 750 mg iv or po qid or moxifloxacin 400 mg iv or po qid x 10-14 days.

NB1: Streptomycin (2 g, or 30 mg/kg, im od x 10 days) and chloramphenicol (12.5 mg/kg iv/po qid x 10 days) have been the historical (and most studied) therapies for plague but are not available any more in Belgium.

NB2: Penicillin's, cephalosporins and macrolides were inconclusively effective in animal models (although in vitro effective at least for cephalosporins), but show higher case fatality rates in humans when compared to more effective antimicrobials (C. A. Nelson et al. 2020).

NB3: Cases of multidrug resistant plague has been occasionally reported (but only from Madagascar or in case of engineered resistance as part of a bioterrorist attack).

NB4: Prognosis (in particular of the most severe forms) highly depends on early administration of antimicrobials AND quality of sepsis/shock care.

Alternative regimens

- Bubonic and pharyngeal plague
  - Chloramphenicol 12.5-25 mg/kg iv qid or TMP-SMZ 5 mg/kg TMP component iv or po tid.
- Pneumonic and septicemic plague
  - Doxycycline 200 mg loading dose, then 100 mg po bid or chloramphenicol 12.5-25 mg/kg iv qid or TMP-SMZ 5 mg/kg TMP component iv or po tid.
- Plague meningitis
  - Replace chloramphenicol by other first or second line non-fluoroquinolone antimicrobial used to treat pneumonic or septicemic plague.

Special situations

Post-exposure prophylaxis:

- Ciprofloxacin/levofloxacin, doxycycline (and cotrimoxazole) for 7 days have been used/are suggested for post-exposure prophylaxis (should be administered within 6 days maximum).

Pregnancy and children > 8 years:

- Gentamycin (or ciprofloxacin)

63 Q fever (Coxiella burnetti)

Selected References

1. https://dx.doi.org/10.1128/CMR.00045-16 (Eldin et al. 2017)
2. https://dx.doi.org/10.1586/14787210.2013.840534 (Kersh 2013)
3. http://www.ncbi.nlm.nih.gov/pubmed/23535757 (Anderson et al. 2013)
4. https://dx.doi.org/10.1097/MD.0000000000004287 (Eldin et al. 2016)
5. https://dx.doi.org/10.1016/S1473-3099(10)70135-3 (Eldin et al. 2016)
6. https://dx.doi.org/10.1097/MD.0000000000002810 (Million et al. 2010)
7. https://dx.doi.org/10.1093/cid/cix886 (van Roeden et al. 2018)
8. https://dx.doi.org/10.1093/cid/ciu259 (Million et al. 2014)
9. https://dx.doi.org/10.1517/14740338.2016.1133584 (Million et al. 2014)
10. https://dx.doi.org/10.1093/cid/cit419 (Million et al. 2013)
11. https://dx.doi.org/10.1093/cid/cix013 (Keijmel et al. 2017)

Pre-treatment assessment in all Q fever patients:

- Transthoracic echocardiogram, to be completed with transesophageal echocardiogram if TTE inconclusive.
- Abdominal imaging to exclude aneurysm in at-risk patients: > 65 years, tobacco use, family history of aneurysm.
- Antiphospholipid antibodies in acute Q-fever are associated with an elevated risk for chronic Q-fever.

No need of treatment in asymptomatic individuals, or after resolution of symptoms, except in pregnant women and if risk factors of persistent infection, mainly valvulopathy.
There is continuous controversy between Dutch and French about the terminology of "chronic Q fever" versus "persistent focalized infection" (see Eldin C's review).

Acute Q fever with symptoms

Diagnosis by PCR in blood/serum or fourfold increase of phase II IgG antibodies in paired sera, but initiate treatment as soon as the diagnosis is suspected: DON'T wait for the results of paired serology!

First-line treatment

- Doxycycline 100 mg (children 2.2 mg/kg) BID po for 14 days.
- Pregnancy: TMP/SMX 160/800 mg po bid for the duration of pregnancy but discontinue prior to delivery to lessen risk of hyperbilirubinemia in the baby.
- If known cardiac valvulopathy or elevated anti-phospholipid antibodies: doxycycline 100 mg po bid + hydroxychloroquine 200 mg po tid x 12 months (Todd et al. 2015).
- Doxycycline for up to 21 days is safe in children. An alternative treatment is TMP/SMX 4/20 mg/kg po bid x 14 days (Riedner et al. 2005).

Alternative regimens

Fluoroquinolones:

- moxifloxacin 400 mg po od for 2 - 3 weeks
- ciprofloxacin 400 mg po bid for 2 - 3 weeks

Macrolides, but concern about QTc prolongation:

- clarithromycin 500 mg po BID
- azithromycin 500 mg po OD, but higher MIC

Special situations

Acute Q fever and immunosuppression:

- No clear guideline exists but close serological monitoring is required.

Chronic Q fever (endocarditis, or vascular infections, or persistent focalized infections, such as lymphadenitis or osteoarticular):

- Diagnosis of chronic Q fever relies either on PCR of heart valves/endovascular grafts or on a high Phase 1 IgG titer > or = 1/800.

First-line treatment

- Doxycycline 100 mg po bid + hydroxychloroquine 200 mg po tid for at least 18 months in native heart valves (and persistent focalized infections) and at least 24 months in prosthetic valves or in vascular infections. Duration will mainly depend on serological response and PET Scan evolution.
- Pregnancy: TMP/SMX 160/800 mg po bid until the delivery, followed by doxycycline and hydroxychloroquine for 12 months post-partum (in women who develop a serologic profile of chronic Q fever (Phase 1 IgG titers > or = 1/800).
- Children < 8 years: a course of doxycycline for up to 3 weeks is considered safe. There is insufficient data to make recommendations for this group. Expert consultation is advised. Case reports mention prolonged use of doxycycline (Maltezou and Raoult 2002). Another publication mentions 3 children with Q fever osteomyelitis: 1 treated with ciprofloxacin + rifampin for 12 months with a relaps 4 years later treated with doxycycline + hydroxychloroquine + rifampin; a second child treated successfully with TMP/SMX for 12 months and the third treated with rifampin + TMP/SMX (Dabaja-Younis et al. 2020).

NB1: The risk of retinopathy should be monitored every 6 months by ophthalmoscopy in patients treated with hydroxychloroquine.

NB2: Surgery is often required for prosthetic valves and vascular infections (especially aneurysms), and significantly reduces mortality.

Alternative regimens

A large retrospective trial with 276 patients receiving treatment for chronic Q fever demonstrated that doxycycline + quinolones provided similar outcomes than the first-choice treatment (doxycycline + hydroxychloroquine) and could be a good the best alternative if hydroxychloroquine is not tolerated (van Roeden et al. 2018).

Fluoroquinolones penetrate well in the cerebrospinal fluid, so could be of use in Q fever meningoencephalitis.

Special situations

Chronic fatigue after Q fever

- A recent study in the Netherlands showed that there is no benefit for long-term therapy of doxycycline, in contrast with cognitive-behavioral therapy.

64 Rickettsioses

Rickettsioses are classically divided in two groups: (1) Spotted Fever group [SFG] (*R. conorii, R. africae*, *R. rickettsia…* agents of tick-borne spotted fevers, or *R. Felis* agent of flea-borne spotted fever) and (2) Typhus group [TG] (*R. prowazecki,* agent of louse-borne epidemic typhus, *R. typhi,* agent of flea-borne murine typhus), to which the group *Orientia tsutsugamushi* (agent of scrub typhus) is usually associated. They differ mainly by way of acquisition and by severity, but treatment of all species is very similar, and therefore grouped here below. Therapeutic differences will be highlighted whenever relevant.

Selected References

1. https://dx.doi.org/10.1097/QCO.0b013e328363811b (Blanton 2013)
2. https://dx.doi.org/10.1586/eri.12.139 (Botelho-Nevers et al. 2012)
3. https://dx.doi.org/10.1258/td.2010.100311 (Rajapakse, Rodrigo, and Fernando 2011)
4. https://dx.doi.org/10.1086/425008 (Kim et al. 2004)
5. https://dx.doi.org/10.1016/S0140-6736(00)02728-8 (Watt et al. 2000)

First-line treatment

- Doxycycline 100 mg (2.2 mg/kg) po/(iv) bid x 1 week.

NB1: in uncomplicated Mediterranean spotted fever (MSF, due to *R. conorii*), African tick bite fever (ATBF, due to *R. africae*) and murine typhus and scrub typhus, doxycycline 200 mg single dose po was as effective as a 1-week treatment (Watt 2000 RICKETTSIOSES).

NB2: in severe disease, doxycycline is superior (lower mortality) to all other alternative drugs.

Alternative regimens

- Clarithromycin 500 mg (7,5 mg/kg) po bid x 1 week for all SFG; not really studied in TG (but should work based on in vitro data); azithromycin has been sometimes found less effective than clarithromycin for SFG but is at least as effective (azithromycin 500 mg po od x 3 days or even one day) as 7-day doxycycline for mild scrub typhus.
- Ciprofloxacin 500 mg po bid x 1 week, but delayed fever clearance (compared to doxycycline) and sometimes found deleterious in severe cases of SFG and scrub typhus; not really tested for TG; probably less effective for scrub typhus in general.
- Rifampicin 300 mg po bid x 5 days, but delayed fever clearance (compared to doxycycline); several less common Rickettsia species are intrinsically resistant.

NB: cotrimoxazole is ineffective for both SFG and TG; activity of erythromycin is too variable to be promoted; penicillin's and cephalosporins are ineffective.

Special situations

Pregnancy

- Clarithromycin 500 mg po bid x 1 week or azithromycin 500 mg po od x 1-3 days.
- In case of severe rickettsial infection, consider anyway doxycycline po or iv (at least a single 200 mg dose).

Children < 8 years:

- Clarithromycin 7.5 mg/kg bid x 7 days (or azithromycin for 3 days).
- In case of severe disease, consider anyway at least a single 2,2 mg/kg dose of doxycycline.

Treatment failure

- (To consider mainly for scrub typhus acquired in North Thailand): rifampicin 300 mg bid or tid x 1 week.

65 Salmonellosis

Selected References

1. https://dx.doi.org/10.1111/j.1469-0691.2011.03552.x (Butler 2011)
2. https://dx.doi.org/10.1002/14651858.CD006083.pub2 (Effa and Bukirwa 2008)
3. https://dx.doi.org/10.1128/CMR.00002-15 (Crump et al. 2015)
4. https://dx.doi.org/10.1016/S0140-6736(13)62708-7 (Wain et al. 2015)
5. https://dx.doi.org/10.1016/j.vaccine.2015.03.102 (Kariuki et al. 2015)
6. WHO, "Background document: The diagnosis, treatment and prevention of typhoid fever, " World Health Organization, pp. 1-38, 2003. http://www.who.int/rpc/TFGuideWHO.pdf (WHO 2003)
7. https://dx.doi.org/10.1016/j.tim.2014.06.007 (Gunn et al. 2014)
8. https://dx.doi.org/10.3855/jidc.3030 (Jain and Chugh 2013)
9. https://dx.doi.org/10.1093/cid/cix342 (Phoba et al. 2017)
10. https://dx.doi.org/10.1093/cid/cix652 (Kleine et al. 2017)

65.1 Typhoidal Salmonella (*S. typhi, S. paratyphi*)

General principles

- Antibiotics with intracellular activity (e.g., fluoroquinolones, macrolides, ceftriaxone) are preferred for their curative effectiveness as well as eradication of carriership and prevention of relapses.
- Widespread prevalence of multidrug resistance (*i.e.,* for amoxicillin, co-trimoxazole and chloramphenicol) and decreased susceptibility to fluoroquinolones (especially in Asia) preclude the empiric use of these drugs.
- XDR *S. typhi,* resistant to third generation cephalosporins (ESBL) and/or azithromycin is increasingly reported, especially in India and Pakistan but also in Cambodia, Bangladesh, China, Indonesia, Nepal, Nigeria and DRC (Browne et al. 2020).

Empirical treatment:

- Ceftriaxone 2 g (50-75 mg/kg) iv bid (severe cases) or
- Azithromycin 500-1000 (10-20 mg/kg) mg d1, followed by 500 mg po od (milder cases).

Documented treatment based on susceptibility test:

- Ciprofloxacin (provided MIC < 0.125 µg/ml): 500 mg bid or
- Azithromycin (provided MIC ≤ 16 µg/ml): 500-1000 mg d1, followed by 500 mg od

NB: when susceptible, ciprofloxacin is preferred over azithromycin because of a more rapid bacteremia- and fever clearance (related to its high extracellular concentration when compared to azithromycin).
In cases of multidrug resistance where macrolides, ceftriaxone and ciprofloxacin cannot be used, meropenem with or without other molecules (tigecyclin, fosfomycin) has been used successfully.

Total treatment duration (empirical + documented): average 7-14 d:

- Shorter courses (5-7 d) apply for mild cases and when azithromycin or fluoroquinolones can be used.
- Longer courses (10-14 d) apply when ceftriaxone is used.

Special situations

For pregnant women and children, the same treatment choices may apply as the benefits outweighs the possible risks.

Chronic carriership:

- First choice: ciprofloxacin 500-750 mg BID po for 14-28 days +/- cholecystectomy
- In case of underlying decreased fluoroquinolone susceptibility to be tailored to susceptibility pattern

65.2 Non-typhoidal Salmonella (NTS)

Antimicrobial agents are not recommended for treatment of non-severe, nontyphoidal *Salmonella* diarrhea in healthy adults or children.
Treatment recommended for:

- Severe diarrhea (febrile, dysenteric).
- Bloodstream infection or extraintestinal infection.
- Any infection in patients at risk for bacteremia and disseminated disease (*i.e.,* immune compromised).

There is less evidence about treatment schedules, same as for *S. typhi* may be applied so far.
NTS are associated with higher prevalence of antibiotic resistance for third generation cephalosporins, fluoroquinolones, azithromycin.
Deep-seated extra-intestinal infection (e.g., osteomyelitis, vasculitis) may require prolonged treatment (up to 4-6 w).

66 Shigellosis

Selected References

1. https://dx.doi.org/10.1016/S0140-6736(17)33296-8 (Kotloff et al. 2017)
2. https://dx.doi.org/10.1016/S2214-109X(17)3(Baker et al. 2015)0392-3 (Tickell et al. 2017)
3. https://dx.doi.org/10.1002/14651858.CD006784.pub4 (Christopher et al. 2010)
4. https://dx.doi.org/10.1093/ije/dyq024)(Traa et al. 2010)
5. https://dx.doi.org/10.1586/14787210.2015.983902 (Klontz and Singh 2015)
6. https://dx.doi.org/10.1177/2049936117744429 (Mokomane et al. 2018)
7. https://dx.doi.org/10.1016/j.jinf.2012.01.006 (Pfeiffer, DuPont, and Ochoa 2012)
8. https://dx.doi.org/10.1016/j.ijantimicag.2012.02.005 (Gu et al. 2012)
9. https://dx.doi.org/10.1128/AAC.02360-12 (Karlsson et al. 2013)
10. https://dx.doi.org/10.3201/eid2211.160883 (Gaudreau et al. 2016)
11. https://dx.doi.org/10.3201/eid2211.160653 (Mook et al. 2016)
12. https://dx.doi.org/10.1016/S1473-3099(15)00002-X (Baker et al. 2015)

General principles

- Data and guidelines on the treatment of Shigellosis are scarce, which is problematic in view of fast evolving antibiotic resistance.
- Any Shigella infection probably requires treatment, i.e., also non-dysenteric infections; some experts recommend a more selective approach (small children, elderly, severe disease, immunosuppression, food handlers,).
- There is globally fast spreading of fluoroquinolone resistance, ESBL, and emerging decreased susceptibility to azithromycin, e.g., among MSM
- Any empiric treatment requires adaptation according to susceptibility testing. Where local antimicrobial sensitivities are known, local guidelines should be followed.

Empiric treatment recommendations (based on WHO 2012).

First line treatment

- Non-severe disease, no immune suppression: Ciprofloxacin 12,5-15 mg/kg up to 500 mg po bid x 3 - 5 days
- Severe disease, immune suppression, infants < 3 months: Ceftriaxone: 50–80 mg/kg im/iv od.

2nd line treatment: (adults):

- Azithromycin 10 mg/kg up to 500 mg po od for 3 - 5 days; or cefixime 8 mg/kg po bid x 2 - 5 days (Martin et al. 2000).

Alternatives (only if proved susceptibility):

- TMP-SMZ 4+20 mg/kg up to 160+800 mg) bid x 3-5 days or ampicillin 50-100 mg/kg po qid 50-200 mg/kg iv qid (Shane et al. 2017).

