Leishmania tropica in children: A retrospective study

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Background: Limited data are available regarding topical and systemic therapies for *Leishmania tropica* in children.

Objective: We sought to characterize the clinical presentation and evaluate the efficacy and safety of topical and systemic treatments in pediatric patients infected with *L tropica*.

Methods: A retrospective study was performed on 47 children with *L tropica* cutaneous leishmaniasis. Treatments included topical or systemic therapy with liposomal amphotericin B or pentavalent antimony.

Results: Seventy patients with *L tropica* cutaneous leishmaniasis were treated at our center between 2008 and 2012, of which 47 (67%) were children. The average age of the pediatric population was 8.8 years, and the face was the most common site of involvement (76%). The average number of lesions was 2.6. 24 children (51%) required systemic therapy. The patients were treated with 3 to 5 mg/kg/d of intravenous liposomal amphotericin B, and a response was observed in 83% of the patients within 3 months.

Limitations: This was a retrospective study.

Conclusion: The disease burden of *L tropica* in children is high, and because of facial involvement and a low response to topical therapies, systemic therapy is often required. In our experience, liposomal amphotericin B treatment in children is safe and effective and is required for a considerably shorter duration than treatment with pentavalent antimony. (J Am Acad Dermatol 2014;71:271-7.)

Key words: children; cryotherapy; intralesional; *Leishmania tropica*; liposomal amphotericin B; paromomycin ointment; sodium stibogluconate.

Cutaneous leishmaniasis (CL) is endemic to Israel and has been attributed almost exclusively to *Leishmania major*.[1,2] However, during the last decade, CL caused by *L tropica* has been increasingly reported in several regions of Israel. *L tropica* has a predominantly anthroponotic transmission, and its vectors have been identified as *Phlebotomus sergentii* and *Phlebotomus arabicus*. However, in Israel the putative reservoir was found to be *Procavia capensis* (the rock hyrax),[3] which is a relatively small mammal, resembling a guinea pig, found across Africa and the Middle East. After an incubation period of 3 to 12 weeks, noduloulcerative skin lesions are formed at the site of the sandfly bite. The disease is self-limiting usually during a period of 12 months or longer, leaving significant disfigurement and scarring. *L tropica* CL heals more slowly

Abbreviations used:

CL:	cutaneous leishmaniasis
IL:	intralesional
IV:	intravenous
L-AmB:	liposomal amphotericin B
SSG:	sodium stibogluconate

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and is relatively resistant to treatment in contrast to *L major* CL.[4-7] In addition, *L tropica* may cause leishmaniasis recidivans, and rarely may cause visceral leishmaniasis.[8]

Children represent a substantial portion of the *Leishmania* infection burden. However, direct comparisons between data for children and adults are limited. Nonetheless, the impression is that young children are at an increased epidemiologic and biological risk for infection.[9-13] Children also have higher clearance rates of antimonial drugs, leading to significantly lower drug exposure.[14] This, in turn, probably contributes to the lower response rate observed in children with CL or visceral leishmaniasis.[14-16] In addition, clinicians often face a challenge when treating pediatric patients because of low compliance.

Here, we characterize the clinical presentation and evaluate the efficacy and safety of topical and systemic treatments in a pediatric population affected with skin lesions of the *L tropica* type.

CAPSULE SUMMARY

- Cutaneous leishmaniasis caused by *Leishmania tropica* in pediatric patients is a therapeutic challenge.
- Our retrospective study characterizes the clinical presentation and evaluates the efficacy and safety of topical and systemic treatments in *L tropica*—affected children.
- In our experience, when systemic therapy is indicated, treatment with liposomal amphotericin B appears to be safe and effective and requires a much shorter treatment duration than pentavalent antimony.

METHODS

A retrospective study was performed on children aged 1 to 15 years with *L tropica* CL. All patients were recruited from the Department of Dermatology or the Center for Geographic Medicine and Tropical Diseases at Chaim Sheba Medical Center, Tel Hashomer, Israel, between the years 2008 and 2012.

L tropica CL was diagnosed when: (1) cutaneous lesions (ulcers, nodules, or papules) clinically compatible with leishmaniasis were noted; (2) a smear or biopsy specimen showed *Leishmania* amastigotes within a dermal infiltrate; and (3) a polymerase chain reaction assay tested positive for *L tropica* or the patient resided in a region endemic only to *L tropica*.

