Antibiotics for human toxoplasmosis: a systematic review of randomized trials

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The efficacy of different treatment regimens in clinical syndromes of toxoplasmosis were assessed by conducting a systematic review of published randomized clinical trials through extensive searches in MEDLINE, EMBASE, and SCOPUS with no date limits, as well as manual review of journals. Outcome measures varied depending on the clinical entity of toxoplasmosis. Risk of bias was evaluated and quality of evidence was graded. Fourteen randomized trials were included of which one was a non-comparative study. One well-designed trial showed that trimethoprim-sulphamethoxazole was more effective than placebo for clinical recovery of toxoplasmic lymphadenopathy in immunocompetent hosts. For toxoplasmic encephalopathy, efficacy of pyrimethamine + sulphadiazine and trimethoprim + sulphamethoxazole were similar, whereas pyrimethamine + sulphadiazine versus pyrimethamine + clindamycin showed no difference, irrespective of the outcome. Intravitreal clindamycin + dexamethasone and conventional treatment with oral pyrimethamine + sulphadiazine had similar efficacy with regard to all outcome measures in ocular toxoplasmosis, and intravitreal therapy was found to be safe. Adverse effects seemed more common with pyrimethamine + sulphadiazine. Most trials for encephalitis and ocular manifestations had a high risk of bias and were of poor methodological quality. There were no trials evaluating drugs for toxoplasmosis in pregnancy, or for congenital toxoplasmosis. Pyrimethamine + sulphadiazine is an effective therapy for treatment of toxoplasmic encephalitis; trimethoprim + sulphamethoxazole and pyrimethamine + clindamycin are possible alternatives. Treatment with either oral or intravitreal antibiotics seems reasonable for ocular toxoplasmosis. Overall, trial evidence for the efficacy of these drugs for toxoplasmosis is poor, and further well-designed trials are needed.

Keywords: Toxoplasmosis, Toxoplasma, Toxoplasmic encephalitis, Ocular, Systematic review, Treatment, Antibiotics

Background

Toxoplasmosis is a cosmopolitan disease caused by infection with the Apicomplexan coccidian protozoan *Toxoplasma gondii*, an obligate intracellular parasite that forms cysts in mammalian tissues throughout the body.¹ It is an important public health problem, with high socio-economic impact in terms of human suffering including the cost of caring for sick, mentally handicapped, and blind children,² and is the commonest opportunistic infection causing focal brain disease in patients with acquired immune deficiency syndrome (AIDS).³ The parasite is an extremely successful pathogen, responsible for significant morbidity and mortality, especially in congenitally infected and immunocompromised individuals.^{3,4} The most important channels for transmission to humans are by ingestion of food or

water contaminated with oocysts shed by cats, by eating undercooked or raw meat containing infective tissue cysts, and via transplacental transfer, notably when the mother becomes infected for the first time during pregnancy.⁵

Toxoplasmosis in those with normal immunity is usually a self-limiting disease. If symptomatic, the most commonly recognized feature is painless cervical lymphadenopathy, sometimes accompanied by low-grade fever.⁶ Drug treatment is usually not required unless there is clinically severe or persistent disease, or other symptoms such as pneumonitis, myocarditis, meningoencephalitis, or polymyositis. Current practice is to treat such patients with pyrimethamine and sulfadiazine for 2–4 weeks.⁷

If infection occurs during pregnancy, the parasite can be transmitted to the fetus, resulting in congenital toxoplasmosis in the baby. The risk of congenital infection depends on gestational age at the time of

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maternal parasitemia. The aim of treatment is to prevent fetal infection.^{8,9} Depending on the trimester of pregnancy and whether or not the fetus is infected, drugs used include spiramycin and pyrimethamine + sulfadiazine. Nonetheless, current evidence is unclear as to whether congenital transmission can be prevented with antenatal treatment.¹⁰ Children with congenital toxoplasmosis usually receive treatment for 1 year with a practical dosage regimen of pyrimethamine + sulfonamides.