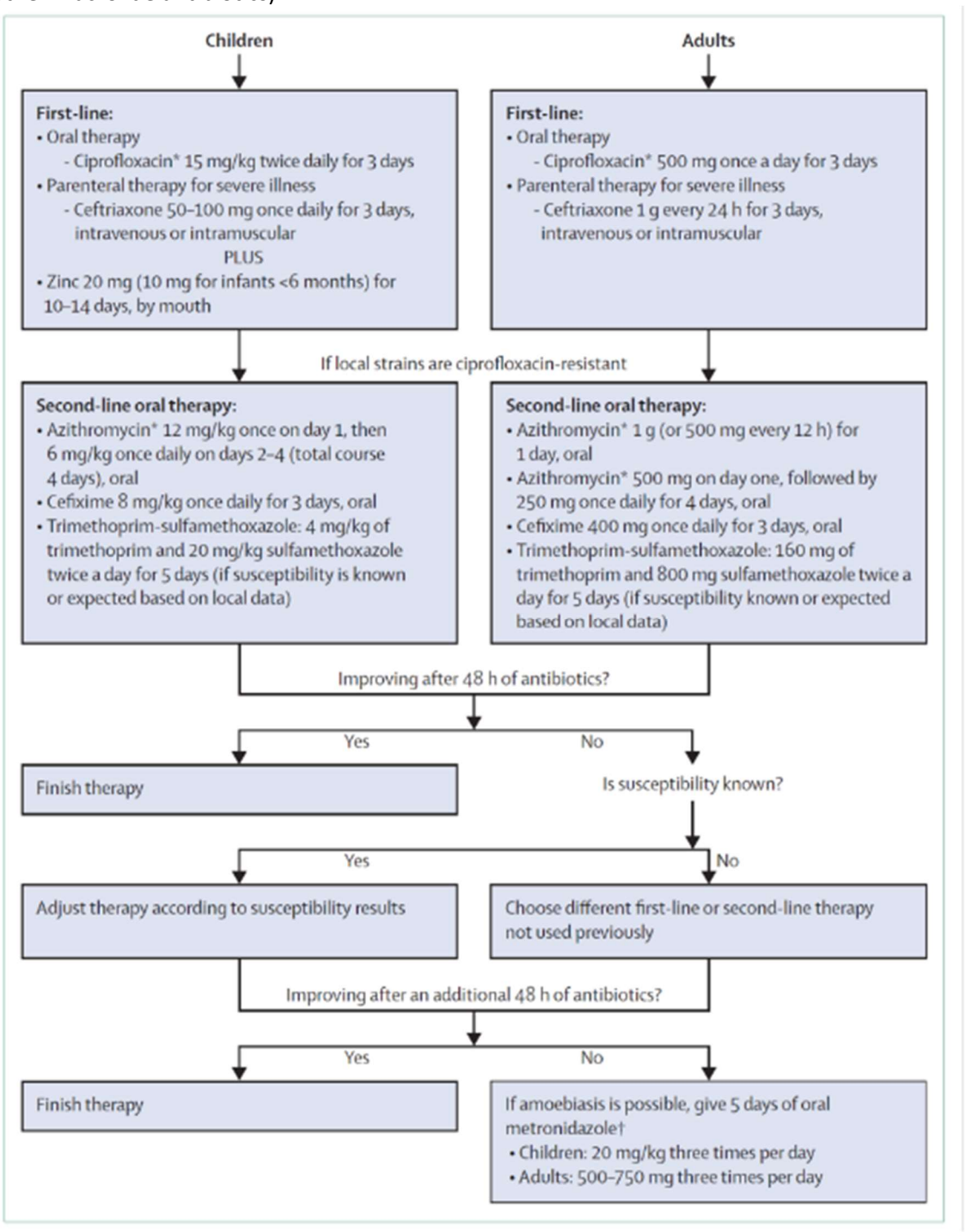
Severe/complicated disease:

- Consult with a specialist for guidance on duration of treatment

NB: Role of azithromycin

No published trials comparing the efficacy of azithromycin to ciprofloxacin to treat *Shigellosis* in children, previous trials in adults have revealed similar efficacy to ciprofloxacin and higher *in vitro* susceptibility.
Azithromycin may be an appropriate second-line alternative therapy due to its oral administration and affordability.
However, there are increasing reports of azithromycin-resistant strains.

Safety concerns have been documented regarding both ciprofloxacin use (risk of polyneuropathy) and azithromycin (risk of prolonged QT syndrome although this risk is lower for azithromycin than that among other macrolide antibiotics).



Source: Kotloff K *et al.* Shigellosis. *Lancet.* 2018

67 Tuberculosis

Selected References

Latent tuberculosis

https://www.fares.be/tuberculose/publications/recommandations/belgian-guidelines-on-the-diagnosis-and-management-of-latent-tuberculosis-infection

https://www.nice.org.uk/guidance/ng33/chapter/Recommendations

Tuberculosis disease

ECDC and ERS : https://www.ecdc.europa.eu/en/all-topics-z/tuberculosis/prevention-and-control/european-union-standards-tuberculosis-care

WHO : https://www.who.int/publications/m/item/international-standards-for-tuberculosis-care-(istc)

IDSA : https://www.idsociety.org/practice-guideline/treatment-of-drug-resistant-tb/

NICE : https://www.nice.org.uk/guidance/ng33/chapter/Recommendations

68 Tularemia

Selected References

1. WHO, "WHO guidelines on Tularaemia," World Health Organization, pp. 1-125, 2007. http://www.ncbi.nlm.nih.gov/pubmed/5107036
2. https://dx.doi.org/10.1016/j.idc.2006.03.002 (Eliasson et al. 2006)
3. https://dx.doi.org/10.3109/00365548.2012.720027 (Yeşlyurt et al. 2013)
4. https://dx.doi.org/10.1089/vbz.2013.1406 (Yilmaz et al. 2014)
5. https://dx.doi.org/10.1056/NEJMra1409755 (Adalja, Toner, and Inglesby 2015a)

First-line treatment

Mild to moderate disease:

- Adults: doxycycline 100 mg PO bid x 14-21 days.
- Children: gentamicin 2,5 mg/kg IM or iv bid or tid x 5-10 days.

Severe disease:

- Streptomycin 10 mg/kg im bid x 10 days (children 15-20 mg/kg bid) or gentamycin (for children gentamycin is the preferred treatment) 2,5 mg/kg im or iv bid or tid x 10 days.

Meningitis:

- On top of an aminoglycoside, add chloramphenicol 15-25 mg/kg iv qid x 14-21 days (nB: not available in Belgium).

Endocarditis (extremely rare)

Alternative regimens

Mild to moderate disease:

- Ciprofloxacin 500 mg po bid (adults) or 15 mg/kg bid (children) x 10-14 days (preferred to doxycycline by some experts because of lower rates of relapse in two publications).

Meningitis:

- On top of an aminoglycoside, add doxycycline 100 mg bid po or ciprofloxacin 400 mg iv bid (adults) or 15 mg/kg iv bid (children) when chloramphenicol is unavailable

Special situations

Pregnancy:

- Gentamicin and ciprofloxacin were effective in case reports;
- PEP after bioterrorism exposure
- Doxycycline 100 mg po bid x 14 days or ciprofloxacin 500 mg po bid x 7-14 days.

NB: Dosing of aminoglycosides must be adapted according to serum concentrations; for streptomycin audiometry is advised if there is risk for toxic serum concentration (renal insufficiency, elderly, pediatric patients).

69 Yaws (Treponema pallidum subsp. pertenue)

Selected References

1. https://dx.doi.org/10.1016/S0140-6736(12)62130-8 (Mitjà, Asiedu, and Mabey 2013)
2. https://dx.doi.org/10.1177/0956462414549036 (Marks et al. 2015)
3. https://dx.doi.org/10.1016/S0140-6736(11)61624-3 (Marks et al. 2015)
4. https://dx.doi.org/10.1056/NEJMoa1408586 (Mitjà et al. 2015)
5. https://dx.doi.org/10.4269/ajtmh.16-0943 (González-Beiras et al. 2017)
6. https://dx.doi.org/10.1016/S2214-109X(17)30388-1 (Mitjà et al. 2017)
7. https://doi.org/10.3390/tropicalmed3030092 (Marks 2018)

First-line treatment (primary and secondary yaws)

- Benzathine benzylpenicillin G 600,000 IU single dose im in children < 10 years and 1,200,000 IU single dose im in older children and adults OR azithromycin 30 mg/kg single dose po (non-inferior to benzathine penicillin).

NB1: Cure rate of about 95% for both regimens; disappearance of treponemes in lesions within 8-10 hours, disappearance of joint pains within 48 hours, healing of skin lesions within 2-4 weeks, and 90% of four-fold decrease or seronegativation of RPR after 12 months.

NB1: Azithromycin mass treatment (WHO recommendation) is effective to control yaws at the community level; studies with lower dose of azithromycin (20 mg/kg single dose, like that needed for trachoma) are ongoing, but non-inferiority has not been demonstrated so far (Marks 2018).

NB3: There are case reports of complete cure of yaws osteoperiostitis with single dose azithromycin

NB4: there are also some concerns about emergence of azithromycin resistance (Mitjà et al. 2018).

Alternative regimens

- Doxycycline 100 mg po bid x 15 days and erythromycin 8-10 mg/kg qid x 15 days have been used sporadically.
- Penicillin V has been found successful in some case series.

Special situations

Latent yaws:

- Azithromycin 30 mg/kg po single dose.
    - 92% efficacy in a large longitudinal series.
    - WHO recommendation for eradication.

Treatment failure of primary and secondary yaws:
Repeat the same treatment or use the alternative one.

Treatment of tertiary yaws:
Is unknown.

Pregnancy:
Treat similarly (if symptoms or f latent), because no risk of vertical transmission, unlike syphilis.

70 Yersinia enterocolitica

Selected References

1. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5850553/pdf/cix669.pdf (Shane et al. 2017).

Clinical benefit from antimicrobial treatment for uncomplicated enterocolitis has not been demonstrated.

First-line treatment

Mild to moderate disease (enterocolitis):

- Adults: Ciprofloxacin 500 mg po bid x 5 days.
- Children: TMP-SMZ 8 mg/kg per day and SMX 40 mg/kg per day in two divided doses.

Severe disease (septicemia):

- Ceftriaxone 2 gr iv qid (adults) or 100 mg/kg in one or two divided doses (children) + gentamycin 5 mg/kg in one or three divided doses, with oral switch to ciprofloxacin 500 mg PO BID after clinical improvement. Total duration of treatment 21 days. (Gayraud M et al, *Clin Infect Dis.*1993)

Alternative treatment

- Mild to moderate disease in adults
- Doxycycline 100 mg po bid or TMP-SMZ 8 mg/kg per day and SMX 40 mg/kg per day in two divided doses.

Severe disease:

- Ciprofloxacin 400 mg iv bid or cefotaxime 2 gr iv tid.

Chapter 4: Ectoparasites

71 Bed bugs

Pathogens: *Cimex lectularius* (temperate) and *Cimex hemipterus* (tropical).
No transmission of infectious diseases, so far.

Selected References

1. https://dx.doi.org/10.1128/CMR.05015-11 (Doggett et al. 2012)
2. https://dx.doi.org/10.1093/cid/ciq102 (Delaunay et al. 2011)
3. https://dx.doi.org/10.1001/jama.2009.405 (Goddard and DeShazo 2009)
4. https://dx.doi.org/10.1016/j.jemermed.2013.05.014 (Sheele et al. 2013)
5. https://dx.doi0.1056/NEJMcp1905840 (Parola and Izri 2020)

First-line treatment

Symptomatic treatment only (corticosteroids topical or systemic).

Alternative regimen

Place of ivermectin in severe cases?

Advice to patients for control and elimination of bedbugs:

- Physically remove bedbugs with a typical vacuum cleaner and seal the vacuum bag to prevent the infestation of neighbouring locations.
- Dry brushing or surface cleaning is a complementary action for removing the eggs and nymphs that remain attached.
- Wash textiles (e.g., bedsheets, clothes, and blankets) at 60°C (140°F).
- Directly kill bedbugs by heating and steaming with the help of experienced professionals from a pest-control company.
- Do not use insect foggers, also known as bug bombs.
- Avoid the use of commercial insecticide
- For complete eradication of bed bugs, the intervention of a specialized company is highly recommended.

NB: A common misconception is to “wash all clothes,” which is not necessary if no signs of bedbugs have been found in or on the furniture. If an item (e.g., wool clothes, books, shoes, or children’s toys) or material cannot be laundered, it can be placed at −20°C for 2 hours to kill all bedbugs and eggs. Placement in a domestic-level freezer will not kill all bugs because some bugs will tolerate these conditions.

72 Tungiasis (Tunga penetrans)

Selected References

1. https://dx.doi.org/10.1586/14787210.4.1.151 (Jorg Heukelbach 2006)
2. https://dx.doi.org/10.1371/journal.pntd.0003058 (Thielecke et al. 2014)
3. https://dx.doi.org/10.1179/000349803225002408 (J Heukelbach et al. 2003)
4. https://dx.doi.org/10.1016/j.actatropica.2006.05.013(Feldmeier, Kehr, and Heukelbach 2006)
5. https://dx.doi.org/10.1371/journal.pntd.0002426 (Thielecke et al. 2013)
6. https://dx.doi.org/10.1590/S0074-02762004000800015 (Jörg Heukelbach, Franck, and Feldmeier 2004)
7. https://doi.org/10.1016/j.jaad.2019.05.110 (Coates et al. 2020)

First-line treatment

No drugs available with proven efficacy; removal by shave, or in case of early stage with a sterile needle remains the first choice.

Alternative regimens

- Oral ivermectin: placebo controlled RCT (n=27 in each arm) with 300 µg/kg single dose, repeated after 24h: no clinical benefit.
- Topical ivermectin (lotion), thiabendazole (ointment and lotion), metrifonate (lotion) have been evaluated in a placebo controlled RCT (n=169 feet); each treatment significantly reduced the number of lesions caused by embedded sand fleas; these products do not seem to have been further developed.

The future? Topical dimeticone of low viscosity (NYDA): a proof-of-principle RCT (n=88 lesions in each arm) in rural Kenya showed a reduction of 78% of viable fleas (with 3 applications within 10 minutes), compared to KMnO4 0,05% for 10 minutes + vaseline application (39% reduction, P<0.001).

Special situations

Prevention:

- Walking with shoes is often insufficient in endemic areas.
- A plant-based repellent (Zanzarin®) protects against *Tunga penetrans* infestation and sand flea disease, as demonstrated by an RCT in rural Madagascar (n=72 in the intervention/repellent arm, n=77 in one arm "wearing shoes" and n=70 in the control arm); the attack rate of tungiasis dropped to zero from 2 to 10 weeks during twice-daily applications of Zanzarin (Germany), compared with no effect in the control group and slight decrease in the shoes group.

73 Myiasis

Selected References

1. https://dx.doi.org/10.1111/jtm.12203 (Lachish et al. 2015)
2. https://dx.doi.org/10.1128/CMR.00010-11 (F. Francesconi and Lupi 2012)
3. https://dx.doi.org/10.1111/j.1365-4632.2010.04577.x (Robbins and Khachemoune 2010)
4. https://dx.doi.org/10.1001/jama.1993.03510170077034 (Brewer, Wilson, and Gonzalez 1993)

73.1 *Cordylobia anthropophaga* (Africa)

First-line treatment

Vaseline application and extraction of the larva after a couple of minutes with the help of a pair of tweezers. Gentle "expression" without vaseline is also often possible (sometime with cruciate incision).

73.2 Dermatobia hominis (South America)

First-line treatment

Usually larger, deeper and more difficult to remove, so that cruciate incision and surgical removal of larva are often required.
A surgical extraction may sometimes be avoided after vaseline application for a couple of hours.

NB1: There are many more etiologies of myiasis but the two abovementioned are by far the most frequent causes of furuncular myiasis in travelers. Almost all superficial anatomic sites may be affected. Wound myiasis is seen in exceptional circumstances and is caused by other species.

NB2: Other local (cryotherapy, injection of lidocaine 1% or topical ivermectin) and systemic treatments (oral ivermectin) have been anecdotally reported but are not recommended because of the lack of therapeutic evidence or of the risk of killing the parasite into the lesion (complicating the complete removal). Oral ivermectin (200 µg/kg single dose) might be exceptionally considered in very selected cases.
Bacterial superinfection is possible and should be treated accordingly.

NB3: Mentioned in older versions of the State of the Art: application of the white part of raw pork bacon can also be considered for a couple of hours until the larva is immobilized. Then the piece of bacon is removed and the larva is extracted with a rapid movement of the tweezers.

74 Pediculosis

There are 3 types of pediculosis due to *Pediculus capitis*, *P. corporis* and *Phthirus pubis*.

Selected References

1. https://dx.doi.org/10.1007/s40257-014-0094-4 (Feldmeier 2014)
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13. https://dx.doi.org/10.1086/499279 (Foucault et al. 2006)
14. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5165061/ (Meister and Ochsendorf 2016)

74.1 Pediculus capitis (head louse)

First-line treatment

- Topical treatment with Permethrin 1% *rinsable cream* (Nix Crème Rinse®); cure rate > 90%.
  - To apply for 10 minutes (but in practice can be left for hours, or even a whole night in severe cases, with a shower cap at night).
  - Not for children under 2 months.
  - To repeat after 9-10 days (pediculocidal, but not ovicidal); no need for a third application.
  - To associate with concomitant removal of nits with a nit comb (best in metal) 2x/week for 2 weeks as described below.

- Topical treatment with Dimeticon; cure rate 70-97%.
  - Is available in Belgium: e.g., Silikon).
  - Non-toxic, causing a "mechanical" coating that asphyxiates lice.
  - No age restriction.
  - To apply for only 5-10 minutes.
  - To repeat after 9-10 days (not ovicidal).
  - To associate with concomitant removal of nits with a nit comb (best in metal) 2x/week for 2 weeks as described below.
  - Very promising because of emerging resistance against permethrin and malathion.

Alternative regimens

Topical treatment with Malathion 0.5% *capillary lotion* (Prioderm®); cure rate 85-95%.

- To apply for at least 8 hours and preferably 12 hours.
- Not for children under 2 years.
- No need to repeat normally (ovicidal).
- To associate with concomitant removal of nits with a nit comb (best in metal) 2x/week for 2 weeks as described below.

NB: the association of malathion 0.5% + permethrin 1% + piperonyl butoxyde in spray (Para Plus®) is not recommended.

(Topical treatment with ivermectin lotion 0.5%; cure rate 75%)

Special situations
Refractory/difficult-to-treat cases
"Aggressive" hair care:

- Cut hair short if they are too long (it doesn't have to be "excessively" short)
- Repeat the "WET COMB" method:
  1. Wash hair 2 x/ week with a neutral shampoo.
  2. Then apply liberally a conditioner: get hair as smooth as possible.
  3. Then use a thin comb (lice comb) through the hair.
  4. First comb from back to front starting with the back of the neck, with the thin comb as close as possible to the scalp.
  5. Start with one ear and move towards the other ear after every combing; left to right and right to left.
  6. After every passage of the comb clean the comb with tissue paper and check it.
  7. Wash the hair and keep them wet then comb with a normal comb.
  8. Next apply the conditioner again liberally but comb this time from front to back starting by the front.
  9. In total comb for at least 15 minutes.
  10. When finished wash the comb at 60 degrees at least.