Treatments were administered in an outpatient setting. The children were treated with topical cryotherapy, topical paromomycin ointment, or intralesional (IL) injections of sodium stibogluconate (SSG) (Pentostam, GlaxoSmithKline, London, United Kingdom).

SSG was injected until the entire lesion had blanched (up to 0.5 mL [50 mg] per ulcer). In view of severe localized pain induced by the injected drug, children younger than 6 years were sedated. The treatment was repeated every 3 to 4 weeks until the lesions flattened, either with complete re-epithelialization or reduction of the ulcer to less than 3 mm.

Systemic treatments included intravenous (IV) SSG and IV liposomal amphotericin B (L-AmB).

The indications for systemic treatment were as follows: topical treatment failure; multiple lesions (>5); or nonfeasibility of IL SSG injection because of the anatomic location (eg, face and eyelid).

IV L-AmB was administered in ambulatory settings at a dose of 3 to 5 mg/kg daily for 5 consecutive days, with a sixth dose administered on day 10. Laboratory parameters monitored included a complete blood cell count, electrolyte measurement, and liver and renal function tests conducted on alternate days. Tests were repeated 1 month after the cessation of treatment. In the case of treatment failure, children were subsequently treated with IV SSG at a dose of 20 mg/kg/day for 20 days. During IV SSG treatment, blood counts, liver function test, renal functions, amylase, lipase, and electrocardiography were monitored each day and 1 month after the end of treatment.

Clinical responses were categorized as follows. A complete response was defined as 100% re-epithelialization of the ulcer (or for nonulcerative lesions, regression of the lesion) within 3 months after treatment. A partial response was defined as greater than 50% re-epithelialization of the ulcer within the same period. Treatment failure was defined as less than or equal to 50% re-epithelialization of the ulcer within the same period. In addition, any patient who achieved either a complete or partial response within 3 months but had a relapse during the follow-up period was also considered a case of treatment failure.

Patients were followed up every 3 to 4 weeks until completely cured. The study was approved by the review board of our institute.

RESULTS

Seventy patients with *L tropica* CL were referred to our center between the years 2008 and 2012, and of these, 52 (74%) were children. Five children were withdrawn for follow-up, and the rest (47 pediatric

Table I. Clinical and demographic data of pediatric patients with *Leishmania tropica*

	Patients (n = 47)
Mean age, y (range)	8.8 (1-15)
Gender	
M (%)	31 (66)
F (%)	16 (34)
Exposure area	41 Eastern Israel 6 Galilee, Israel
Time to diagnosis, mo (range)	3.8 (1-15)
Mean no. of lesions (range)	2.8 (1-10)

F, Female; *M*, male.

patients) formed the study group. All infections were acquired in *L tropica*—endemic areas. Giemsa staining yielded positive results in all patients. Polymerase chain reaction analysis, performed for 14 patients, yielded a positive result for *L tropica* infection in 13 and a negative result in 1 patient.

Clinical and demographic data are presented in Table I. Of the 47 cases, 11 were familial (5 families with 2-3 affected siblings). The lesions were most commonly located in exposed areas and were grouped; hence, the number of body areas involved ranged from 1 (30 patients, 64%) to 2 (17 patients, 36%). Lesions were commonly located in the head and neck areas (36 patients, 76%), including the lips (10 patients, 23%, Fig 1). The distribution of the lesions is presented in Table II. In 1 patient, there was a sporotrichoid distribution of lesions.

In all, 36 patients received topical therapy before their referral or as first-line therapy. Topical treatment included paromomycin ointment (n = 5), IL SSG (n = 15), cryotherapy (n = 4), or a combination of these methods (n = 12). Overall, 17 patients were treated with paromomycin and only 1 (5.9%) of these showed a complete response.

Overall, 21 patients were treated with IL SSG. Five children younger than 6 years were sedated to obtain their passive cooperation during the treatment. The average number of serial injections was 3 (range, 1-5). Fourteen of the 21 patients (66.6%) were completely cured of CL within 3 months of treatment initiation. The side effects included localized pain and prolonged edema (cysts formation) at the injection site.