Toxoplasmic retinochoroiditis can occur at any age, and results in an acute intraocular inflammation, with sudden onset visual loss and pain. The condition often resolves without treatment within 6–8 weeks, leaving a healed scar.¹¹ Recurrences are known to occur.¹² Retinochoroiditis is treated for variable periods, ranging from 4 weeks to several months, with both anti-toxoplasma drugs and corticosteroids to reduce inflammation.¹³

Toxoplasmosis is a life-threatening disease for persons with impaired cellular immunity, in particular those with HIV infection and persons receiving immunosuppressive or cancer therapy.^{3,14} In this group, the most common reason for occurrence of disease is reactivation of chronic infection, rather than newly acquired infection.^{15,16} The predominant manifestation of toxoplasmosis in immunocompromised individuals is multifocal necrotizing encephalitis.^{3,15} Immunocompromised patients require therapy to control progressive disease, and therapy needs to be continued for the period of cell-mediated immunosuppression to prevent relapse.^{3,14}

Several drugs are used in the treatment of toxoplasmosis. These drugs act primarily against tachyzoites, and do not eradicate encysted forms. The most commonly used drugs target the folate pathway of the parasite. The best established regimen is a combination of pyrimethamine and sulfadiazine which inhibit parasite folate metabolism. Alternatively spiramycin, a macrolide, which has not been shown to be teratogenic, is used to treat infection in pregnant women.¹⁷ Other macrolides, notably azithromycin, have also been shown to be effective.¹⁸ Clindamycin, a lincomycin, inhibits *T.gondii* by an unknown mechanism that involves the parasite organelle apicoplast.¹⁹ Other drugs against *T.gondii* include dapsone, azithromycin, minocycline, and rifabutin.²⁰ Combinations of drugs are thought to be more effective.

Many of the current treatment regimens are based on case series and case studies. There are no large-scale trials on drugs used to treat toxoplasmosis. Thus there is a need to evaluate the available trial evidence with regard to efficacy and safety of drugs used to treat symptomatic toxoplasmosis in immunocompetent and immunocompromised hosts, pregnant women, and also patients with ocular toxoplasmosis.

Methods

We searched MEDLINE, EMBASE, and SCOPUS for publications, using the keywords 'toxoplasma' OR 'toxoplasmic' OR 'toxoplasmosis' OR 'toxoplasm*' AND 'randomized' OR 'randomised' OR 'random*' OR 'trial' in title, abstract, and keywords with no date limits. The search was performed in January 2013. The reference lists were imported into ENDNOTE X5®, and duplicates were removed. There were 949 hits in the combined search of MEDLINE, EMBASE, and SCOPUS. Three investigators (SR, NS, and MCS) independently went through the abstracts to identify relevant papers detailing the results of randomized trials of any drug or combination of drugs compared with placebo or other drug or combination of drugs given for treatment of toxoplasmic encephalitis, ocular toxoplasmosis, toxoplasmosis during pregnancy, or congenital toxoplasmosis. We excluded trials of drugs given for prophylaxis of toxoplasma infections. We also searched related publications and papers referenced in review articles on toxoplasmosis. Full papers of relevant studies were read through by two investigators (SR and SDF) who performed risk of bias analysis, and extracted the data into Revman 5® for analysis of pooled data. Duplicate publications of the same data were excluded. Where more than one trial was available with comparable outcomes, meta-analysis was performed. Results are presented as risk ratios with 95% confidence intervals for dichotomous data, and mean differences for continuous data. Risk of bias analysis and grading of methodological quality was performed by two authors independently (SR and SDF). Inter-rater agreement was 100%. (Fig. 1). The quality of studies was graded based upon the principles developed by the GRADE working group.²¹

Results

Fourteen randomized trials were eligible for inclusion. One trial was on treatment of toxoplasmic lymphadenitis, five trials were related to treatment of toxoplasmic encephalitis in AIDS patients, and the remaining were on treatment of ocular toxoplasmosis. No randomized comparative trials were identified on treatment for other manifestations of toxoplasmosis. One study was a non-comparative study, and was therefore not included in the quantitative analysis.²² Our results are summarized in Table 1.