Wash clothes and bedding at > 60°C or dry clean; items not suitable for washing can be decontaminated by storing them in a plastic bag for 3 days (only).
Consider oral treatment with ivermectin 400 µg/kg po single dose; cure rate 93-97%; to repeat after 7-10 days since no activity against nits.

Some other treatments in refractory/resistant cases:

- Custom-built machine called LouseBuster00% killing effect on eggs, and 80% on hatched lice.
- Association topical permethrin 1% + trimethoprim/sulfamethoxazole 5/25 mg/kg BID po for 10 days

For the future:

- Anti-symbiotic treatment with doxycycline or macrolide.
- Synergetic treatment combining ivermectin and doxycycline or macrolide.

74.2 Pediculus corporis (body louse)

First-line treatment

- Permethrin cream 5% (Zalvor®), applied to entire body skin for 6-8 hours once.
- Wash clothes and bedding > 60°C, dry clean or discard.
- Consider shaving body hair if abundant.

Alternative regimens (difficult cases)

- Ivermectin 200-400 µg/kg po single dose on days 0, 7, and 14.

74.3 Phthirus pubis (crab louse)

First-line treatment

- Same treatment as head lice.
- Wash clothes and bedding used within 3 preceding days > 60°C, dry clean or discard.
- Consider shaving pubic hair.
- Screen for other STDs.
- Treat sexual contact within the previous 30 days.

Alternative regimen (difficult cases)

- Ivermectin 200-400 µg/kg po single dose on days 0, 7, (and 14).

Availability and costs

Ivermectin: see additional and updated information via contact with ITM.

75 Scabies (Sarcoptes scabiei)

Selected References

1. https://dx.doi.org/10.1056/NEJMct0910329 (Currie and McCarthy 2010)
2. https://dx.doi.org/10.1111/j.1529-8019.2009.01243.x (Hicks and Elston 2009)
3. https://dx.doi.org/10.1086/511428 (Leone 2007)
4. https://dx.doi.org/10.1056/NEJMcp052784 (Chosidow 2006)
5. https://dx.doi.org/10.1016/S0140-6736(06)68772-2 (Jörg Heukelbach and Feldmeier 2006)
6. https://dx.doi.org/10.1016/S0190-9622(00)90131-2 (Usha and Gopalakrishanan Nair 2000)
7. https://dx.doi.org/10.1016/j.jinf.2004.08.033 (L. J. Roberts et al. 2005)

First-line treatment

Permethrin 5% cream (Zalvor® tube 30 g):

- Adults and children > 12 years old tube of 30g (per application).
- Children 5-12 years old: up to half a tube.
- Children 1-5 years old: up to a quarter of a tube.
- Children 2 months-1year old: up to 1/8th of a tube.

Apply the cream on the whole body from the lower jaw to the feet included without forgetting every cutaneous crease, the genitals, the tip of the nails (cut short) and the hands if they have been washed in the last 8 hours. Wash after 8 to 24 hours.

In most cases, a single treatment should be is enough although a second application is often recommended after 24 hours or 7 days apart.

Other important measures (essential for severe cases):

- Bedding and clothing should be machine-washed and -dried using hot water/high heat; temperatures above 50°C for 10 min will kill mites and eggs.
- Items that cannot be dry-cleaned or laundered can be disinfested by storage in a closed plastic bag for at least 3 days (preferentially 7 days).
- All clothing and bedding used by the exposed persons at any time during the 3 days preceding treatment should be machine-washed and -dried using hot water/high heat.

NB:

- In pediatric and geriatric patients, the face and scalp are also treated due to more generalized skin involvement in these groups.
- Infectiousness is virtually stopped after one day of treatment.
- Pruritus may persist for 2-6 weeks after successful treatment; consider topical steroids (even oral) in some severe cases (post-scabies nodular prurigo).
- Cure rate with permethrin 5% has been estimated at 85%.
- It is unnecessary to wash furniture, floors, toys, … (except in case of crusted scabies, see below).

Alternative regimens

- Crotamiton 10%; (benzyl benzoate 10 to 25%); (malathion 0.5%)
  These products are not commercially available in Belgium but may be prepared magisterially. They are however less effective than permethrin 5% or cause more side effect (skin irritation). Procedures of application are like that of permethrin 5%, but more than 2 applications are often needed.
- Ivermectin (Stromectol®: tablet of 3 mg at ITM): 200 µg/kg po od on day 0 and on day 7.
  Since ivermectin is not widely available, it should be reserved to more severe cases, not responding to the first-line topical treatment.
  It is increasingly recommended to administer a second course after 7 days, to obtain a cure rate of 100% (since ivermectin is not active against eggs).
- Ivermectin safety has not been studied in children < 15kg.

Special situations

Pregnancy:

- Permethrin 5% cream (or crotamiton 10%) can be used, but application time should be limited to 2 hours.
- Norwegian scabies ("scabies crustosa") and/or scabies in immunosuppressed individuals.

NB1: always screen for HIV and HTLV-1 for crusted scabies of unknown cause.
Combination of permethrin 5% cream every 2 to 3 days for 1 to 2 weeks (or od x 7 days, then 2x/week until cure) and ivermectin (200 µg/kg/dose), administered po as three doses (days 1, 2, and 8), five doses (days 1, 2, 8, 9, and 15) or seven doses (days 1, 2, 8, 9, 15, 22, and 29), depending on severity of infection.

NB2:

- Keratolytic creams should be used for skin crusts.
- Maintain vigilance for the development of sepsis.
- Apply appropriate measures to control the spread of scabies infection, including patient isolation (and in some instances disinfection of environment).

Outbreak in institutions

- Ivermectin in "mass treatment" should be considered since all other treatments will probably fail to contain the epidemic.

Availability and costs

Ivermectin: see additional and updated information via contact with ITM.

Recurrence

In Antwerp, one can ask a special team from the city to help with the eradication of recurrent outbreaks in some families. Therefore, one should refer the family/ patient to a “sociaal centrum” linked to his official address for a financial screening. When the family is considered eligible (very low income/ OCMW), the treatment and (medical + cleaning) is offered without any costs for the patient.
Ref: draaiboek schurft stad Antwerpen: https://assets.antwerpen.be/srv/assets/api/download/db3f4819-5796-48fe-941d-757152bd1908/Draaiboek_CD.pdf

Material for the patient:
Informatiefolder: https://www.zorg-en-gezondheid.be/folder-schurft-of-scabi%C3%ABs
Practical guidance for the patient: https://www.zorg-en-gezondheid.be/scabies

Chapter 5: Mycoses

76 Mycoses

Classification

Superficial Mycoses:
- Tinea (= *dermatophytosis*)
- Malassezia furfur (= *Pityriasis versicolor*)
- Superficial candidiasis

Subcutaneous Mycoses:
- Chromoblastomycosis (=chromomycosis)
- Mycetoma
    - Eumycetoma
    - Actinomycetoma (= bacterial)
- Sporotrichosis
- Rhino-entomophtoromycosis
- Lobomycosis

Deep Mycoses:
- Cosmopolitan
- Aspergillosis
- Deep candidiasis
- Cryptococcosis
- Pneumocystosis
- Mucormycosis
- Phaehyphomycosis

Exotic:
- Histoplasmosis
- Blastomycosis
- Talaromycosis (former Penicilliosis)
- Emmonsiosis
- Coccidioidomycosis
- Paracoccidioidomycosis

76.1 Superficial mycoses

76.1.1 Tinea

Selected References
(John W. Ely, Sandra Rosenfeld 2014) 1,2

First-line treatment

General comments

- Do **not** use topical corticosteroids in the treatment of dermatophyte infections. Combination therapy is not necessary for achieving cure and may induce skin atrophy.
- Patients with chronic or recurrent tinea pedis may benefit from wide shoes, drying between the toes after bathing, and placing lamb's wool between the toes.
- Because toenails grow slowly, assessment of cure for onychomycosis takes nine to 12 months.
- Do baseline complete blood count (CBC) and ALT/AST measurement; CBC at six weeks for courses lasting more than 6 weeks.

Tinea corporis, tinea cruris, and tinea pedis:

- Mild to moderate disease:
  - Topical cream terbinafine 1% (10 mg/1 gr) bid x 1-3 weeks till clinical resolution
  - Miconazole cream, ointment, lotion or powder 2% (Daktarin®) bid for 1-3 weeks till clinical resolution.
- Extensive disease, failed topical treatment, immunocompromised patients, or severe moccasin-type tinea pedis:
  - Terbinafine 250 mg (< 25 kg: 125 mg od, 25-35 kg: 187,5 mg od) po x 2-3 weeks.
  - Fluconazole 6 mg/kg (adult 150-200 mg) od po x 2-4 weeks (or weekly 6 mg/kg x 6 weeks).
  - Itraconazole 5 mg/kg (adult 200 mg) od po for capsules x 1-2 weeks, 3 mg/kg for oral solution x 1-2 weeks.

Tinea capitis:

- Initiate treatment based upon clinical suspicion before availability of culture results. Delay of treatment increases risk of diseases progression and disease transmission.
- Combination of shampoo with oral treatment.
  - Shampoo:
    - Seleniumsufide shampoo (Selsun®) 25 mg/1 ml x 2 weeks
    - Ketoconazole shampoo (Nizoral®) 20 mg/1 ml x 2 weeks
  - Oral treatment:
    - Terbinafine 250 mg (< 25 kg: 125 mg od, 25-35 kg: 187,5 mg od) po x 6 weeks (assume *Trichophyton* unless culture reveals *Microsporum*).
    - *Microsporum* infections: griseofulvine 20-25 mg/kg od po x 6-12 weeks (X. Chen et al. 2017).

Alternatives

- Fluconazole 6 mg/kg once weekly instead of od x 6-12 weeks.
- Fluconazole 6 mg/kg (adult 150-200 mg) od x 4-6 weeks (or weekly 6 mg/kg).
- Itraconazole 5 mg/kg (adult 200 mg) od for capsules x 4-6 weeks, 3 mg/kg for oral solution x 4-6 weeks.

Tinea unguium (onychomycosis)

- Terbinafine 250 mg (10-20 kg: 62,5 mg od, 20-40 kg: 125 mg od) po x 6 weeks for fingernails; x 12 weeks for toenails (Kuokkanen et al. 2000).
- Alternative: itraconazole 200 mg (< 20 kg: 5 mg/kg od, 20-40 kg: 100 mg od) po x 6 weeks for fingernails; x 12 weeks for toenails.

76.1.2 Pityriasis versicolor

Selected References
(A. Gupta and Foley 2015),(Renati, Cukras, and Bigby 2015)

First-line treatment
Topical therapy is the preferred first line treatment. Several topical treatments can be used as first line treatments:

- Ketoconazole 2% shampoo (Nizoral®) 5-min application od x 3-14 days.
- Terbinafine 1% cream or gel bid x 1 week.
- Ciclopirox (Mycosten®) 10 mg/1 gr cream bid x 2 weeks.
- Selenium sulfide 2,5% shampoo (Selsun®) 10-min application od x 1 week.
- Zinc pirythione 1 á 2% shampoo 5-min application od x 2 weeks.
- Ketoconazole 2% cream + adapalene 0,1% gel.
- Various other topical azoles are treatment options:
  - Miconazole cream, spray, powder or solution (Daktarin®) 20 mg/1gr (or 20 mg/1ml) bid.
  - Clotrimazole cream (Canestene®) 10 mg/1gr bid.
  - Ketoconazole cream 20 mg/1 gr or Shampoo 2% (Nizoral®) od.

Alternative regimens
Systemic oral therapy is reserved for patients with widespread or recurrent tinea versicolor, or for patients who have failed topical therapy:

- Itraconazole 200 mg od po x 5-7 days: children 2,5-5 mg/kg.
- Fluconazole 300 mg once weekly po x 2-4 weeks; children 6-12 mg/kg.
- Oral ketoconazole is to be avoided due to risk of serious hepatotoxicity. Oral terbinafine is **NOT** effective.

NB: Changes in cutaneous pigment often persist after successful treatment. Restoration of normal pigmentation may take months after the completion of successful therapy. Scaling skin plus a positive potassium hydroxide (KOH) preparation is indicative of active infection.

Special situations
Recurrent disease (mainly in immunosuppressed patients):

- Selenium sulfide 2,5% or ketoconazole 2% shampoo once monthly.

Alternative regimen

- Itraconazole 400 mg po once monthly.

76.1.3 Superficial candidiasis

Candida intertrigo

Selected References

1. https://academic.oup.com/cid/article/62/4/e1/2462830 (Pappas et al. 2015

First-line treatment

- Topical antifungal treatment is the preferred first line treatment:
- Miconazole cream, spray, powder or solution (Daktarin®) 20 mg/1gr (or 20 mg/1ml) bid; hydrocortisone (Daktacort®) is added if there is significant pruritus, pain or burning.
- Clotrimazole cream (Canestene®) 10 mg/1gr bid.
- Ketoconazole cream 20 mg/1 gr or Shampoo 2% (Nizoral®) od.
- Terbinafine 1% cream or gel bid.
- Ciclopirox (Mycosten®) 10 mg/1 gr cream bid.

Treatment till resolution of symptoms, usually within 2 weeks (sometimes 4 weeks).

Special situations

In case of treatment failure or extended disease systemic treatment is used:

- Fluconazole 50-100 mg od (or 150 mg weekly) po x 2-6 weeks; children 6 mg/kg once, then 3 mg/kg.

NB: In case of maceration: use compresses with a drying solution before application of the antifungal cream. Patients at risk for recurrence should use a drying agent indefinitely; a possible drying agent is miconazole powder (Daktarin®).

Vulvovaginal Candida (due to *Candida albicans*, not *C. glabrata*)

Selected References

1. (Pappas et al. 2015)

First-line treatment

- Uncomplicated: Fluconazole 150 mg single dose po, often perceived as more convenient than topical treatment applied intravaginal.
- Severe disease: Fluconazole 150 mg po every 72 hours for a total of 2-3 doses.

Alternative regimens

Topical antifungal agent:

- Clotrimazole (Canestene Gyn®) cream 20 mg/1 gr od x 3 days (apply at night).
- Clotrimazole (Canestene Gyn®) vag tablet 500 mg 1 tablet single dose (apply at night).
- Butoconazole (Gynomyk®) cream 20 mg/ 1 gr or vag ovule 100 mg od x 3 days (apply at night).
- Fenticonazole (Gynoxin®) cream 20 mg/ 1 gr or vag ovule 200 mg od x 3 days (vag ovule 600 mg single dose) (apply at night).
- Miconazole (Gyno-Daktarin®) cream 20 mg/ 1 gr or vag caps 200 mg od x 7 days (apply at night).

NB: Partner treatment is not recommended in the first instance.

Special situations

Pregnancy:

- Miconazole (Gyno-Daktarin®) cream 20 mg/ 1 gr or vag caps 200 mg od x 7 days (apply at night).

- Clotrimazole (Canestene Gyn®) cream 20 mg/1 gr od for 7 days (apply at night)

Recurrent disease:
- fluconazole 150-200 mg po 3 times in week 1, followed by fluconazole 150-200 mg weekly for 6 months; consider continuing fluconazole 200 mg monthly till 12 months. (Matheson and Mazza 2017)
- In recurrent infection, partner with fluconazole 150 mg single dose po or topical cream can be considered.

Oropharyngeal Candida

Selected References
1. (Pappas et al. 2015)

First-line treatment
- Mild disease: clotrimazole troches, 10 mg 5 times od or miconazole mucoadhesive buccal 50-mg tablet applied to the mucosal surface over the canine fossa od x 7–14 days.
- Moderate to severe disease: fluconazole 100–200 mg od po x 7–14 days.
- Fluconazole refractory disease: itraconazole solution 200 mg od po or posaconazole suspension 400 mg bid po x 3 days, and then 400 mg od for up to 28 days.

Alternative regimens
- Mild disease: nystatin suspension (100 000 U/mL) 4–6 mL qid or 1–2 nystatin pastilles (200 000 U each) qid x 7–14 days
- Fluconazole refractory disease: voriconazole 200 mg bid po or amphotericin B deoxycholate oral suspension 100 mg/mL qid
- Intravenous echinocandins (caspofungin: 70-mg loading dose, then 50 mg od; micafungin: 100 mg od; or anidulafungin: 200-mg loading dose, then 100 mg od) or intravenous amphotericin B deoxycholate, 0.3 mg/kg od

76.2 Subcutaneous mycoses

76.2.1 Chromoblastomycosis

Selected References
(Krzyściak, Pindycka-Piaszczyńska, and Piaszczyński 2014a)

First-line treatment
- Often treatment resistant.
- There is no treatment of choice.
- Success is related to causative agent, the clinical form and the severity of the lesions (*Cladophialophora carrionii* and *Phialophora verrucosa* are less sensitive in vitro to antifungal drugs than *Fonsecaea pedrosoi*).
- In the case of extensive lesions even long-term treatment may not be successful and may only result in reduction and control of the disease to prevent complications.

- There are 3 treatment modalities: physical treatment, chemotherapy or a combination therapy:
    1. Cryotherapy/cryosurgery or standard excision surgery:

Most effective if early stage and small lesions; often combined with chemotherapy (itraconazole and/or terbinafine). Caution: surgical manipulation around the lesion may favor dissemination.

2. (Combination) chemotherapy:
    - Posaconazole 800 mg/day: good efficiency, good tolerance, high cost(Negroni et al. 2005).
    - Alternated weeks of itraconazole 200-400 mg/d po and terbinafine 500-750 mg/d po (A. K. Gupta, Taborda, and Sanzovo 2002) or itraconazole 200-400 mg/d po and terbinafine 250-1000 mg/d po in monotherapy or concomitantly (Zhang et al. 2009)
3. Combination therapies:
    - Itraconazole + cryotherapy
    - Terbinafine + cryotherapy
    - Itraconazole + terbinafine (see above)
    - Itraconazole and/or terbinafine + dry heat

Alternative regimens

- Voriconazole 200 mg bid: good response in long-standing refractory cases (Krzyściak, Pindycka-Piaszczyńska, and Piaszczyński 2014b),(Criado et al. 2011),(De Lima et al. 2016).
- Second-generation triazoles (voriconazole, ravuconazole, posaconazole, and isavocunazole) present *in vitro* activity against dematiaceous fungi and are promising drugs for treatment of deep dermatomycoses, but the experience is limited by the prohibitive costs (Cardoso De Brito and Semblado 2018).
- Laser vaporization.
- Thermotherapy: pocket warmers placed on the lesions 24h/day for a couple of months; is used in combination with chemotherapy.