A total of 24 patients required systemic treatment. Thirteen patients received L-AmB because of the failure of previous treatments, including paromomycin ointment, IL SSG, cryotherapy, oral ketoconazole or fluconazole, and a combination of these methods (Table III). Eleven additional patients with previously untreated lesions received L-AmB as primary treatment (Table III). In all patients, treatment was administered for 6 days, at a cumulative dose of 18 to 30 mg/kg. Among the L-AmB-treated patients, 18 (75%) showed a complete response and 2 (8.3%), a partial response.

Table II. Anatomic location of skin lesions (n = 47)

Anatomic location	Patients	Percentage
Head and neck	36	76
Trunk	9	19.1
Upper limbs	16	34
Lower limbs	1	2.1

Percentages sum to >100% as multiple locations per patient were included.

Lesions located on the lip responded rapidly to L-AmB treatment in 3 patients, demonstrating regression in less than 1 month. The mean follow-up was 2.6 months (range, 1-8 months), and no relapses were observed. Examples of cutaneous lesions before and after treatment are shown in Figs 2 and 3.

One patient had abdominal pain during treatment, which resolved after treatment completion. Complete blood cell count, electrolyte analysis, and liver and renal function tests yielded normal results in all patients. One patient experienced nausea and vomiting, but none of the side effects resulted in premature discontinuation of L-AmB treatment.

L-AmB treatment failed in 4 of the 24 patients. One of these patients presented leishmaniasis recidivans infection, and all 4 received 20 $mg/kg^{-1}/d^{-1}$ IV SSG treatment for 20 days, whereby they were completely cured.

Adverse effects included hyperamylasemia in all the patients, increased liver function test results in 2 patients (up to 3 times normal), and mild leukopenia in 1 patient.

DISCUSSION

Children affected with *L tropica* seem to be an especially challenging population. Although the disease is self-limiting, it leads to scarring and disfigurement, particularly with facial lesions, which can have adverse psychosocial effects on patients.[17]

Children represent the majority of the patient population referred to our center. In the current study, we have summarized our experience with pediatric patients affected by *L tropica* CL. The children in this study tended to have multiple lesions, most commonly on the face, and many of them were recalcitrant to topical treatments. Importantly, we found that a short course of L-AmB was a safe and effective treatment for this patient group.

CL caused by *L tropica* is more resistant to treatment compared with that caused by *L major*.

Table III. Comparison of pediatric patients treated with intralesional sodium stibogluconate versus intravenous liposomal amphotericin B (n = 45)*

	IL SSG (n = 21)	IV L-AmB (n = 24)
Failure of prior topical treatment	n = 4†	n = 13‡
Treatment duration	3 Sessions (mean, range 1-9) Clinic visits	6 d (dose range 18-30 mg/kg)
Sedation for the procedure	5	0
Treatment response		
Complete response	14/21 (66.6%)	18/24 (75%)
Partial response	0/21 (0%)	2/24 (8.3%)
No response	7/21 (33.3%)	4/24 (16.6%)
Treatment of failure cases	L-AmB (n = 7)	IV SSG (n = 4)

IL, Intralesional; *IV*, intravenous; *L-AmB*, liposomal amphotericin B; *SSG*, sodium stibogluconate.
*Two of the 47 patients were treated with liquid nitrogen.
†Prior treatment included paromomycin ointment.
‡Prior treatment included paromomycin ointment (n = 3), IL SSG (n = 4), cryotherapy, oral ketoconazole or fluconazole (n = 1), or a combination of these methods (n = 5).