Toxoplasmic lymphadenopathy

One study compared treatment with trimethoprim-sulphamethoxazole (TS) for toxoplasmic lymphadenopathy in immunocompetent individuals attending an infectious diseases clinic in Iran, in a randomized double blind trial.²³ Clinical response was the main outcome measure, and was defined by the following: impalpable lymph nodes and toxoplasma IgM titre <6 IU. Clinical response was measured at 1 month

and 6 months. At both reference time points, TS was superior to placebo. The trial was well designed and methodologically sound with a low risk of bias, although numbers were relatively small.

Toxoplasmic encephalitis

We considered randomized controlled trials (RCTs) incorporating pyrimethamine in one or both arms for the treatment of toxoplasmic encephalitis (TE). There were no RCTs comparing pyrimethamine versus placebo.

Two RCTs compared pyrimethamine + sulfadiazine (PS) with TS.^{24,25} Both studies included AIDS patients with clinical and radiological evidence of TE. In the study by Kongsangdao *et al.*²⁴ patients had, in addition, positive CSF serology for *T. gondii*. Baseline characteristics were similar in the different treatment arms of both studies. Kongsangdao *et al.*²⁴ treated patients with the same dose for 6 weeks, while Torre *et al.*²⁵ treated patients with a 30-day full dose course followed by a half dose maintenance course for 3 months. The randomization process was not detailed in Kongsangdao's study, while Torres used a computer generated random sequence. Procedures for allocation concealment were unclear, and both trials appeared largely un-blinded, although interpretation of radiological findings was blinded in Torres' study. Outcome measures in both studies were similar; complete recovery (or treatment failure), death, and adverse effects of medications. The pooled total number of participants was 112. One study compared two dosage regimens of pyrimethamine (50 mg and 100 mg) with TS,²⁴ while the other study used 50 mg pyrimethamine.²⁵ A total of 55 patients received PS, and 47 patients received TS. No statistically significant difference was seen with regard to the outcomes of complete recovery or death between the two groups, at any dosage of pyrimethamine. Adverse effects appeared less common with TS; however numbers were small. The total number of deaths was six in these studies.

Two trials compared PS and pyrimethamine + clindamycin (PC)^{26,27} Both studies were multicentre randomized studies, and were open labelled, recruiting AIDS patients with TE based on clinical signs and radiology. The pooled total number of participants was 358 (PS=180, PC=178). The study by Katlama *et al.*²⁷ was an intention-to-treat study, but had significant cross-overs. In this study, 37 patients in the PC group crossed over to PS, the majority (20) because of lack of response to treatment. However, only six of them improved with PS. Forty-five patients crossed over from PS to PC, and most of them (44) crossed over due to side effects from sulphonamides. No significant difference was observed with regard to the outcomes of complete recovery, death, or adverse effects.

There was one published non-comparative randomized trial of pyrimethamine + atovaquone versus atovaquone + sulphadiazine for toxoplasmic encephalitis.²² Response rates were similar in the two groups, with regards to complete recovery and adverse effects.

Ocular toxoplasmosis

There is a controversy regarding the necessity or efficacy of treatment of ocular toxoplasmosis. We found three RCTs comparing the effect of antibiotic treatment (together with steroids) for ocular toxoplasmosis compared with placebo.^{28–30} One study compared pyrimethamine + trisulphapyrimidines (PS) versus placebo,²⁸ a second compared TS versus placebo,²⁹ and the other compared pyrimethamine versus placebo.³⁰ These studies were small and were of poor methodological quality and had high heterogeneity, rendering the results difficult to interpret. Effects on visual acuity were not reported in any of these trials. The studies failed to show significant benefit with any treatment regimen. The study by Silveira *et al.*²⁹ showed that recurrences of ocular toxoplasmosis were commoner in those untreated. This study heavily influenced the pooled data; patients were treated for 14 months in this study, which did not include any patients with acute ocular toxoplasmosis. Adverse events were more frequent with treatment in all three studies.