Duration of treatment

Treatment might be necessary for months or several years.
Clinical cure is defined as a complete resolution of the lesions, typically with the remaining sclerotic scar. Mycological cure is defined as the absence of the fungus in repeated microscopic specimens and the absence of growth in repeated cultures.

76.2.2 Eumycetoma

Selected References

(Welsh et al. 2014),(Ahmed Hassan Fahal 2010)

First-line treatment

- Eumycetoma is difficult to treat.
- Combined surgical and medical treatment appears to be the management of choice.
- The timing of surgery in relation to antifungal therapy is not well established. One prospective study indicates that medical therapy may limit the disease and make complete excision of the lesions more feasible.

NB: Monthly transaminases determination during azole therapy.

Treatment options:

- Itraconazole 400 mg/day x 3 months, followed by 200 mg/day x 9 months followed by wide surgical excision; continuation of itraconazole post-surgery might be beneficial given viable fungal grains found in operative specimens at the end of the course (A. H. Fahal et al. 2011).
- Posaconazole 400 mg bid with food x 9-36 months; therapeutic drug monitoring (TDM) can guide dosing(Diaye et al. 2006); surgical excision to be considered.
- Voriconazole 200-350 mg bid outside meals for 9-36 months; TDM (Therapeutic Drug Monitoring) can guide dosing (Diaye et al. 2006) (Loulergue et al. 2006) (Oliveira et al. 2013); surgical excision to be considered.
- Combination treatment of abovementioned drugs (itraconazole, posaconazole and voriconazole) with terbinafine is described but numbers too small to make firm conclusions (Elkheir et al. 2020).

Alternative regimens

- *Madurella mycetomatis* is highly sensitive to ravuconazole in-vitro (Ahmed et al. 2014).
- Terbinafine 500 mg bid x 24-48 weeks: 25% cure, 55% improvement (Diaye et al. 2006).
- Ketoconazole 400-800 mg od; ketoconazole should not be used as first-line treatment due to hepatic and adrenal toxicity; only to be used for life-threatening fungal infections (endemic mycoses) when alternative antifungal therapies are not available or tolerated.

76.2.3 Actinomycetoma

Note that the etiological agents are bacteria! The 3 most important genera: *Nocardia, Streptomyces and Actinomadura.*

Selected References

(Welsh et al. 2014), (Ahmed Hassan Fahal 2010)

First-line treatment

In contrast to eumycetoma, in actinomycetoma, surgery is seldom used. Most cases respond to medical therapy, although some require prolonged administration of antimicrobial combinations (for weeks or months).

- Welsh regimen: Amikacin 7.5 mg/kg bid im x 3 weeks simultaneously with trimethoprim-sulfamethoxazole 8/40 mg/kg/day po x 5 weeks.
- Amikacin can be replaced with amoxicillin-clavulanic acid (500/125 mg tid) continuously with trimethoprim-sulfamethoxazole continuously x 3 to 6 months or longer. This has less toxicity and is easier to administrate (de la Garza et al. 2020).
- Depending on the clinical response, this cycle of treatment is consecutively repeated: 5 and up to 10 cycles can be necessary.

Alternative regimens

- Other aminoglycosides, minocycline (200 mg/day in divided doses), moxifloxacin (400 mg od po or iv), linezolid (600 mg od po), and carbapenems (imipenem 500 mg tid iv or meropenem 500 mg tid iv) are options for recalcitrant cases.
- Rifampin (10 mg/kg od po) can be added to the Welsh regimen.

NB: Renal function monitoring and audiometry are advised every 3 to 5 weeks to avoid toxicity of amikacin.

76.2.4 Sporotrichosis

Infection with *Sporothrix schenckii* is discussed. Sporotrichoid distribution can be due to various infectious organisms.

Selected References
(Kauffman et al. 2007)

First-line treatment
Lymphocutaneous and cutaneous sporotrichosis:

- Itraconazole 200 mg po od to be given till 2-4 weeks after all lesions have resolved, usual total duration is 3-6 months.

Osteoarticular, pulmonary, meningeal and disseminated sporotrichosis:

- See (Kauffman et al. 2007): IDSA Guidelines for the management of sporotrichosis.

Manifestation	Preferred treatment	Alternative treatment	Comments
Lymphocutaneous/cutaneous	Itr 200 mg/day (A-II)	Itr 200 mg b.i.d. (A-II); or terbinafine 500 mg b.i.d. (A-II); or SSKI with increasing doses (A-II); or fluconazole 400–800 mg/day (B-II); or local hyperthermia (B-III)	Treat for 2–4 weeks after lesions resolved.
Osteoarticular	Itr 200 mg b.i.d. (A-II)	Lipid AmB 3–5 mg/kg/day (B-III); or deoxycholate AmB 0.7–1 mg/kg/day (B-III)	Switch to Itr after favorable response if AmB used; treat for a total of at least 12 months.
Pulmonary	Lipid AmB 3–5 mg/kg/day, then Itr 200 mg b.i.d. (B-III); or Itr 200 mg b.i.d. (A-III)	Deoxycholate AmB 0.7–1 mg/kg/d, then Itr 200 mg b.i.d. (B-III); surgical removal (B-III)	Treat severe disease with an AmB formulation followed by Itr; treat less severe disease with Itr; treat for a total of at least 12 months.
Meningitis	Lipid AmB 5 mg/kg/day, then Itr 200 mg b.i.d. (B-III)	Deoxycholate AmB 0.7–1 mg/kg/day, then Itr 200 mg b.i.d. (B-III)	Length of therapy with AmB not established, but therapy for at least 4–6 weeks is recommended; treat for a total of at least 12 months; may require long-term suppression with Itr.
Disseminated	Lipid AmB 3–5 mg/kg/day, then Itr 200 mg b.i.d. (B-III)	Deoxycholate AmB 0.7–1 mg/kg/day, then Itr 200 mg b.i.d. (B-III)	Therapy with AmB should be continued until the patient shows objective evidence of improvement; treat for a total of at least 12 months; may require long-term suppression with Itr.
Pregnant women	Lipid AmB 3–5 mg/kg/day or deoxycholate AmB 0.7–1.0 mg/kg/day for severe sporotrichosis (B-III); local hyperthermia for cutaneous disease (B-III)	…	It is preferable to wait until after delivery to treat non–life-threatening forms of sporotrichosis.
Children	Itr 6–10 mg/kg/day (400 mg/day maximum) for mild disease (B-III); deoxycholate AmB 0.7 mg/kg/day for severe disease (B-III)	SSKI with increasing doses for mild disease (B-III)	Treat severe disease with an AmB formulation followed by Itr.

NOTE. AmB, amphotericin B; b.i.d., twice per day; Itr, itraconazole; SSKI, saturated solution potassium iodide.

Source: Kauffman C *et al.* Clinical Practice Guidelines for the Management of Sporotrichosis: 2007 Update by the Infectious Diseases Society of America. *Clin Infect Dis*. 2007

Alternative regimens

- Nonresponding patients: a higher dosage of itraconazole (200 mg bid po) or terbinafine (500 mg bid po) or saturated solution of potassium iodide (SSKI), initiated at a dosage of 5 drops (using a standard eyedropper) 3 times daily and increasing, as tolerated, to 40–50 drops 3 times daily.
- Fluconazole 400–800 mg daily po only if the patient cannot tolerate the other agents.

Special situations

- Children: itraconazole, administered at a dosage of 6–10 mg/kg to a maximum of 400 mg daily po.
- Pregnancy and lactation: Local hyperthermia (induced by a variety of different warming devices or baths) can be used in case of fixed cutaneous sporotrichosis, in this group which cannot safely receive any of the previous regimens

76.2.5 Rhinoentomophtoromycosis

Selected References
(Prabhu and Patel 2004)

First-line treatment
Treatment is often difficult due to late presentation. Relapse is common, even after successful treatment.

- Itraconazole 200-400 mg/day po(Seth 1998), to be continued for at least 1 month after the lesions have cleared.
- This can be combined with potassium iodide 30 mg/kg od or 10 mg/kg tid.

Alternative regimens
- Monotherapy or combination of terbinafine (500 mg bid po), fluconazole (5 mg/kg od po), liposomal amphotericin B (3-5 mg/kg od iv x8-10 weeks), anhydrous potassium iodide (30 mg/kg od or 10 mg/kg tid) and trimethoprim-sulfamethoxazole (4/20 mg/kg bid po x 12 weeks).

- Surgical resection is seldom helpful, and it may hasten the spread of infection

76.2.6 Lobomycosis

Selected References
(V. Francesconi et al. 2014)

First-line treatment
For patients with localized, surgically amenable disease, wide surgical excision is the preferred treatment. The intent is to remove all infected tissue, leaving the surgical margins clear of disease. The efficacy of pharmacological therapy in conjunction with surgery is unclear.
Caution: instruments contaminated during surgery might lead to reinfection.

For patients who are not candidates for surgery, medical treatment is given but results can be unsatisfying:
- Clofazimine 100-300 mg od po + itraconazole 100 mg od po.
- Posaconazole 200 mg bid

For up to 2 years (or more)(Bustamante et al. 2013).

Alternative regimens
- Cryosurgery with liquid nitrogen + itraconazole 400 mg od po.
- Ketoconazole, amphotericin B, sulfa compounds, clofazimine alone and 5-fluorocytosine have been used with mostly disappointing results.

NB: Long-term follow-up is mandatory since there is a high relapse rate in lobomycosis.

76.3 Deep Mycoses

76.3.1 Deep candidiasis

Selected References
(Pappas et al. 2015)

76.3.2 Cryptococcosis

Selected References
(Perfect et al. 2010),("EACS Guidelines 10.1 October 2020" 2020)

Cryptococcal Meningitis in HIV-infected patients:

First-line treatment

- Induction therapy: Liposomal amphotericin B 3-4 mg/kg od iv + flucytosine 25 mg/kg qid iv x 2 weeks; deoxycholate amphotericin B 0.7-1.0 mg/kg od iv is an alternative.
- Consolidation therapy: fluconazole 400 mg od x 8 weeks (children 10-12 mg/kg/day).
- Maintenance therapy: fluconazole 200 mg od (children 6 mg/kg/day) for minimum 1 year; stop if on HAART, CD4 > 100 cells/mm³ and undetectable vl for ≥ 3 months.

Alternative regimens

- Induction therapy: Liposomal amphotericine B 3-4 mg/kg od iv + fluconazole 800-1200 mg po od x 2 weeks.
- Maintenance therapy: itraconazole 400 mg od po for minimum 1 year; stop if on HAART, CD4 > 100 cells/µl and undetectable VL for ≥ 3 months.
- Voriconazole 200-400 mg bid po or posaconazole 400 mg bid po are alternatives in disease relapse.
- Successful treatment with isavuconazole is described (G. R. Thompson et al. 2016).

Special situations

Meningitis with increased intracranial pressure:

- If the CSF pressure is ≥ 25 cm of CSF and there are symptoms of increased intracranial pressure during induction therapy, relieve by CSF drainage: by lumbar puncture reduce the opening pressure by 50% if it is extremely high or to a normal pressure of ≤ 20 cm of CSF.
- If there is persistent pressure elevation ≥ 25 cm of CSF and symptoms, repeat lumbar puncture daily until the CSF pressure and symptoms have been stabilized for 2 days and consider temporary percutaneous lumbar drains or ventriculostomy for persons who require repeated daily lumbar punctures.
- HAART should be started 2-10 weeks after the start of the induction therapy. In patients with close follow-up, access to preventive treatment for other OI's, the 10 week delay might reduce the risk of IRIS and drug interactions with high-dose antifungal therapy.

Pregnancy

- Deoxycholate amphotericin B or liposomal amphotericin B with or without flucytosine. Flucytosine is a Cat C drug for pregnancy and risks must be weighed against benefits.
- Start fluconazole (Cat C drug) after delivery; avoid fluconazole during the first trimester; in the last 2 trimesters the risk must be weighed against benefit.

Cryptococcal Meningitis in non-HIV-infected patients and in organ transplant recipients and non-meningitis cryptococcosis: see (Perfect et al. 2010)

76.3.3 Aspergillosis

Selected References

(Patterson et al. 2016)

76.3.4 Pneumocystosis

HIV-infected patients

Selected References
(Prevention 2009)("EACS Guidelines 10.1 October 2020" 2020)

First-line treatment
- Trimethoprim-sulfamethoxazole (TMP-SMX) 5/25 mg tid iv or po x 21 days

Alternative regimens
- Pentamidine 4 mg/kg od iv infused over at least 60 minutes; may reduce the dose to 3 mg/kg od iv because of toxicities.
- Primaquine 30 mg od po + clindamycin 600 mg qid or 900 mg tid iv; or 450 mg qid or 600 mg tid po
- If mild disease:
  - Dapsone 100 mg od po + trimethoprim 5 mg/kg tid po
  - Atovaquone 750 mg bid po

Special situations
Pregnancy:
TMP/SMX is the preferred treatment (dapsone + trimethoprim is an alternative).

Pneumocystosis with hypoxemia:
Adjunctive corticosteroids can be given if PaO2 is < 70 mmHg at room air, if alveolar-arterial (A-a) oxygen gradient ≥35 mmHg. Start prednisolone 40 mg bid po x 5 days, followed by 40 mg od x 5 days, followed by 20 mg od x 11 days.
Intolerance to TMP/SMX
- Reasons to stop TMP/SMX:
- Persistent rash and/or fever for more than five days
- Absolute neutrophil count <500 cells/mm^3

Hypotension:
Intractable hyperkalemia
- Fever and flu-like symptoms, followed by conjunctival irritation, mucous membrane involvement, painful skin, target lesions, blistering, or desquamation of the skin
- For patients with non-life-threatening adverse reactions to TMP-SMX, the drug should be continued if clinically feasible
- If TMP-SMX is discontinued because of a mild adverse reaction, re-institution should be considered after the reaction has resolved. The dose can be increased gradually (desensitization) or given at a reduced dose or frequency
- Therapy should be permanently discontinued, with no rechallenge, in patients with possible or definite Stevens-Johnson Syndrome or toxic epidermal necrolysis

Prophylactic treatment:
- TMP/SMX 160/800 mg od po.

Alternative regimen
- TMP/SMX 160/800 mg three times per week
- Dapsone 100 mg od or 50 mg bid po
- Aerosolized Pentamidine 300 mg monthly

- Atovaquone 1500 mg od po

- Prophylactic treatment can be discontinued if CD4-count is ≥ 200 cells/mm³
- If Pneumocystis jirovecii pneumonia is diagnosed when CD4-count is ≥ 200 cell/mm³, prophylactic treatment should be continued for life.

Non-HIV-infected patients
See (Maschmeyer et al. 2016)

76.3.5 Histoplasmosis

Selected References
(L. J. Wheat et al. 2007)·("EACS Guidelines 10.1 October 2020" 2020)

Table 4. Treatment regimens for pulmonary endemic mycoses based on available guidelines

	Recommended regimen	Duration	Alternative treatment	Commentary
Histoplasmosis	**Mild to moderate:** Itraconazole 200 mg p.o. t.i.d. for 3 days (loading dose) followed by 200 mg p.o. once daily or b.i.d. **Severe:** Liposomal amphotericin B 3–5 mg/kg/day IV (preferred) for 2 weeks or until clinical improvement followed by itraconazole (see above) or Deoxycholate amphotericin B 0.7–1.0 mg/kg/day IV for 1-2 weeks or until clinical improvement followed by itraconazole (see above)	6–12 weeks	Posaconazole 400 mg (oral suspension) b.i.d. [58] Voriconazole 200 mg p.o. b.i.d. [59] Isavuconazole 200 mg t.i.d. for 2 days, followed by 200 mg once daily [60]	– No treatment recommended for mild symptoms <4 weeks or for pulmonary nodules or broncholithiasis or mediastinal fibrosis only – Oral solution has a better absorption – 12-month treatment duration is recommended in patients with chronic (cavitary) histoplasmosis – Surgery (e.g., lobectomy) should be discussed in patients with residual pulmonary cavities (CAVE: risk of relapse or long-term complications such as CPA) – Echinocandins are not effective
Paracoccidioidomycosis	**Mild to moderate:** Itraconazole 200 mg p.o. once daily **Severe:** Liposomal amphotericin B 3–5 mg/kg/day IV (preferred) until clinical improvement followed by itraconazole (see above) or Deoxycholate amphotericin B 0.5–0.7 mg/kg/day IV until clinical improvement followed by itraconazole (see above)	12 months (9–18 month)	Cotimoxazole 960 mg p.o. b.i.d. or t.i.d.	– Cotrimoxazole increases treatment duration to 18–24 months
Coccidioidomycosis	**Mild:** No treatment recommended **Severe:** Fluconazole 400 mg p.o. once daily **Severe disease in immunocompromised hosts:** Liposomal amphotericin B 4–6 mg/kg/day plus fluconazole 400 mg daily until clinical improvement or Deoxycholate amphotericin B 0.7–1.0 mg/kg/day IV plus fluconazole 400 mg daily until clinical improvement	3–6 months 12 months	Itraconazole 200 mg p.o. b.i.d. Liposomal amphotericin B 3–5 mg/kg/day IV	– Patients with a mild disease usually recover without antifungal treatment – Fluconazole has fewer side effects and drug interactions compared to itraconazole – Liposomal amphotericin B as an alternative for more severe cases – Treatment duration of 6–12 months in immunocompromised patients
Blastomycosis	**Mild to moderate:** Itraconazole 200 mg p.o. t.i.d. for 3 days (loading dose), followed by 200 mg p.o. b.i.d. **Severe:** Liposomal amphotericin B 3-5 mg/kg/day IV (preferred) for 1–2 weeks or until clinical improvement followed by itraconazole (see above) or Deoxycholate amphotericin B 0.7–1.0 mg/kg/day IV until clinical improvement followed by itraconazole (see above)	6–12 months	Fluconazole 400–800 mg p.o. per day Voriconazole 200 to 400 mg p.o. b.i.d. after amphotericin B therapy for CNS disease	– Alternative treatment with ketoconazole or fluconazole less effective – CAVE: higher toxicity of ketoconazole – Voriconazole or posaconazole may also be effective, but lack of evidence
Sporotrichosis	**Mild to moderate:** Itraconazole 200 mg p.o. b.i.d. **Severe:** Liposomal amphotericin B 3–5 mg/kg/day IV until clinical improvement followed by itraconazole (see above) or Deoxycholate amphotericin B 0.7–1.0 mg/kg/day IV until clinical improvement followed by itraconazole (see above)	≥12 months	Fluconazole 400–800 mg p.o. daily	– Surgical resection should be discussed – Alternative treatment less effective
Talaromycosis	**Regardless of disease severity:** Liposomal amphotericin B 3–5 mg/kg/day IV for 1–2 weeks followed by itraconazole (see above) or Deoxycholate amphotericin B 0.7–1.0 mg/kg/day IV for 2 weeks or until clinical improvement followed by itraconazole (see above)	12 weeks	Voriconazole 400 mg b.i.d. on day 1 followed by 200 mg b.i.d. for 12 weeks Itraconazole 200 mg p.o. t.i.d. for 3 days, followed by 200 mg p.o. b.i.d. for 12 weeks for patients unable to tolerate or have no access to amphotericin B	– Initial treatment with amphotericin B deoxycholate reduces mortality by 50% compared to itraconazole at 6 months in HIV-associated talaromycosis in the IVAP trial [52]

CPA, chronic pulmonary aspergillosis; b.i.d., twice a day; p.o., per os; t.i.d., three times a day; IV, intravenously.