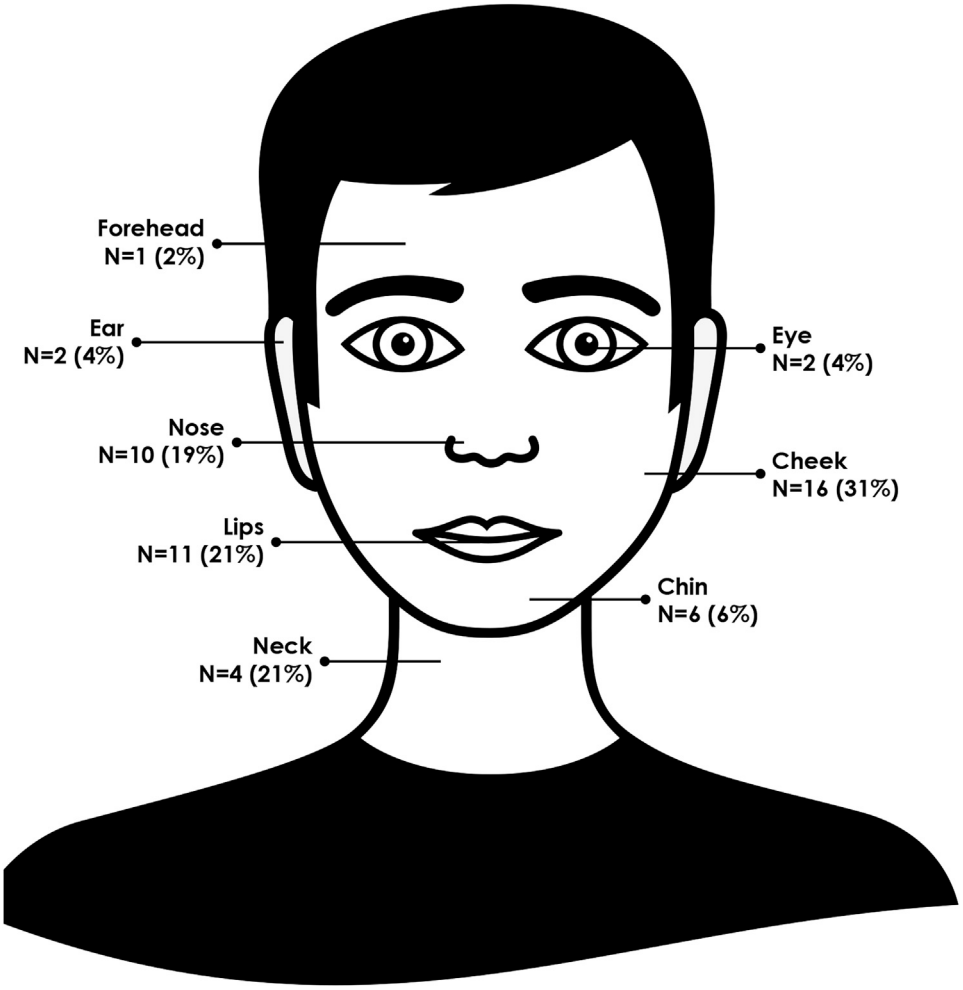

Fig 1. *Leishmania tropica* in children: percentage of facial cutaneous lesions. Percentages sum to >100% as multiple locations per patient were included.

Although topical treatment is an attractive alternative, the efficacy of paromomycin ointment in *L tropica* CL has been reported to be only 39% in a previous Israeli study,[18] in comparison with its superior efficacy (76%-86% complete cure rate) in the case of Israeli *L major* CL.[19,20] In Turkey, the cure rate

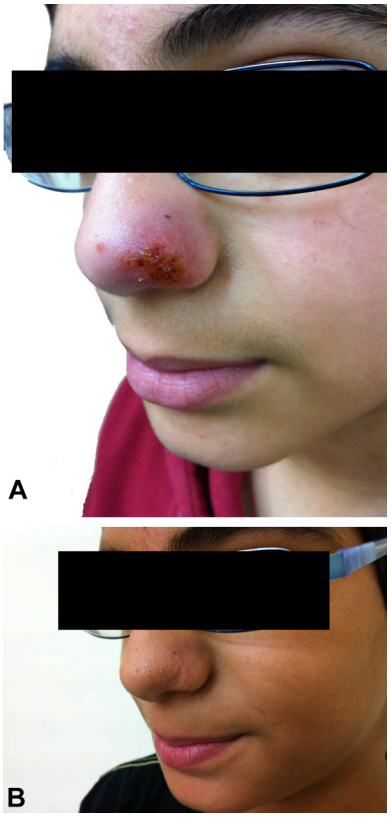

Fig 2. *Leishmania tropica* cutaneous ulcer on child's nose before (**A**) and after (**B**) liposomal amphotericin B treatment.