We considered randomized trials comparing PS versus other drugs in the treatment of ocular toxoplasmosis. Two trials compared PS with intravitreal clindamycin and dexamethasone (IVCD).^{31,32} One study showed IVCD to be superior in terms of improvement in visual acuity, but pooled data showed no difference. There were also no differences between the two treatment regimens with regard to reduction in retinal lesion size, improvement in vitreous inflammation, adverse effects, or recurrence rates. Importantly, intravitreal injection of drugs appeared to be safe; subconjunctival hemorrhage and transient raised intraocular pressure were observed in four patients in the study by Soheilian *et al.*³²

Three trials compared different oral regimens against PS.^{33–35} Trials comparing PS with either TS³³ or the combination of pyrimethamine and azithromycin (PA)³⁴ showed no difference in improvement in visual acuity, reduction in vitreous inflammation, reduction in lesion size, or recurrence rates. In one study however, adverse effects appeared more common with PS compared with PA, although the results just failed to reach statistical significance. Another pilot randomized study compared azithromycin alone with PS³⁵ and showed equivalence with regard to the outcomes of time to sharpening of retinal lesions and time to disease inactivity. Visual acuity was not evaluated in this study. Comparison with other

Table 1 Summary of findings of all trials

Comparison	Outcome	Studies	N	Relative effect	95% CI	Grade
<i>Toxoplasmic lymphadenopathy</i> TS vs placebo	Clinical response at 1 month	Alavi 2010	46	RR:5.00	1.67–14.97*	Moderate
	Clinical response at 6 months	Alavi 2010	46	RR:2.00	1.22–3.27*	Moderate
<i>Toxoplasmic encephalitis</i> PS-50 vs TS	Complete recovery	Kongsaengdao 2008 Torre 1998	92	RR:1.04	0.77–1.40	Low
	Death	Kongsaengdao 2008 Torre 1998	97	RR:0.14	0.01–2.45	Low
	Adverse effects	Kongsaengdao 2008 Torre 1998	97	RR:2.03	0.77–5.32	Low
	Complete recovery	Kongsaengdao 2008	20	RR:1.00	0.56–1.78	Low
PS-100 vs TS	Death	Kongsaengdao 2008	20	RR:0.33	0.04–2.69	Low
	Adverse effects	Kongsaengdao 2008	20	RR:9.00	0.55–147.95	Low
PS vs PC	Complete ^{\$} recovery	Dannemann 1992 Katlama 1996	358	RR:0.68	0.19–2.47	Low
	Death	Dannemann 1992 Katlama 1996	358	RR:0.71	0.44–1.14	Low
	Adverse effects	Dannemann 1992 Katlama 1996	358	RR:1.12	0.96–1.31	Low
<i>Ocular toxoplasmosis</i> Any drug vs placebo IVCD vs PS	Recurrence	Acers 1963 Silveira 2002	144	RR:0.33	0.12–0.87**	Low
	Improvement in visual acuity	Baharivand 2013 Soheilian 2011	134	MD: 0.10*	–0.01–0.22	Low
	Reduction in retinal lesion size	Baharivand 2013	66	RR:1.06	0.54–2.10	Low
	Improvement in inflammation	Baharivand 2013 Soheilian 2011	168	RR:1.03	0.7–1.53	Low
	Adverse effects	Baharivand 2013 Soheilian 2011	136	RR:1.45	0.34–6.20	Low
	Recurrence	Baharivand 2013 Soheilian 2011	136	RR:0.74	0.08–7.13	Low
PS vs TS	Improvement in visual acuity	Soheilian 2005	59	RR:1.72	0.45–6.57	Low
	Improvement in inflammation	Soheilian 2005	58	RR:1.26	0.85–1.86	Low
	Adverse reactions	Soheilian 2005	58	RR:1.07	0.07–16.32	Low
	Recurrence	Soheilian 2005	59	RR:1.03	0.23–4.71	Low
PS vs PA	Improvement in visual acuity	Bosch-Driessen 2002	42	RR:1.10	0.77–1.56	Low
	Improvement in inflammation	Bosch-Driessen 2002	34	RR:1.02	0.66–1.58	Low
	Adverse reactions	Bosch-Driessen 2002	46	RR:1.91	1.00–3.65	Low
	Recurrence	Bosch-Driessen 2002	24	RR:1.67	0.66–4.2	Low