Source: Salzer H *et al.* Diagnosis and Management of Systemic Endemic Mycoses Causing Pulmonary Disease. *Respiration.* 2018

First-line treatment
Moderate to severe acute pulmonary histoplasmosis:

- Liposomal amphotericin B 3,0 - 5,0 mg/kg od iv x 1 - 2 weeks followed by itraconazole 200 mg tid po x 3 days and then 200 mg bid po x 12 weeks.
- Methylprednisolone 0.5 - 1.0 mg/kg od iv initially if respiratory complications (hypoxemia or respiratory distress) occur.

Mild to moderate acute pulmonary histoplasmosis:
- Treatment usually unnecessary
- If symptoms > 1 month: itraconazole 200 mg tid po x 3 days and then 200 mg od or bid x 6 - 12 weeks

Chronic cavitary histoplasmosis:
- Itraconazole 200 mg tid po x 3 days and then od of bid x 1 or 2 years.
- Blood levels of itraconazole should be obtained after the patient has been receiving this agent for at least 2 weeks to ensure adequate drug exposure.

Mediastinal lymphadenitis:
- Treatment usually unnecessary.
- If symptoms > 1 month or if severe symptoms: itraconazole 200 mg tid po x 3 days and then 200 mg od or bid x 6 - 12 weeks.
- Severe cases with obstruction, compression or contiguous structures: prednisone 0,5-1 mg/kg od iv in tapering doses over 1-2 weeks.

Mediastinal granuloma:
- Treatment usually unnecessary.
- If symptoms: itraconazole 200 mg tid po x 3 days and then 200 mg od or bid x 6 - 12 weeks.

Broncholithiasis:
- Antifungal treatment is not recommended.
- Bronchoscopic or surgical removal of the broncholithiasis

Pulmonary nodule:
Treatment unnecessary.

Progressive disseminated histoplasmosis:
- Moderate to severe disease: liposomal amphotericin B 3,0 - 5,0 mg/kg iv od x 1 – 2 weeks followed by itraconazole 200 mg tid x 3 days and then 200 mg bid for a total of at least 1 year.
- Mild to moderate disease: itraconazole 200 mg tid x 3 days and then 200 mg od or bid for at least 1 year.
- Blood levels of itraconazole should be obtained to ensure adequate drug exposure.

Central nervous system histoplasmosis:
- Liposomal amphotericin B 5,0 mg/kg od for a total of 175 mg/kg given over 4 - 6 weeks followed by itraconazole 200 mg 2 or 3 times daily for at least 1 year and until resolution of CSF abnormalities, including Histoplasma antigen levels.
- Blood levels of itraconazole should be obtained to ensure adequate drug exposure.

Alternative regimens
- Deoxycholate amphotericin B 0,7 - 1 mg/kg iv od is an alternative for liposomal amphotericin B in patient who are at low risk for nephrotoxicity.
- Voriconazole 200 mg bid or posaconazole 400 mg bid have been used successfully in small numbers of patients with a variety of different forms of histoplasmosis (Freifeld et al. 2009), (Reports, n.d.), (J. L. Wheat et al. 2006). Since data are still scarce, they remain second-line alternatives to itraconazole.
- Isavuconazole has a good in-vitro activity against Histoplasma but is not studied in patients (G. R. Thompson et al. 2016), (Falci and Pasqualotto 2013)

Special situations
Pregnancy:
- Liposomal amphotericin B 3.0-5.0 mg/kg daily for 4-6 weeks.
- Azoles should be avoided because of possible teratogenicity.

Children:
Acute pulmonary histoplasmosis
- Deoxycholate amphotericin B 1 mg/kg iv od for 1-2 weeks is usually well tolerated. Lipid formulations are not recommended.
- Itraconazole is 5.0 - 10.0 mg/kg od in 2 divided doses (not to exceed 400 mg od), generally using the solution formulation.

Disseminated histoplasmosis:
- Deoxycholate amphotericin B 1 mg/kg iv od x 4 - 6 weeks.
- Alternative: Amphotericin B deoxycholate 1.0 mg/kg od x 2 - 4 weeks followed by itraconazole 5,0 – 10,0 mg/kg od in 2 divided doses to complete 3 months of therapy.

Immunosuppression (HIV infection):
- Longer therapy may be needed for patients with severe disease, immunosuppression, or primary immunodeficiency syndromes
- There are important interactions between itraconazole (and other antifungals) and antiretrovirals. Doses to be adapted accordingly.

Primary Prophylaxis:
- Itraconazole 200 mg po od in HIV-infected patients with a CD4-count of < 150 cells/mm² in high-endemic regions (incidence > 10 cases/100 patient years).

Secondary Prophylaxis:
- Itraconazole 200 mg po od.

76.3.6 Blastomycosis

Selected References
(Chapman et al. 2008)

First-line treatment

Pulmonary blastomycosis:
- Moderate to severe disease: liposomal amphotericin B 3–5 mg/kg per day or AmB deoxycholate 0,7 - 1 mg/kg od x 1 - 2 weeks or until improvement is noted, followed by oral itraconazole, 200 mg tid x 3 days and then 200 mg bid, for a total of 6 - 12 months.
- Mild to moderate disease: oral itraconazole, 200 mg tid x 3 days and then od or bid x 6–12 months.
- Serum levels of itraconazole should be determined after the patient has received this agent for at least 2 weeks, to ensure adequate drug exposure.

Disseminated extrapulmonary blastomycosis:
- Same treatment as pulmonary blastomycosis. For osteoarticular disease at least 12 months of treatment

CNS blastomycosis:

- Liposomal amphotericin B 3 - 5 mg/kg od iv x 4 - 6 weeks followed by an oral azole: itraconazole, 200 mg bid or tid po or voriconazole 200-400 mg bid po or fluconazole 800 mg od po. Treatment for at least 12 months and until resolution of CSF abnormalities.

Alternative regimens

- Voriconazole 200-350 mg bid po (Bariola et al. 2010). Successful case reports exist; especially for central nervous system involvement voriconazole seems a valid option.
- Posaconazole 400 mg bid po (Proia and Harnisch 2012): some successful case reports
- Isavuconazole: in-vitro susceptible. Only a few cases described with variable outcome (G. R. Thompson et al. 2016).

Special situations

Pregnancy

- Liposomal amphotericin B 3-5 mg/kg od iv.
- Azoles should be avoided because of possible teratogenicity.

Children:

- Severe forms: Amphotericin B deoxycholate 0,7 - 1, 0 mg/kg od iv, or lipid formulation amphotericin B, at a dosage of 3 - 5 mg/kg od iv, followed by itraconazole 10 mg/kg od po (up to 400 mg od) for a total of 12 months.
- Mild to moderate infection: itraconazole 10 mg/kg od po (to a maximum of 400 mg od po) x 6 - 12 months.

Immunosuppression (HIV infection):

- There are important interactions between itraconazole (and other antifungals) and antiretrovirals. Doses to be adapted accordingly.
- Lifelong suppressive therapy with itraconazole 200 mg od po may be required for immunosuppressed patients if immunosuppression cannot be reversed and in patients who experience relapse despite appropriate therapy

76.3.7 Talaromycosis (former penicilliosis)

Selected References

(Kaplan, Benson, and Holmes 2009) ("EACS Guidelines 10.1 October 2020" 2020)

First-line treatment

- Severe disease: Liposomal amphotericin B 3 to 5 mg/kg od iv x 2 weeks (Le et al. 2017); followed by itraconazole 200 mg tid po x 3 days and then 200 mg bid for at least 10 weeks; followed by maintenance therapy with itraconazole 200 mg od till CD4-count > 100 cells/mm³ for ≥ 6 months in response to ART.
- Mild disease: itraconazole 200 mg tid po x 3 days, then itraconazole 200 mg bid po x 8 weeks, followed by chronic maintenance therapy (see above).

Alternative regimens

- Severe disease: Voriconazole 6 mg/kg bid iv x 1 day, then 4 mg/kg bid for at least 3 days, followed by voriconazole 200 mg bid po for a maximum of 12 weeks, followed by chronic maintenance therapy with itraconazole 200 mg od po till CD4-count > 100 cells/mm³ for ≥ 6 months in response to ART.

- Mild disease: Voriconazole 400 mg bid po x 1 day, then 200 mg bid po for a maximum of 12 weeks followed by chronic maintenance therapy (see above)
- Posaconazole shows good in-vitro activity (Lau et al. 2017).
- Isuvaconazole shows good in-vitra activity against Rasamsonia species, of which some are related to Taralomyces (J. Steinmann et al. 2016).

Special situations
Immunosuppression (HIV infection):
- There are important interactions between itraconazole (and other antifungals) and antiretrovirals or immunosuppressive therapies. Doses to be adapted accordingly.

Primary prophylaxis:
- Itraconazole 200 mg od po for HIV-infected patients with CD4 count <100 cells/mm³ who reside or stay for an extended period in northern Thailand, Vietnam, and Southern China, in rural areas (alternative fluconazole 400 mg once weekly po).

76.3.8 Emmonsiosis (also known as Emergomycosis)

Selected References
(Schwartz et al. 2015), (Mendelson, Meintjes, and Maartens, n.d.)

First-line treatment
Deoxycholate amphotericin B 1 mg/kg od iv (or liposomal amphotericin B 3-5 mg/kg od iv) for 2 weeks or until improvement, followed by itraconazole 200 mg tid po x 3 days, then 200 mg bid for at least 12 months (Samaddar and Sharma 2021). Maintenance treatment on itraconazole 200 mg od po till CD4-count > 200 cells/mm³ for ≥ 6 months.

Alternative regimens
Fluconazole 400 mg od po appears to be active in-vitro and could be considered instead of itraconazole and does not have important drug interactions with ART. Maintenance treatment with fluconazole 200 mg od may be an option.

Special situations
Immunosuppression: There are important interactions between itraconazole (and other antifungals) and antiretrovirals or immunosuppressive drugs. Doses to be adapted accordingly.

76.3.9 Coccidioidomycosis

Selected References
(Galgiani et al. 2016)

First-line treatment
Pulmonary nodules:
- Treatment unnecessary if asymptomatic.

Pulmonary cavities:
- If asymptomatic: no treatment.
- If symptomatic: Fluconazole 400 mg od or itraconazole 200 mg bid po for at least 1 year.
- May return when treatment is discontinued.

- Resection can be considered in young, healthy patients whose symptoms persist despite after a one- or two year trial of azoles. VATS (Video-Assisted thoracoscopic surgery) is the preferred technique.
- In case of rupture of the cavity, surgical resection often requiring lobectomy is required.

Diffuse reticulonodular pneumonia:
- Deoxycholate amphotericin B 1 mg/kg od iv followed by an oral azole for 1 year in immunocompromised patients.
- Liposomal amphotericin B 3-5 mg/kg of iv is an alternative.

Extrapulmonary soft tissue coccidioidomycosis
- Fluconazole 400 mg od or itraconazole 200 mg bid x 6-12 months.
- Deoxycholate amphotericin B 1 mg/kg od iv in case of azole failure.

Bone and/or joint coccidioidomycosis:
- Itraconazole 200 mg bid or fluconazole 800 mg od x 6-12 months (itraconazole seems to be more potent for bone and joint disease).
- Liposomal amphotericin B 3-5 mg/kg od iv if severe (limb threatening or spinal cord compromise) for 2-4 weeks followed by azole.
- Surgical consultation is indicated in case of spinal instability or cord compression.

Cerebral coccidioidomycosis:
- Fluconazole 400-1200 mg od po or iv (higher dose if more severely ill) or itraconazole 200 mg bid or tid po if fluconazole not tolerated.
- Echinocandins (amphotericin B deoxycholate or liposomal amphotericin B) have no proven benefit in humans with coccidioidal meningitis.
- Intrathecal deoxycholate amphotericin B can be given if there is failure on high dose azoles. Intrathecal dose of amphotericin B normally ranges between 0,01 mg and 1,5 mg per dose administered at intervals ranging from daily to weekly, beginning at a low dose and increasing the dose until patient intolerance appears. Administration through direct cisternal injection or via an Ommaya reservoir or through ventricular injection.
- Azole treatment is continued for life since relapses are common and potentially fatal.

Alternative regimens
- Voriconazole 200-400 mg bid (Freifeld et al. 2009)
- Posaconazole solution 400-800 mg od (or 300 mg extended release daily).

Special situations
Immunosuppression:
- Fluconazole 400 mg po od.
- Severe disease: Deoxycholate amphotericin B 1 mg/kg od iv till stabilized, followed by fluconazole.
- In HIV-infected patients: continue antifungal treatment at least as long as CD4-count is < 250 cells/mm³.
- There is no place for primary prophylaxis for HIV-infected or immune-compromised patients living in endemic areas. In coccidioidal-endemic regions yearly serological screening is advised in HIV-patients with low CD4-count.

Pregnancy:

- Amphotericin B IV is the preferred treatment in the first trimester if symptoms are severe; if symptoms are less severe no treatment with close monitoring is an option
- After the first trimester itraconazole and fluconazole can be considered. An alternative is amphotericin B iv throughout pregnancy.

Children:

- Deoxycholate amphotericin B 1 mg/kg od iv
- Fluconazole 12 mg/kg od po or itraconazole 10 mg/kg od po.

76.3.10 Paracoccidioidomycosis

Selected References

(Marques 2013), (Shikanai-Yasuda 2015)

First-line treatment

- Mild to moderate disease: Itraconazole 200 mg od po x 6-9 months (mild) or x 12-18 months (moderate).
- Children: itraconazole 5-10 mg/kg od po
- Severe disease and pregnancy: liposomal amphotericin B 3 mg/kg od iv x 1 month, followed by itraconazole or TMP-SMX for 6-12 months.

Alternative regimens

- Voriconazole 400 mg bid po on the first day, followed by 200 mg bid x 6 months (Telles et al. 2007).
- Fluconazole 300-400 mg od po (also good CNS penetration).
- Trimethoprim-sulfamethoxazole 800/160 mg bid po x 12 months (mild) or 18-24 months (moderate)
- Children: Trimethoprim-sulfamethoxazole 50/10 mg/kg bid po.
- Deoxycholate amphotericin B 0.5-1.0 mg/kg od iv.
- Cases that were successfully treated with isavuconazole are described(G. R. Thompson et al. 2016).

Special situations

Adjunctive corticosteroids can potentially help in the management of selected cases of severe forms, particularly when there is a risk of acute complications (cerebral forms, edema, stenosis, IRIS).(Benard et al. 2012)

Chapter 6: Viruses

77 Viroses (Tropical)

Viruses covered

Selected References
(to be seen = all Selected References from below)

77.1 Chikungunya

First-line treatment

- Acute disease: supportive treatment only.
- Persistent arthralgia:
  - NSAIDs
  - If insufficient response on NSAIDs: prednisolone 10-30 mg/day to be tapered over 10-60 days.
  - If persistent > 3 months, start DMARDs:
    - Methotrexate oral or IM: start 7,5 mg once weekly and increase gradually till max 30 mg once weekly) or Sulfasalazine enteric coated tablet: start 0,5 to 1gr daily; increase weekly to maintenance 2gr daily in 2 divided doses; maximum: 3gr daily.
  - Anti-TNF treatment is used in patients with insufficient response or intolerance for methotrexate.

Selected References

1. https://dx.doi.org/10.1016/j.medmal.2015.05.007 (Simon et al. 2015)
2. https://dx.doi.org/10.1371/journal.pntd.0003603 (Javelle et al. 2015)
3. https://dx.doi.org/10.1002/art.39775 (Blettery et al. 2016)

77.2 Crimean Congo Hemorrhagic Fever

Supportive treatment:

- For severe disease: case reports of successful treatment with ribavirin exist. Ribavirin is given for 10 days, preferably IV:
  - IV loading dose of 30 mg/kg (maximum 2 gr), followed by 15 mg/kg (maximum 1 g) iv every 6h for 4 days, followed by 7,5 mg/kg iv (maximum 500 mg) every 8h for 6 days.
  - Oral loading dose consists of 35 mg/kg every 6h for 4 days, followed by 15 mg/kg (maximum 1 g) every 8h for 6 days.