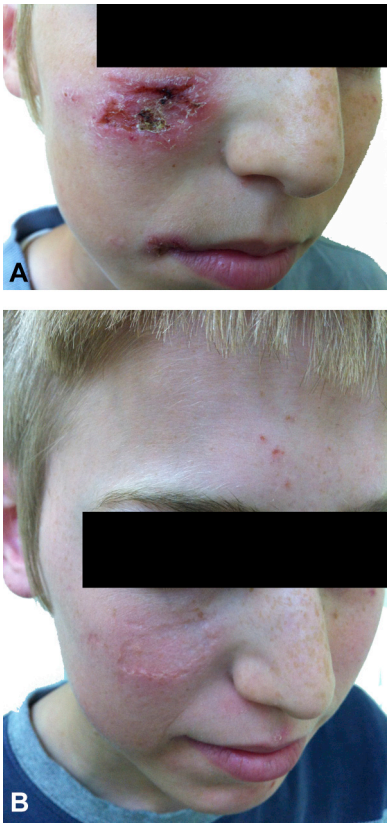

Fig 3. *Leishmania tropica* cutaneous ulcer on child's cheek after failure of intralesional sodium stibogluconate treatments (**A**), and after liposomal amphotericin B treatment (**B**).

reported with paromomycin for *L tropica* CL was even lower (37.5%).[21] In our study as well, the response to paromomycin was poor (5.9%), although referral bias could not be excluded.

Topical treatment with paromomycin ointment may also cause adverse effects, especially significant local irritation; therefore, it is not recommended for lesions near the eyes. A new paromomycin ointment was recently tested in a Tunisian population with *L major* CL, with an 82% cure rate and less irritation[22]; however, its effectiveness against *L tropica* CL was not tested.

IL antimonial injections are considered safe and effective for all types of CL, although this treatment is not available in the United States. However, our response rate for IL antimonials in this study was only 66.6% as compared with the 83.3% obtained for L-AmB. Besides, severe localized pain at the site of injection is a major drawback of this treatment mode, and several children had to be sedated for the injections. In light of the growing concern over the effects that anesthesia can have on neurocognitive development in pediatric populations,[23] the risks and benefits of topical IL treatments over systemic ones must be carefully considered and explained clearly to the parents. In addition, IL SSG treatment may not be suitable in case of multiple lesions or for some facial lesions.

Systemic treatment of Old World CL with pentavalent antimony (SSG or meglumine antimoniate, 20 mg/kg antimony per day administered as IV or intramuscular injections over 20 days) has been traditionally considered as the mainstay therapy.[24] However, there are no randomized, double-blind, placebo-controlled clinical studies for the treatment of *L tropica* CL. This regimen has been reported to have a cure rate of 85% to 90%,[25] but, it often requires a long hospitalization period and can be associated with several adverse effects.

Lipid-based amphotericin B products are well-established treatments for visceral leishmaniasis.[26] In previously published studies from our institute, we provided data showing that L-AmB administered at 3 mg/kg over 6 days is safe and effective for both Old and New World CL, with a cure rate of 84% to 100%.[27-29] A similar treatment efficacy was observed in a retrospective study on CL resulting from various strains.[30] The results of the current study, focusing specifically on the pediatric population, support our

