Protocol for a systematic review and meta-analysis on the therapeutic efficacy and safety of treatment of visceral leishmaniasis in children

Description of the PICO-S criteria used to define the research question

Parameter	Description
Population	Children with visceral leishmaniasis <18 years of age
Intervention	Drug treatment of VL – Amphotericin B (conventional or liposomal), Pentavalent antimonials, Miltefosine and Paromomycin
Comparison	Standard treatment or placebo
Outcome	Outcomes of treatment – drug efficacy/cure, treatment failure, safety (adverse events), relapse, death
Setting	**Randomized** clinical trials
Time	Manuscripts published after year 2000
Research question	What are the outcomes of drug management of visceral leishmaniasis in children?
Study title	A systematic review and meta-analysis on the therapeutic efficacy and safety of treatment of visceral leishmaniasis in children
Objectives	**General objective:** To evaluate the efficacy and safety of the main antileishmanial agents (Amphotericin B (conventional or liposomal), Pentavalent antimonials, Miltefosine and Paromomycin) recommended for the treatment visceral leishmaniasis in children.

	Specific objectives 1. To review the dosing regimens of antileishmanial drugs in children studied in interventional trials. 2. To evaluate the efficacy of the antileishmanial drugs in children by assessing outcome measures; cure rate/failure rate/mortality rate 3. To review the safety (by reported adverse events) of antileishmanial drugs in children
Main concepts	Visceral leishmaniasis, antileishmanial agents, drug treatment (Amphotericin B (conventional or liposomal), Pentavalent antimonials, Miltefosine and Paromomycin), efficacy of drugs, safety of drugs, children
Inclusion criteria	Randomized clinical trials/interventional trials evaluating treatment of VL in children or including children, clinical trials that assess treatment efficacy at $\geq$ 6 months, papers written in English, full text available, any country, gender or race
Exclusion criteria	Other types of leishmaniasis, studies where data are not separately presented for children, other types of study designs including case reports/series/non-interventional studies, animal studies, experimental/in-vitro studies, papers in languages other than English, free full text not available, abstract only papers- Conference / symposium abstracts, articles not presenting interventional studies like reviews, meta-analysis, etc

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Databases, registries and web search engines for the literature search

- PubMed
- Cochrane Reviews
- Google scholar
- Clinical trials.gov

Main concepts

Visceral leishmaniasis	children	Antileishmanial drugs	Efficacy	Safety
Kala-azar	Paediatic/Pediatric – wildcard characters	Amphotericin B	Effectiveness	Tolerability
	infant	Ambisome		
		Pentavalent antimonial		
		Sodium stibogluconate		
		Meglumine		
		Miltefosine		
		Paromomycin		

Outcomes

Justification – Randomized trials that assess treatment efficacy/cure at minimum of 6 months and beyond will be considered for this study. A relapse is reappearance of parasites after initial cure, usually within 6 months of follow-up. As per this general definition trials that assess efficacy at least for 6 months is necessary to assess efficacy.

Efficacy/cure/ treatment failure

- Visceral leishmaniasis - comparable clinical picture combined with demonstration of parasites/DNA or positive serology
- Initial response to treatment and at the end of 6 months post treatment – efficacy assessed at the end of therapy in those who complete treatment and defined as clinical improvement +/- parasitological cure
- Treatment failure - lack of clinical improvement or parasitological improvement after completion of treatment (or within a defined time period after completion of treatment)

Treatment failure can manifest as initial treatment failure (failure to clear parasites at the end of the treatment course) or relapse (reappearance of parasites after initial cure, usually within 6 months of follow-up) (Ref: Kala-azar in South Asia - Eisei Noiri ·T.K. Jha / Control of the leishmaniases Report of a meeting of the WHO Expert Committee on the Control of Leishmaniases, Geneva, 22–26 March 2010-technical report series)

Mortality/ death

- At the end of treatment or at ≥6 months post treatment among those who completed treatment for VL

Safety (adverse events)

- Reported adverse events - either systematically (collecting adverse events in the same manner for each participant using defined methods such as a questionnaire or a laboratory test) or non-systematically (refers to collection of information on adverse events using methods such as open-ended questions (e.g. 'Have you noticed any symptoms since your last visit?'), or reported by participants spontaneously)

- Despite of the collection method the data on AE events will be recorded - Coding systems or standard terminology used, name of AE, Intensity (mild, mod, severe), whether AE was identified as related to the intervention, time point, reporting methods (eg. only report AE that occurred in 5% of the participants)

Risk of bias assessment (quality of the studies)

Revised Cochrane risk-of-bias tool for randomized trials (RoB 2) will be used to assess the risk of bias in each selected study. The domains of risk of bias including those arising from the randomization process, deviations from the intended intervention, missing data, measurement of the outcome and reporting are covered.

Data extraction

Data extraction will be performed using a modified version of the Cochrane data extraction form for RCTs only. Extractable data specific to the paediatric will be recorded.

Qualitative synthesis and meta-analysis

If the selected studies include trials with multiple treatment arms (more than two), they will be included in the meta analysis after included in the meta-analysis after they are suitably combined using the ‘combination of groups to create a single pair-wise comparison’ approach (Cochrane Handbook guiding systematic reviews). Random effects model meta-analysis using Review Manager 5.4 software will be performed. Dichotomous data will be combined to calculate pooled risk ratios (RR) and 95% confidence intervals (CI). Heterogeneity will be assessed with the I2 statistic and funnel plots. Subgroup meta-analysis and descriptive analysis will be performed if appropriate data is available for different VL treatments, age categories, gender etc. Results will be presented as forest and funnels plots, tables, figures and text descriptions.