Selected References

1. https://dx.doi.org/10.1016/S1473-3099(06)70435-2 (Ergönül 2006)
2. https://dx.doi.org/10.1016/S0140-6736(95)91323-8 (Khan et al. 1995)

77.3 Dengue

Supportive treatment only:

- No role for corticosteroids, IV immunoglobulins, pentoxifylline or activated factor VII.
- Aspirin and NSAIDS to be avoided to reduce de risk of hemorrhagic dengue.

77.4 Ebola

Supportive treatment
Several experimental drug were evaluated during the 2013-2016 West African outbreak, but none of the novel treatments achieved to prove significant efficacy

Following drugs could be considered in compassionate use:
- ZMapp 22 vs 37% mortality, but did not meet the prespecified threshold for efficacy.
- GS-5734, successful case reports, although late relapse is described.
- Favipiravir showed conflicting results.
- Monoclonal antibodies, promising result in macaques.
- Antisense oligonucleotides (PMO's), promising results in animal studies.
- BCX4430, broad spectrum antiviral activity with promising results against Ebola and Marburg in animal studies.

Selected References
1. https://dx.doi.org/10.1056/NEJMoa1604330 (Article 2016)
2. https://dx.doi.org/10.1016/S0140-6736(16)30386-5 (M. Jacobs et al. 2016)
3. https://dx.doi.org/10.1371/journal.pmed.1001967 (Sissoko et al. 2016)
4. https://dx.doi.org/10.1093/cid/ciw571 (Bai et al. 2016)
5. https://dx.doi.org/10.1056/NEJMoa1504874 (Uyeki et al. 2016)

77.5 Hanta Virus

77.5.1 Hanta virus cardiopulmonary syndrome (HCPS)

Supportive treatment
No place for ribavirin ("Ribavirin IV for HCPS.pdf," 1999), though prevention of seroconversion and diminished multiplication described in a deer mouse model so ribavirin to be considered in case of extremely early detection.
The role of antisera taken from convalescent patients is not clear ("IgG's for HCPS.pdf," 2015).

77.5.2 Hemorrhagic fever with renal syndrome (HFRS)

Supportive treatment
- Ribavirin IV
  - IV loading dose of 30 mg/kg (maximum 2 gr), followed by 15 mg/kg (maximum 1 gr) IV every 6h for 4 days, followed by 7,5 mg/kg IV (maximum 500 mg) every 8h for 6 days.
  - Oral loading dose consists of 35 mg/kg every 6h for 4 days, followed by 15 mg/kg (maximum 1 g) every 8h for 6 days.

Additional comments
Monitor for hemolytic anemia.

Selected References
1. https://dx.doi.org/10.1086/425007 (Mertz et al. 2004)
2. https://dx.doi.org/10.1099/vir.0.82459-0 (Medina et al. 2007)
3. https://dx.doi.org/10.1093/infdis/164.6.1119 (Huggins et al. 1991)

77.6 Herpes simian B virus

First-line treatment

- CNS symptoms absent: acyclovir 12,5-15 mg/kg IV every 8h; alternative ganciclovir 5 mg/kg iv every 12h.
- CNS symptoms present: ganciclovir 5 mg/kg iv every 12h.

Treatment to be given until symptoms resolve and the results of 2 cultures are negative for B virus:

- Prophylaxis after exposure to B virus
- Valacyclovir 1 gr po 3 TDS x 14 days

Alternative regimen

- Acyclovir 800 mg po 5 times per day x 14 days.
- Indications for prophylaxis.

Table 5. Recommendations for postexposure prophylaxis for persons exposed to B virus.

Prophylaxis recommended
Skin exposure[a] (with loss of skin integrity) or mucosal exposure (with or without injury) to a high-risk source (e.g., a macaque that is ill, immunocompromised, or known to be shedding virus or that has lesions compatible with B virus disease)
Inadequately cleaned skin exposure (with loss of skin integrity) or mucosal exposure (with or without injury)
Laceration of the head, neck, or torso
Deep puncture bite
Needlestick associated with tissue or fluid from the nervous system, lesions suspicious for B virus, eyelids, or mucosa
Puncture or laceration after exposure to objects (a) contaminated either with fluid from monkey oral or genital lesions or with nervous system tissues, or (b) known to contain B virus
A postcleansing culture is positive for B virus
Prophylaxis considered
Mucosal splash that has been adequately cleaned
Laceration (with loss of skin integrity) that has been adequately cleaned
Needlestick involving blood from an ill or immunocompromised macaque
Puncture or laceration occurring after exposure to (a) objects contaminated with body fluid (other than that from a lesion), or (b) potentially infected cell culture
Prophylaxis not recommended
Skin exposure in which the skin remains intact
Exposure associated with nonmacaque species of nonhuman primates

[a] Exposures include macaque bites; macaque scratches; or contact with ocular, oral, or genital secretions, nervous system tissue, or material contaminated by macaques (e.g., cages or equipment) (see the Postexposure Prophylaxis section of the text for details).

Source: J.I. Cohen et al. Recommendations for Prevention of and Therapy for Exposure to B Virus *Clin Infect Dis.* 2002f

Selected References

1. https://dx.doi.org/10.1086/344754
2. https://dx.doi.org/10.1016/j.jemermed.2015.06.012

77.7 HIV

Selected References

EACS : https://www.eacsociety.org/guidelines/eacs-guidelines/

77.8 HTLV-1

Treatment is not indicated for asymptomatic patients.
The role of antiretroviral treatment is not clear.

77.8.1.1 HTLV-1 associated myelopathy/Tropical Spastic paraparesis

Conflicting results on the use of glucocorticoids (Library et al. 2000), ("Prednisolone for HTLV-1 HAM-TSP.pdf," n.d.)
Small studies suggest benefit of IFN-β1 and danazol.

77.8.1.2 Adult T-cell leukemia/lymphoma

First-line treatment

- Chemotherapy with CHOP or VCAP-AMP-VECP
- Zidovudine plus IFN-α has activity against adult T-cell leukemia–lymphoma, even if prior cytotoxic therapy has failed.

Selected References

1. https://dx.doi.org/10.1016/j.jns.2008.01.004 (Croda et al. 2008)
2. https://dx.doi.org/10.1002/ana.20429 (Oh et al. 2005)
3. https://dx.doi.org/10.1089/aid.1991.7.1031 (Harrington et al. 1991)
4. https://dx.doi.org/10.1056/NEJM199506293322603 (Gill et al. 1995)

77.9 Japanese Encephalitis

Supportive treatment

- No benefit of ribavirin, corticosteroids or INF-α2a

Selected References

1. https://dx.doi.org/10.1086/596309 (R. Kumar et al. 2009)
2. https://dx.doi.org/10.1016/S0140-6736(03)12709-2 (Solomon et al. 2003)

77.10 Lassa Fever

Supportive treatment

- Ribavirin, preferably IV (Haynes et al. 2009)
  - IV loading dose of 30 mg/kg (maximum 2 gr), followed by 15 mg/kg (maximum 1 gr) iv every 6h for 4 days, followed by 7,5 mg/kg IV (maximum 500 mg) every 8h for 6 days.
  - Oral loading dose consists of 35mg/kg every 6h for 4 days, followed by 15mg/kg (maximum 1 g) every 8h for 6 days.

NB: Monitor for hemolytic anemia

Selected Reference

1. WHO, "Clincial Management of Patients with Viral Haemorrhagic Fever: A Pocket Guide for the Front-line Health Worker," World Health Organization, pp. 1-191, 2016. https://www.who.int/csr/resources/publications/clinical-management-patients/en/

77.11 Marburg

Supportive treatment

There are no date on role of monoclonal antibodies, favipiravir, BCX4430 and GS-5734 in humans.

Selected Reference

1. https://dx.doi.org/10.1093/cid/ciw571 (Bai et al. 2016)

77.12 Nipah Virus

Supportive treatment

Ribavirin might reduce mortality, though the supportive trial was held at the end of an epidemic when mortality is often lower as in the beginning of an epidemic (during which in control patients were included). Ribavirin is given for 10 days: 30 mg/kg as an initial loading dose, then 15 mg/kg every 6h for 4 days, and then 7,5 mg/kg every 8h for 6 days; (oral alternative: Ribavirin 2 g on day 1 followed by 1,2 g 3x/d on day 2 to 4, 1.2g 2x/d on days 5 to 6, 0.6g 2x/d for another 1 to 4 days).
Monoclonal antibodies showed promising results in non-human primates .

Selected References

1. https://dx.doi.org/10.1002/ana.1062 (Chong et al. 2001)
2. https://dx.doi.org/10.1007/s00401-015-1526-9 (Toledo et al. 2016)

77.13 Poliomyelitis

Supportive treatment

Polioviruses are part of human enterovirus group C. Pleconaril has been tried for entervirus infections of whom 3 were poliovirus infected and 2 of these patients had a favorable clinical evolution.

Selected Reference

1. https://dx.doi.org/10.1086/318452 (Rotbart, Webster, and Pleconaril Treatment Registry Group 2001)

77.14 Rabies

Supportive care in a critical care unit

A combination of following treatments can be tried:

- Immunotherapy with vaccination and Human rabies Immunoglobulines (HRIG) even though it's not known whether this is useful, all but one rabies survivors received one or more vaccine doses prior to symptom onset.
- INF-alpha IV and intrathecal

- Ribavirin IV +/- intrathecal
- Amantadine
- Favipiravir
- Brain hypothermia
- Ketamine

Selected References

1. https://dx.doi.org/10.1016/j.antiviral.2013.01.003 (A. C. Jackson 2013)
2. https://dx.doi.org/10.1017/cjn.2015.331 (Zeiler and Jackson 2016)
3. https://dx.doi.org/10.1086/344905 (A. C. Jackson et al. 2003)

77.15 Rift Valley Fever

Supportive treatment

Some data support the use of ribavirin and favipiravir, though trial data in humans are lacking.

Selected References

1. http://www.dtic.mil/get-tr-doc/pdf?AD=ADA233097 (Monath 1990)
2. https://dx.doi.org/10.1016/j.antiviral.2014.01.016 (Scharton et al. 2014)

77.16 Tick-borne Encephalitis

Supportive treatment

77.17 Venezuelan- Eastern- and Western Equine Encephalitis

Supportive treatment

77.18 West Nile Virus

Supportive treatment

Case reports of successful treatment with Interferon-α2a exist, though it is not clear whether improvement was due to interferon or spontaneous recovery.

NB:

- Ribavirin seems ineffective and possibly detrimental.
- There are promising results in mice and case reports of successful treatment intravenous immunoglobulins from convalescent donors.

Selected References

1. https://dx.doi.org/10.1592/phco.27.3.455 (M. Lewis and Amsden 2007)
2. https://dx.doi.org/10.1086/427945 (Kalil et al. 2005)
3. https://dx.doi.org/10.3201/eid0704.017414 (Chowers et al. 2001)
4. https://dx.doi.org/10.1086/376871 (Agrawal and Petersen 2003)
5. https://dx.doi.org/10.1086/519392 (Planitzer, Modrof, and Kreil 2007)

77.19 Yellow Fever

Supportive treatment

- Ribavirin is promising in hamsters, but failed to proof benefit in non-human primates. It is questioned wetter higher doses might be beneficial.

Selected References

1. https://dx.doi.org/10.4269/ajtmh.2004.71.306 (GUZMAN et al. 2004)
2. https://dx.doi.org/10.1016/j.antiviral.2007.10.009 (Monath 2008)

77.20 Zika

Supportive treatment

Chapter 7: Other

78 Ciguatera-poisoning

Selected References

1. https://dx.doi.org/10.1056/NEJM200103013440914 (Buckner and Moynihan 2001)
2. https://dx.doi.org/10.1016/S1474-4422(05)70041-7 (Isbister and Kiernan 2005)
3. https://dx.doi.org/10.3390/md15030072 (M. A. Friedman et al. 2017)

Very long duration of symptoms; no evidenced-based therapy.
No antidote is available.

First-line treatment

Acute symptoms (within 2-3 days):

- Mannitol iv 1.g/kg over 30-45 minutes (but controversial results)

Long-term symptoms:

- Gabapentin (Neurontin® 400 mg) tid x 20 days.
- Pregabalin (Lyrica®)
- Amitriptyline
- Doses and duration are not established.

79 Sexually transmitted infections (STIs)

Preliminary remarks

The recommendations are based on the following national and international guidelines.

- CDC guidelines: https://www.cdc.gov/std/default.htm
- European guidelines (IUSTI): https://iusti.org/treatment-guidelines/
- Dutch guidelines (in Dutch): https://www.nhg.org/sites/default/files/content/nhg_org/uploads/multidisciplinaire_richtlijn_soa_herziening_2018.pdf
- Handy overview Dutch guidelines (in Dutch): https://storage.googleapis.com/alii-ea36b.appspot.com/images/099e1599-0101-409f-b053-694702a733ed.pdf
- WHO guidelines https://www.who.int/reproductivehealth/publications/rtis/clinical/en/

General principles regarding STI treatment

- Treat empirically awaiting the result of the diagnostic tests in case of serious complaints, ongoing transmission risk or risk of lost-to-follow-up. In other cases, it is advisable to wait for the results of microbiological investigations.
- Treat all partner(s) of the preceding X days to avoid "ping pong" effect (exception for some infections mentioned in the text).
  - X is determined by the STI (For details per STI see (in Dutch): https://storage.googleapis.com/alii-ea36b.appspot.com/images/099e1599-0101-409f-b053-694702a733ed.pdf
- Sexual abstinence is also recommended for one week after the end of the treatment.
- All patients with an STI diagnosis should be retested for STI's at 3 months. This is a highly cost-effective strategy to pick up reinfections.
- No STI tests have a 100 % sensitivity, so treat a patient with suggestive complaints even if the test is negative.

79.1 Bacterial vaginosis (*Gardnerella vaginalis*)

In general treat only if symptoms as spontaneous clearance is usually observed among asymptomatic women. The choice between local and peroral treatment is made based on drug availability, cost and patient's preference.

Selected References

1. https://dx.doi.org/10.1002/14651858.CD000262.pub4 (Brocklehurst et al. 2013)
2. https://dx.doi.org/10.1097/01.AOG.0000157108.32059.8f (Okun, Gronau, and Hannah 2005)

First-line treatment

- Metronidazole (Flagyl®) 500 mg po bid x 7 days.
- Clindamycin (Dalacin®) 300mg po bid x 7 days.
- Metronidazole (Flagyl®): 500 mg od intravaginal ovules x 7 days.
- Clindamycin (Dalacin(r))00mg OD intravaginal cream (=5g of cream) x 7 days.

Alternative regimens

- Tinidazole (Fasigyn®): several doses are proposed ranging from 1g po od x 5 days to 2 gr po od x 2-3 days. There is not enough conclusive data to recommend a single dose treatment. Of note, not available anymore in Belgium since 2021.

NB: Insufficient evidence yet for probiotics or acidifying products. Vaginal douching is not recommended.

Special situations

Pregnancy or breast-feeding

- Treat as non-pregnant except for tinidazole (lack of data).

Recurrent bacterial vaginosis

- No strong data about this issue, but an oral course of 7 days with a different drug may be tried.
- Condom use may be advised in case of frequent recurrences. The male partner is generally not treated, as influence on recovery or relapse is controversial.

Other options for recurrent bacterial vaginosis

- Metronidazole 500mg twice daily for 7 days followed by intravaginal metronidazole twice weekly for 4–6 months. It has been shown to reduce recurrences, although this benefit might not persist when suppressive therapy is discontinued
- Metronidazole 500 mg twice daily for 7 days combined with intravaginal boric acid 600 mg daily for 21 days and then suppressive vaginal metronidazole twice weekly for 4–6 months. Do not use chronic clindamycin for the prevention of recurrences.

79.2 Candidiasis, vulvovaginal

Selected References

1. https://dx.doi.org/10.1016/j.idc.2008.05.002 (Nyirjesy 2008)
2. https://dx.doi.org/10.1016/S0140-6736(07)60917-9 (Sobel 2007)
3. https://dx.doi.org/10.1111/j.1471-0528.1986.tb07818.x (BISSCHOP et al. 1986)
4. https://dx.doi.org/10.1136/sti.73.4.267 (Colli, Landoni, and Parazzini 1997)
5. https://doi.org/10.1086/313749 (Rex et al. 2000)
6. CDC guidelines 2021: https://www.cdc.gov/std/treatment-guidelines/candidiasis.htm (cdc 2021a)

Treatment is only indicated in case of symptoms (asymptomatic shedding is frequent). Vulvovaginal candidiasis (VVC) can be complicated or uncomplicated as defined below.
Uncomplicated VVC = Sporadic or infrequent VVC & mild-to-moderate VVC & likely to be *Candida albicans* & non-immunocompromised women.
Complicated VVC = Recurrent VVC or severe symptoms or non-albicans candidiasis (mostly *C. glabrata*) or women with poorly controlled diabetes, immunocompromising conditions (e.g., HIV infection), debilitation, or immunosuppressive therapy (e.g., corticosteroids).

First-line treatment

Uncomplicated infections (lifetime incidence 75%):
This is usually caused by *C. albicans*. This is normally not considered as a sexually transmitted infection and as a rule the treatment of the sexual partner(s) is not recommended. Topical and oral treatments are equivalent, the choice is left to provider's and patient's preference.

- Oral treatment (one day):
  - 1st choice: Fluconazole (Diflucan®) 1 x 150 mg.
  - 2nd choice Itraconazole (Sporanox®): 2 x 100 mg (morning and evening).
- Local anti-mycotic treatment: imidazole derivatives (butoconazole, clotrimazole, fenticonazole or miconazole) cream may be used in case of external itching otherwise vaginal suppository (butoconazole, clotrimazole or fenticonazole) are recommended (dose vary according to drug are applied once a day for 3 to 7 days).

NB: the oils in these topical products may cause condom failure, so counsel patients accordingly.

Complicated infections:
- Culture should be obtained to confirm diagnosis and assess for non-albicans candida (since these may require different therapy).
- Severe symptoms: same treatment as above but longer (topical treatment 7 to 14 days, fluconazole 150mg every three days x 3 doses
- Recurrent infections (with *C. albicans*) (> 4 recurrences/ year): fluconazole 150mg every three days x 3 doses then fluconazole 150mg once a week for 6 months and risk factors reduction

Special situations
"Non-albicans" VVC:
- Azole (other than fluconazole) either oral or topical x 7-14 days. If this fails then boric acid in a gelatin capsule, administered vaginally once daily for 2 weeks.