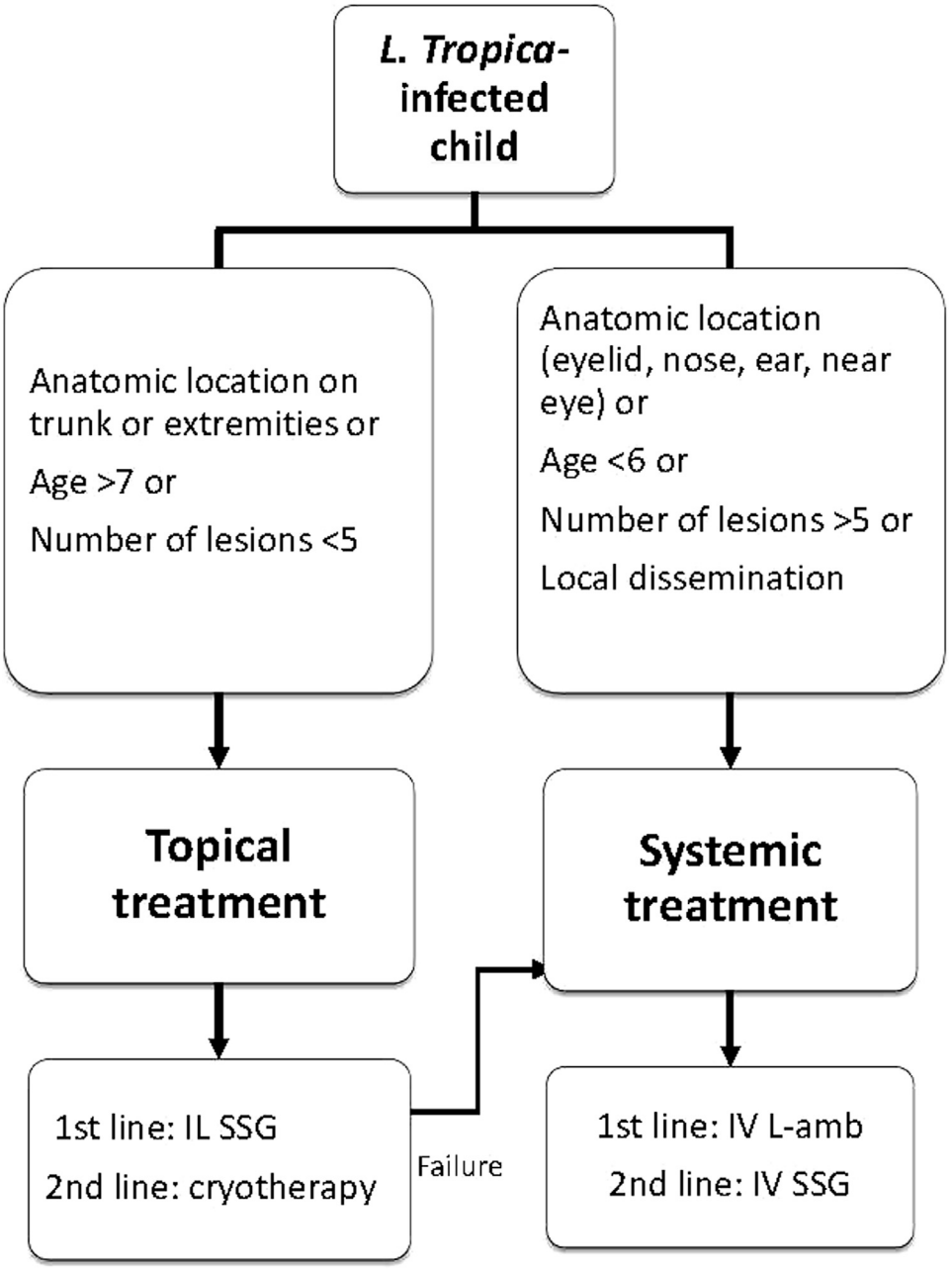

Fig 4. Treatment algorithm for *Leishmania tropica* in children. *IL*, Intralesional; *IV*, intravenous; *L-amb*, liposomal amphotericin B; *SSG*, sodium stibogluconate.

previous findings. The pharmacokinetics of L-AmB in pediatric patients has not been studied; however, L-AmB has been used in pediatric patients with an efficacy similar to that in adult patients.[31] Nonetheless, L-AmB does have adverse effects. Infusion-related fever, chills/rigors, and vomiting have been reported. In our experience, premedication with hydrocortisone is usually not needed as slow infusion can minimize these reactions. An additional drawback of L-AmB is its high cost. However, as dosing is on a per kilogram basis, the cost of this drug for treating children is significantly lower than for treating adults. In Fig 4, we suggest a treatment algorithm for children with CL caused by *L tropica*.[32]

Our study has several potential limitations, of which the main ones are its retrospective nature and the lack of a placebo-control group. In addition, many patients were treated with several treatment modes, making it difficult to assess the efficacy of the various individual treatments and their long-term effects.

In conclusion, treating pediatric CL is often a challenge to the clinician because of the limitations of topical injections and scarce data on the safety and efficacy of systemic therapy. On account of facial involvement and the low response to topical therapies, systemic treatment is often required. Systemic therapy with L-AmB is safe and effective and is required for a considerably shorter duration than treatment with pentavalent antimony. Nonetheless, an effective and safe oral medication or topical ointment is urgently needed for pediatric CL.

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