HIV infected VVC:
- Treatment is the same as for HIV uninfected.

Pregnant VVC:
- Use topical azoles (only) for 7 days

Prevention of relapses according to risk factors:
- No bubble bath, soap only the cutaneous parts of the genitals preferably with an acid soap (**Lactacid®**).
- Change of oral contraceptive pill (lower dose of estrogen)
- Immediate treatment from the first signs of relapse, or after menstruation, or after sexual intercourse with or without use of antimycotic lubrification cream.
- Local prophylactic treatment on the 5th day of the cycle.
- Remove contact allergies (antihistamines before bed, hydrocortisone cream 1 % can be tried for external itching).
- Very rarely is there an indication of susceptibility testing.
- Explain to patient (or partner) that relapses are not necessarily the manifestation of an underlying pathology but that a pragmatic approach is necessary.
- Probiotics nor specific diets seem to play a role in the prevention of VVC recurrences.

79.3 Chancroid (Soft chancre, Ulcus molle*, Haemophilus ducreyi)*

Selected References
1. https://dx.doi.org/10.1016/S2214-109X(14)70019-1 (D. A. Lewis and Mitjà 2016)
2. https://pubmed.ncbi.nlm.nih.gov/26658654/ (D. A. Lewis and Mitjà 2016)
3. http://www.ncbi.nlm.nih.gov/pubmed/6601847 (Fast et al. 1983)
4. Recent Guideline: https://pubmed.ncbi.nlm.nih.gov/25080286/ (O'Farrell and Lazaro 2014)

This is an infrequent cause of, usually multiple, painful genital ulcers associated with tender lymphadenopathy in Europe. A primary syphilis as well as lymphogranuloma venereum and Herpes simplex infection should always be ruled out.

First-line treatment
- Azithromycin 1 g (30 mg/kg) po single dose.

Alternative regimens
- Ceftriaxone 250 mg im single dose (preferred regimen during pregnancy).
- Ciprofloxacin: 500 mg po bid x 3 days (increasing resistance).

NB: Doxycycline is little effective: 30% efficacy.

79.4 Chlamydia trachomatis

Selected References

1. https://pubmed.ncbi.nlm.nih.gov/34045364/ (Van Bergen et al. 2021)
2. https://pubmed.ncbi.nlm.nih.gov/32404400/ (Verougstraete et al. 2020)
3. https://pubmed.ncbi.nlm.nih.gov/19028953/ (Alexander et al. 2008)
4. https://dx.doi.org/10.1056/NEJMcp030542 (Peipert 2003)
5. Guideline 2016: https://dx.doi.org/10.2807/1560-7917.ES.2016.21.22.30248 (Horner et al. 2016)
6. https://doi.org/10.1056/nejmoa1502599 (Geisler et al. 2015)

Empiric therapy combining agents active *Chlamydia trachomatis* and *Neisseria gonorrhea* should always be started. The steady partner(s) should always be treated to reduce the risk of re-infection. It is now well established that self-collected vaginal or rectal samples are as valuable than physician collected samples. There are growing uncertainties about the need to treat asymptomatic infections. Pooling of pharyngeal urinary and rectal samples is possible If screening is recommended.

79.4.1 Uncomplicated urethral or cervical infection

First-line treatment

- Doxycycline 100 mg po bid x 7 days (not recommended during pregnancy).

Alternative regimens

- Azithromycin 1g single dose 1 to 2 hours before a meal (first choice in pregnancy).

79.4.2 Complicated *Chlamydia* infection

Proctitis: a lymphogranuloma venereum (LGV) should be suspected (invasive infection with *C. granulomatis* serovar L1, L2, L3).

- Doxycycline 100 mg po bid x 21 days. The duration of treatment may be reduced to 7 days if serotyping excluded a LGV strain.

79.4.3 Epididymitis

Doxycycline 100mg po bid x 10 days combined with ceftriaxone 250mg im single dose.

79.4.4 Condyloma acuminata (external genital warts)

Selected References

- https://pubmed.ncbi.nlm.nih.gov/31675442/ (Jung et al. 2020)
- https://pubmed.ncbi.nlm.nih.gov/29505317/ (Yuan et al. 2018)
- https://pubmed.ncbi.nlm.nih.gov/24913124 (Leszczyszyn et al. 2014)

First-line treatment by physician

- Liquid nitrogen to be repeated if necessary.
- Electrocoagulation or surgical removal.

First-line treatment by the patient

- Podophyllotoxin. Pharmacies can provide magistral preparation. Can also be ordered via the Netherlands: Condyline application liquid: 5 mg/ml or Wartec(r) cream 1,5 mg/gr; 5 gr). Apply twice daily

during 3 consecutive days per week followed by 4 days' rest. Duration: maximum 4-5 consecutive weeks. Use max 0,5ml per day.
- Imiquimod 5% (Aldara®)apply 3 x/week (f before bed; leave on the skin for 6 to 10 hours; then wash off with soap and water; repeat treatment until the warts disappears; maximum 16 consecutive weeks. Reimbursement only if request by gastro-enterologist, dermatologist, urologist or gynecologist.
- Sinecatechins (Veregen (r) - Green tea extract) 15% ointment applied 3x per day (0,5 cm strand of ointment to each wart) using a finger to ensure coverage with a thin layer of ointment until complete clearance of warts is achieved. Use for a maximum of 16 weeks (Wash off after use). Avoid if HIV positive as efficacy and safety not established.
  NB: Imiquimod and Sinecatechins may weaken condoms.
- Refer all internal warts (vaginal, anal) to proctologist/gynecologist.
- If perianal warts do PPA +- refer for high resolution anoscopy (HRA).

79.4.5 Donovanosis (or granuloma inguinale*, Klebsiella granulomatis)*

This is an unusual cause of, generally painless, genital ulcers.

Selected References

1. https://pubmed.ncbi.nlm.nih.gov/27107782/ (Copeland and Decker 2016)
2. https://pubmed.ncbi.nlm.nih.gov/33069513/ (Belda Junior 2020)
3. https://www.cdc.gov/std/treatment-guidelines/donovanosis.htm (cdc 2021b)
4. https://search.informit.com.au/documentSummary;dn=559741124400483;res=IELHEA (Skov et al. 1998)

First-line treatment
- Azithromycin 1g po od for at least three weeks and until all lesions heal.

Alternative regimens
- Doxycycline 100mg po bid for at least three weeks
- TMP/SMX (Bactrim® or Eusaprim® forte) 1 tablet po bid for at least three weeks.

79.4.6 Genital herpes *(Herpes simplex virus)*

Anti-herpetic treatment must be started as soon as possible after the occurrence of the symptoms.

First-line treatment

Primary herpes genitalis:
- Aciclovir (tablets of 200, 400, or 800 mg) 200 mg 5x/day or 400 mg po tid x 7-10 days.
- Valaciclovir (tablet of 500 mg) 1000 mg po bid x 7-10 days.
- For all these regimens: treatment can be extended if healing is incomplete after 10 days of therapy.

Episodic treatment of recurrent herpes genitalis:
Here the patient is provided with a supply of drug or a prescription for the medication with instructions to initiate treatment immediately when symptoms begin.
- Aciclovir: 800mg po bid x 5 days.
- Aciclovir: 800mg po tid x 2 days.
- Valaciclovir: 500 mg po bid for 5 days.

Suppressive treatment of recurrent herpes genitalis:
The choice between episodic treatment and suppressive therapy is subject to individual evaluation (frequency of recurrences, risk of infecting sexual partner(s), expected adherence, etc..). Suppressive therapy

reduces the frequency of genital herpes recurrences by 70%–80% in patients who have frequent recurrences. It also reduces transmission to partners. The treatment can be continued ias long as needed and doesn't require lab monitoring. The need to continue the therapy should be discussed with the patient at least annually.

- Aciclovir: 400 mg bid (Aciclovir is reimbursed under certain circumstances, see reimbursement form at: http://www.bcfi.be/PDF/RIZIV/510201_FormDem_NS_NL.pdf
- Valaciclovir 500 mg od.

Special situations

Immunocompromised patient:

- Invasive or serious infection should be treated parenterally (aciclovir 10 mg/kg TID iv). The treatment of the primary episode should last until healing of the lesions.
- Episodic treatment of recurrences should at least last five days.
- Suppressive therapy may be a preferred option in patients with frequent relapses, it seems to influence HSV shedding, it reduces HIV viral load and decreases the symptoms associated with herpes genitalis.
- Aciclovir: 400-800 mg bid.
- Valaciclovir 500 mg bid.

Pregnancy:

- Aciclovir is preferably used.

Resistant Herpes simplex virus infection:

- Consider if nonresponsive. Susceptibility testing available at UZ Leuven: antivirale resistentiebepaling (wisser huidletsel): https://laboboeken.nexuzhealth.com/pboek/internet/GHB/4158.
- All aciclovir-resistant strains are also resistant to valaciclovir, and most are resistant to famciclovir. Alternatives are foscarnet 40 mg/kg iv every 8 to 12h for 14-21 days and cidofovir 5 mg/kg/dose once weekly for 3 weeks, then 5 mg/kg/dose once every 2 weeks for 3 doses. Concomitant oral probenecid and hydration has been used to reduce the risk of cidofovir-associated nephrotoxicity.

79.4.7 Gonorrhea *(Neisseria gonorrhea)*

Selected References

1. https://dx.doi.org/10.1258/ijsa.2009.009160 (Bignell and Jensen 2012)
2. https://www.cdc.gov/std/treatment-guidelines/gonorrhea-adults.htm
3. https://www.cnr-ist.fr/ressources/editeur/IUSTI-Gonorrhoea-2020.pdf (Unemo et al. 2094)

Preliminary remark: ALWAYS PERFORM CULTURE AND SUSCEPTIBILITY TESTING FOR NG. IF SCREEN FOR NG WITH NAAT IS POSITIVE THEN DO CULTURE/SUSCEPTIBILITY BEFORE GIVING THERAPY. THIS IS CRUCIAL FOR MONITORING DECREASING SUSCEPTIBILITY TO ANTIBIOTICS. DON'T GO DOWN IN HISTORY AS THE FIRST DOCTOR TO MISS THE XDR NG!

Non-complicated gonococcal infections of the cervix, pharynx, urethra, and rectum:

First-line treatment

- Ceftriaxone 1gr single dose im

OR

- Ceftriaxone 1g single dose im + doxycycline 100mg bid x 7d (if need to treat possible chlamydia infection).
- Ceftriaxone 1g single dose im + azithromycin 2gr po single dose with food.

Alternative regimens
Alternative treatments are much less efficient due to the emergence of resistance. They should be used with extreme caution and in very particular situations. If used, they should be followed by a test-of-cure one week after the treatment.

- Spectinomycin 98% effective for urogenital and anal sites (not for pharyngeal gonorrhea, available from France) 2g single dose im (this may be a suitable alternative for patient with a proven history of severe penicillin allergy).
- Single doses of oral gemifloxacin 320 mg plus oral azithromycin 2 gr (for urogenital gonorrhea cure rates of 99.5% - trial underpowered for assessing treatment efficacy of rectal or pharyngeal infection, but both regimens cured the few extragenital infections)
- If an alternative regimen has been used, then patients should return 14 days after treatment for a test-of-cure using either culture or NAAT.

Disseminated gonococcal infection:

- Ceftriaxone 1g iv od for at least 7days.

79.4.8 Mycoplasma genitalium

Selected reviews

1. https://iusti.org/wp-content/uploads/2021/03/Mg-IUSTI-draft-guideline-2021.docx
2. https://www.cdc.gov/std/treatment-guidelines/mycoplasmagenitalium.htm

First-line treatment

- Azithromycin 500 mg po single dose on day 1, then 250 mg po od on days 2 to 5.

Alternative regimens
Uncomplicated macrolide-resistant *M. genitalium* infection or if exposed in regions where macrolide resistance is common:

- Moxifloxacin 400 mg po od x 7 - 10 days.

The Melbourne protocol is becoming more popular in many clinics around the world including the CDC 2021 STI Guidelines:
Recommended regimens if *M. genitalium* Resistance Testing is Available.

- If *macrolide sensitive:* Doxycycline 100 mg po 2 times/day x 7 days, followed by azithromycin 1 gr po initial dose, followed by 500 mg po od x 3 additional days (2.5 g total).
- If macrolide resistant: Doxycycline 100 mg po 2 times/day x 7 days followed by moxifloxacin 400 mg po od x 7 days.

Recommended regimens if *M. genitalium* Resistance Testing is Not Available

- If *M. genitalium* is detected by an FDA-cleared NAAT: Doxycycline 100 mg po 2 times/day x 7 days, followed by moxifloxacin 400 mg po od x 7 days.

Reference: https://www.cdc.gov/std/treatment-guidelines/mycoplasmagenitalium.htm

Persistent *M. genitalium* infection despite azithromycin and moxifloxacin treatment

- Doxycycline 100 mg po bid x 14 days can be tried and may cure 30%.
- Pristinamycin 1 gr po qid x 10 days.

Special situations
Complicated *M. genitalium* infection (PID, epididymitis)

- Moxifloxacin 400 mg po od x 14 days.

NB: test of cure should be done due to the high prevalence of macrolide resistance according to IUSTI but not CDC or BASHH guidelines. In most circumstances considerations pertaining to AMR suggest that test of cure should NOT be performed.

Syndromic treatment of STIs:

- Urethritis
- Genital Ulcers
- Vaginal Discharge

The syndromic approach to STIs varies according to the local epidemiology of STIs. For example, the genital ulcer algorithm included treatment for chancroid in numerous countries until recently. Since the decline of chancroid this has been removed but of course chancroid could return. Conversely genital herpes has become the most common cause of genital ulcers in certain countries, such as South Africa, and aciclovir has therefore been included in the guidelines for countries such as South Africa. For these reasons it is best to consult local syndromic STI guidelines.

For the WHO training module on syndromic approach please see:
https://www.who.int/reproductivehealth/publications/rtis/9789241593407index/en/

For the South African syndromic guideline please see:
https://www.idealclinic.org.za/docs/National-Priority-Health-Conditions/Sexually%20Transmitted%20Infections_%20Management%20Guidelines%202015.pdf

79.5 Pelvic Inflammatory Disease

Hospitalization is required in case the symptoms are suggestive or if the diagnosis is not clear.
In case of ambulatory therapy, always give a combined treatment:

- Ceftriaxone 500 mg im single dose + (2) doxycycline 100 mg bid x 14 days + (3) metronidazole 500 mg po bid x 14 days.

79.6 Syphilis *(Treponema pallidum)*

Selected References

1. https://dx.doi.org/10.1111/jdv.12734 (Janier et al. 2014)
2. https://dx.doi.org/10.1258/ijsa.2008.008510 (French et al. 2009)
3. https://dx.doi.org/10.1086/511426 (Stoner 2007)
4. https://dx.doi.org/10.1093/cid/cir701 (Ghanem and Workowski 2011)
5. https://dx.doi.org/10.1093/infdis/158.4.881 (Hook, Roddy, and Hunter Handsfield 1988)
6. https://dx.doi.org/10.1056/NEJMoa044284 (Riedner et al. 2005)
7. https://dx.doi.org/10.1056/NEJMoa040216 (Lukehart et al. 2004)
8. https://dx.doi.org/10.1097/00007435-198607000-00018 (Edward W. Hook III, Sharon A. Baker-Zander, Bruce L. Moskovitz, Sheila A. Lukehart, n.d.)
9. https://dx.doi.org/10.1136/sti.79.5.415 (Shann and Wilson 2003)
10. https://dx.doi.org/10.1128/AAC.28.2.347 (Yim, Flynn, and Fitzgerald 1985)
11. *https://www.cdc.gov/std/treatment-guidelines/syphilis-hiv.htm*

79.6.1 Primary syphilis (chancre), secondary syphilis or early latent syphilis (less than a year)

First-line treatment
Benzathine penicillin (vial of 1,2 million units) one vial im in each buttock once (two vials in total). The penicillin can be dissolved in procaine HCL 20 mg-1% in order to decrease the injection pain.
NB: drug shortages are frequent and benzathine penicillin is not always available in Belgium. In that case and in absence of penicillin allergy, it is better to order benzathine penicillin abroad instead of giving a less effective alternative treatment. The treating physicians needs to fill in a declaration for the pharmacist. (http://www.klav.be/klavinfo/files/formulieren/artsenverklaring.pdf)

Alternative regimens
- Doxycycline 100 mg bid x 14 days. Should not be used during pregnancy.
- Ceftriaxone 1g either im or iv od x 10-14 days.

NB1: tetracycline 500mg qid x 14 days (this drug is not readily available anymore in Belgium and the adherence is likely to be less than with doxycycline).

NB2: despite encouraging results from two randomized controlled trials, azithromycin should not be used anymore due to the emergence of resistance. The prevalence of resistance varies widely among risk groups and geographic regions (very high in MSM and less in resource limited settings). Resistance in Antwerp is close to 100% (unpublished data).

Follow up

Risk of Jarisch-Herxheimer reaction:
A Jarisch-Herxheimer reaction is an acute febrile reaction appearing within 24h of the treatment of syphilis. It occurs more frequently in early stages (acute & early latent syphilis). In those stages, it may be warranted to observe the patient one hour after the injection. In any case, all patients should be counselled and reassured about this condition. The treatment is symptomatic. In some cases, prophylactic administration of paracetamol has been proposed to alleviate the symptoms, although no evidence exists that it decreases the occurrence of this reaction. A Jarisch-Herxheimer reaction is probably related to a high bacterial load and is not a reason to interrupt the treatment.

Serological controls (RPR) should be performed after 6 and 12 months. A treatment failure is defined as signs or symptoms that persist or recur or patients who have a sustained [more than 2 weeks] fourfold increase or more in RPR titer during follow-up.

These patients should have CSF examination to assess neurosyphilis:
- If positive treatment for neurosyphilis (see below neurosyphilis).
- If negative retreatment with benzathine penicillin 2,4 million units/week to repeat twice with one-week intervals (see below late latent syphilis), unless they present with clear signs of primary or secondary syphilis or have a convincing recent (<6 months) high risk contact with a confirmed syphilis case (in such cases, 1 x benzathine penicillin 2.4mu im should suffice).

79.6.2 Late latent syphilis (>= one year) or syphilis of unknown duration

First-line treatment
Benzathine penicillin (vial 1,2 million units) one vial im in each buttock, to be repeated twice with a one-week interval (6 vials over 3 weeks in total).

Alternative regimens

There is no reliable and validated alternative for the treatment of late latent syphilis or syphilis of unknown duration. The preference should always go to penicillin-based treatment. In case of (suspected) penicillin allergy, immunologic evaluation and desensitization should strongly be considered. A close clinical and serological follow-up should be started if an alternative therapy is used.

- Doxycycline 100 mg po bid x 28 days.
- Ceftriaxone. This product may theoretically be used; however, the dose and duration of treatment have not been validated.

Special situations

Neurosyphilis:

It may appear at all stages of syphilis. All patients with suspected neurosyphilis should undergo a lumbar puncture.

- Penicillin G 18-24 million units divided in 6 doses iv/day or in continuous injections for 10-14 days. Hospital admission is warranted.
- Ceftriaxone (Rocephine®) 2g OD iv for 14 days. In case of penicillin allergy, cross-reactivity with ceftriaxone may exist but is very rare.

NB: There is some evidence that high-dose doxycycline may cross the blood-brain barrier. Treatment of neurosyphilis with this drug is however not readily recommended.

Syphilis in HIV-positive patients:

HIV positive patients have a few particularities with regards to syphilis.

- The interpretation of serologic tests is more difficult. This is true for diagnosis as for post treatment follow-up.
- There is an increased risk of neurologic manifestations.
- Although treatment guidelines are not substantially different for HIV-positive persons, preference should be given to penicillin-based therapy above alternative treatments.
- Serological controls in HIV positive patients should be performed after 3, 6, 9, 12 and 24 months.

Pregnancy:

- Treatment is with penicillin as above. If they have a convincing history of a penicillin allergy they should be desensitized and treated with penicillin.

79.6.3 Trichomonas vaginitis

Selected References

1. https://dx.doi.org/10.1097/01.AOG.0000157108.32059.8f (Okun, Gronau, and Hannah 2005)
2. https://dx.doi.org/10.1093/cid/cir705 (Bachmann et al. 2011)
3. https://dx.doi.org/10.1016/j.ejogrb.2011.02.024 (Harp and Chowdhury 2011)
4. https://dx.doi.org/10.1086/511144 (Nutman et al. 1988)
5. https://dx.doi.org/10.1097/QAI.0b013e3181eda955 (Kissinger et al. 2011)
6. https://dx.doi.org/10.1002/14651858.CD000218 (Forna and Gülmezoglu 2003)
7. https://www.cdc.gov/std/treatment-guidelines/trichomoniasis.htm

First-line treatment for women

- Metronidazole: 500 mg po bid x 7 days.

NB: The sexual partner(s) should be treated.

First-line treatment for men

- Metronidazole (Flagyl®) 2 gr po single dose.

Alternative regimens

- Metronidazole (Flagyl®) 2 gr po single dose.
- Tinidazole (Fasigyn®) 2gr PO single dose.

Rationale for 7-day therapy in women is based on a meta-analysis and a multicenter, randomized trial of mostly symptomatic women without HIV infection. The study demonstrated that multidose metronidazole (500 mg po bid x 7 days) reduced the proportion of women retesting positive at a 1-month test of cure visit by half, compared with women who received the 2-g single dose.
Follow-up testing is recommended after 3 months.

Special situations

Pregnancy:

- Metronidazole (Flagyl®) 2 gr po single dose.

Recurrent or resistant disease:

- Metronidazole resistance occurs in 4%–10% of cases of vaginal trichomoniasis and tinidazole resistance in 1%. If treatment failure happens with metronidazole 2 gr single dose (and reinfection is excluded/unlikely) the patient can be treated with metronidazole 500 mg po bid x 7 days. If this regimen fails, clinicians should consider treatment with metronidazole or tinidazole at 2 gr po x 7 days. Final option tinidazole at 2 - 3 g po x 14 days, in combination with intravaginal tinidazole.

HIV-positive patients:

- Metronidazole: 500 mg po bid x 7 days is more efficacious than 2gr single dose.

80 Snakebites

First-line treatment

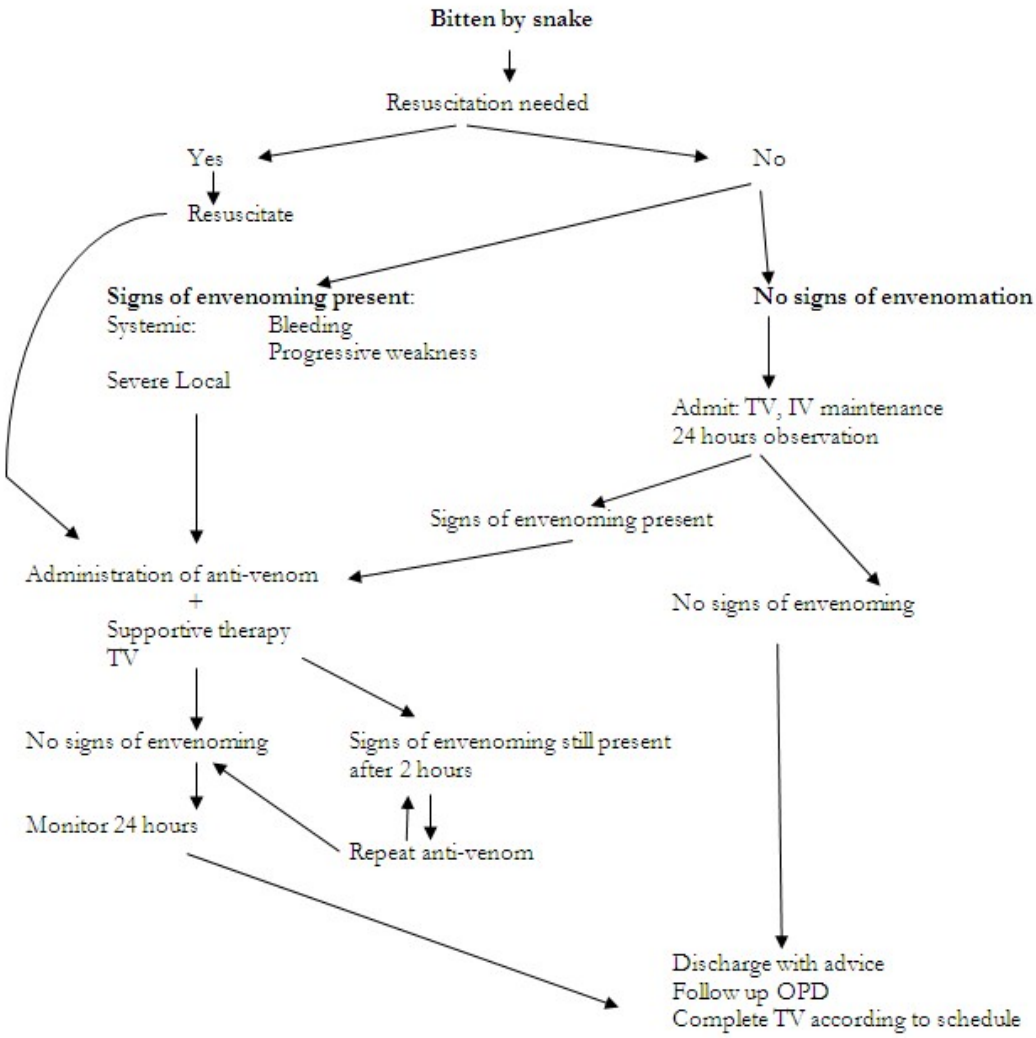
- Most bites are 'dry' bites without systemic effect and without need to administer antivenom.
- Reassure the victim who may be very anxious.
- Immobilize the whole of the patient's body by laying him/her down in a comfortable and safe position and, especially, immobilize the bitten limb with a splint or sling. Any movement or muscular contraction increases absorption of venom into the bloodstream and lymphatics.
- Avoid any interference with the bite wound (incisions, rubbing, vigorous cleaning, massage, application of herbs or chemicals) as this may introduce infection, increase absorption of the venom and increase local bleeding.
- Tight (arterial) tourniquets are not recommended. To be effective, these must be applied around the upper part of the limb so tightly that the peripheral pulse gets occluded. This method can be extremely painful and very dangerous if the tourniquet was left on for too long (more than about 40 minutes), as the limb might be damaged by ischemia.
- ABCDE approach.
- Transport to a hospital as soon as possible with the patient immobilized as much as possible.

Supportive care:

- In case of neurotoxicity: Atropine sulphate 0,5 mg for adults (children 0,02 mg/kg)(IV or IM followed by neostigmine 0,5 mg (children 0,04 mg/kg) iv or im (children 0,02 ml/kg). Neostigmine to be repeated every 20 minutes till recovery of muscular strength; atropine to be repeated prior to every 4th dose.
- For severe neurotoxicity mechanical ventilation can be necessary. Complete recoveries are described after more than 1 month of ventilation.
- Correction of coagulation abnormalities: PPSB, platelet transfusion, fresh frozen plasma; IM injections to be avoided.
- Treatment of shock: intravenous fluid resuscitation with crystalloids and/or colloids, albumin, inotropic agents.
    - Dark brown urine (myoglobinuria or hemoglobinuria): Correct hypovolemia with intravenous fluid, correct acidosis with a slow intravenous infusion of 50-100 mmol of sodium bicarbonate and, by analogy with crush syndrome, consider a single infusion of mannitol. 200 ml of 20% mannitol may be infused intravenously 20 minutes, but this must not be repeated as there is a danger of inducing dangerous fluid and electrolyte imbalance.
    - Severe local envenoming: Local necrosis, intracompartmental syndromes and even thrombosis of major vessels is more likely in patients who cannot be treated with antivenom. Surgical intervention may be needed but the risks of surgery in a patient with consumption coagulopathy, thrombocytopenia and enhanced fibrinolysis must be balanced against the life-threatening complications of local envenoming. Prophylactic broad-spectrum antimicrobial treatment is justified.
    - Tetanus vaccination and immunoglobulins should be given if vaccination > 10 years ago

Antivenom administration:
Antivenom to be given if signs of envenomation: neurotoxicity, coagulation abnormalities, hypotension or shock, oliguria/anuria cardiotoxicity, local edema or necrosis.

Anti-venom administration algorithm (MSF guideline 2010).



Source: MSF Snakebite Management, 2010

Availability and costs

- Antigif centrum possesses 1 dose of antiserum against the Vipera berus (Viperfav®) which is endemic in Belgium, but this adder is rarely really toxic; Antigif centrum 070 24 52 45.
- ZNA Stuivenberg Antwerp: pharmacy to be contacted 03 217 71 11, has SAIMR Polyvalent Snake Antivenom, Antivipmyn Polyvalent Antivenom and Neuro polyvalent snake antivenom.
- NVIC Utrecht (Nationaal Vergifitingen Informatie Centrum) has antisera against most snakes, spiders and scorpions: tel +31-88-7558000.
- MAVIN (Munich AntiVenom Index): http://www.antivenoms.toxinfo.med.tum.de/ ; lists all toxic snakes, spiders and scorpions and where to find antivenom; Tel: +44-20-71880500 (24 hour antivenom line).
- WHO database with info per country and per snake and where to find antivenom: https://www.who.int/teams/control-of-neglected-tropical-diseases/snakebite-envenoming/snakebite-information-and-data-platform/overview#tab=tab_1.

Additional information on antivenoms available in Belgium:
SAIMR Polyvalent Snake Antivenom (South-African Institute of Medical Research), A polyvalent antivenom against the venom of the following sub-Saharan snakes (mambas, cobras, ringkhalses and puff adders):

- Puff adder (*Bitis arietans*)
- Gaboon adder (*Bitis gabonica*)
- Rinkhals (*Haemachatus haemachatus*)

- Green mamba (*Dendroaspis angusticeps*)
- Jameson's mamba (*Dendroaspis jamesoni*)
- Black mamba (*Dendroaspis polylepis*)
- Cape cobra (*Naja nivea*)
- Forest cobra (*Naja melanoleuca*)
- Snouted Cobra previously ' Egyptian cobra' (*Naja annulifera*)
- Mozambique spitting cobra (*Naja Mossambica*)

Not to be used for other snakes or adders than the ones listed above.

Initial dose at least 2 ampullas, but the condition of the patient might require 4 to 5 times as muchs Serum to be injected at room temperature as a slow IV bolus of infusion with 50-100 mg NaCl 0.9% or Glu 5% in 5-10 min. The patient should lay down during the injection and in the hour following injection. No dose reduction for children.
Price per vial: 595.41€

For further product specifications:
http://www.toxinfo.org/antivenoms/resources/antivenom_southafrica-savp-polyvalentsnake_2011-07-04.pdf
http://www.toxinfo.org/antivenoms/productinfo/SAIMR_POLYVALENT_SNAKE_ANTIVENOM.html

Antivipmyn Polyvalent Antivenom, active against a whole range of American snakes. The most important ones:

- *Agkistrodon piscivorus*
- *Agkistrodon spp.* of American continent
- *Bothrops asper*
- *Bothrops spp.* of American continent
- *Crotalus atrox*
- *Crotalus molossus*
- *Crotalus scutulatus*
- *Crotalus simus*
- *Crotalus spp.* of American continent
- *Crotalus viridis*
- *Porthidium nasutum*
- *Sistrurus catenatus*
- *Sistrurus spp.* of American continent

Administer IV: vials should be dissolved in 250 ml NaCl 0.9% and given over 30 min. Dose depends on the degree of toxicity:

		Adult		Children	
Toxicity Grading	**Symptoms and signs**	**Initial**	**Maintenance**	**Initial**	**Maintenance**
Suspicion bite	Bite marks, local pain	Observe			
Grade I	Bleeding of bite marks, absence of pain in area around bite, edema ≤ 10 cm	3 à 5 vials I.V.	5 vials I.V.	6 à 10 vials I.V.	5 vials I.V.
Grade II	Same as grade I; edema ≥ 10 cm, blisters with blood, nausea, vomiting, oliguria	6 à 10 vials I.V.	5 vials I.V.	15 vials I.V.	5 vials I.V.
Grade III	Same as grade II but more pronounced. Necrotic tissue, abdominal pain, myonecrosis, paresthesia, oliguria, oral or rectal bleeding, hemoptoe, hematuria, disturbed coagulation tests	11 à 15 vials I.V.	6 à 8 vials I.V.	20 à 30 vials I.V.	10 à 15 vials I.V.
Grade IV	Same as grade III but more pronounced. Shock, organ failure, coma	16 or more vials I.V.	8 or more vials I.V.	31 or more vials I.V.	16 or more vials I.V.

Price per vial: 1014,11€

European Viper venom Antiserum, active against European viper snakes:

- *Macrovipera lebetina*
- *Vipera ammodytes*
- *Vipera aspis*
- *Vipera berus* (Adder species endemic in Belgium)
- *Vipera ursinii*
- *Vipera xanthina*

Vial of 4 ml to be dissolved in 100 ml physiological serum slowly over 1 hour iv. To be repeated after 4 hours if needed.

Neuro polyvalent snake antivenom**,** Neurotoxic Polyvalent Snake Antivenom for Cobra and King Cobra, Banded Krait, and Malayan Krait Venom. Active against:

- *Ophiophagus Hannah*
- *Naja Kaouthia*
- *Naja Siamensis*
- *Naja Soumatrana*

- *Bungarus fasciatus*
- *Bungarus candidus*

For further product specifications:
http://www.toxinfo.org/antivenoms/resources/antivenom_mexico-bioclon-antivipmyn_2011-07-05.pdf
http://www.toxinfo.org/antivenoms/productinfo/ANTIVIPMYN.html

Observation of the response to antivenom:
If an adequate dose of appropriate antivenom has been administered, the following responses may be observed:

- General: The patient feels better. Nausea, headache and generalized aches and pains may disappear very quickly. This may be partly attributable to a placebo effect.
- Spontaneous systemic bleeding (e.g., from the gums): This usually stops within 15-30 minutes.
- Blood coagulability: This is usually restored in 3-9 hours. Bleeding from new and partly healed wounds usually stops much sooner than this.
- In shocked patients: Blood pressure may increase within the first 30-60 minutes and arrhythmias such as sinus bradycardia may resolve.
- Neurotoxic envenoming of the post-synaptic type (cobra bites) may begin to improve as early as 30 minutes after antivenom, but usually takes several hours. Envenoming with presynaptic toxins (kraits and sea snakes) will not respond in this way.

Active hemolysis and rhabdomyolysis may cease within a few hours and the urine returns to its normal color.

Criteria to give more antivenom:

- Persistence or recurrence of blood coagulopathy after 6 hours or of bleeding after 1-2 hours.
- Deteriorating neurotoxic or cardiovascular signs after 1-2 hours.

Prophylactic treatment with antivenom:

- Since no prophylactic drug regimen has proved effective in reducing the incidence or severity of early antivenom reactions, these drugs should not be standard. All patients should be watched carefully for two hours after the completion of antivenom administration and should be treated with epinephrine/adrenaline at the first sign of a reaction:
    - Epinephrine (adrenaline) is given intramuscularly (into upper lateral thigh) in an initial dose of 0,5 mg for adults and 0,01 mg/kg for children.
    - After epinephrine (adrenaline), an antihistamine anti-H1 blocker such as clemastin IM (Tavegyl®): 1 mg/ml 1 A°), followed by intravenous hydrocortisone (adults 100 mg, children 2 mg/kg body weight) or alternatively methylprednisolone (Solu-Medrol) 40-125 mg IV (children 0.5-1 mg/kg). The corticosteroid is unlikely to act for several hours, but may prevent recurrent anaphylaxis.

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