PS=Pyrimethamine + sulphadiazine, TS=trimethoprim + sulphamethoxazole, PC=Pyrimethamine + clindamycin, PA=pyrimethamine + azithromycin, IVCD=intravitreal clindamycin and dexamethasone.
 OR=Odds Ratio, MD=mean difference.

* TS was more effective than placebo.

** Drug treatment was associated with more side effects than placebo.

\$ Comparisons with high heterogeneity ($I^2 > 70\%$)

GRADE Working Group grades of evidence

1. High quality: Further research is very unlikely to change our confidence in the estimate of effect.
2. Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
3. Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
4. Very low quality: We are very uncertain about the estimate.

Figure 1 PRISMA diagram for selected studies.

regimens was not possible as the measures used to determine response were different.

Other manifestations

No trials were found investigating the efficacy of any other drugs in the treatment of toxoplasmic encephalitis, ocular toxoplasmosis, congenital toxoplasmosis or toxoplasmosis in pregnancy, or for the drugs spiramycin, minocycline, rifabutin, or dapsone, although these have been used in case reports and case series.

Risk of bias, heterogeneity, and quality of trials

The risk of bias for most studies was high or unclear, the main risks being deficiencies in blinding of participants and evaluators (Fig. 2). Where pooled comparisons were performed, heterogeneity was low in all instances except one (Table 1, footnote). Most of the evidence was of poor quality, and studies had significant methodological flaws (Table 1).

Discussion

Overall, trial evidence on treatments for toxoplasmosis is limited, and the grade of recommendations which can be made based on the evidence is low.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)
Acers 1963	?	?	+	+	?	+
Alavi 2010	+	+	+	?	+	+
Baharivand 2013	+	+	+	+	+	?
Balaskas 2012	+	+	?	+	+	+
Bosch-Driessen 2002	?	?	+	+	+	?
Dannemann 1992	?	?	+	+	?	?
Katlama 1996	?	+	+	+	?	?
Kongsaengdao 2008	+	?	+	+	?	+
Perkins 1956	?	?	+	+	?	+
Silveira 2002	+	+	+	+	+	+
Soheilian 2005	+	+	+	+	+	?
Soheilian 2011	+	+	+	+	+	?
Torre 1998	+	?	+	?	?	?

Figure 2 Summary of risk of bias analysis. Key: Green '+': low risk of bias; Red '-': high risk of bias; Yellow '?': unclear risk of bias.

Trials were of poor methodological quality with high risk of bias (Fig. 2).

There is reasonable evidence of benefit for treatment of toxoplasmic lymphadenopathy in immunocompetent individuals; TS would be the preferred drug based on current evidence, although no other drugs have been evaluated in a RCT.

For TE, the most widely recommended drug is PS. Pyrimethamine+sulfadiazine has been used for many years, based on initial case series showing benefit. However there are no trials comparing PS with placebo for toxoplasmic encephalitis, and non-comparative data shows response rates for recovery varying from 51–70%. Mortality rates among patients treated with PS for TE in AIDS also vary from 1.7–14.1%.

However, many other factors contribute to mortality as well as recovery from clinical disease in patients with TE in AIDS; thus in the absence of placebo controlled trials it is difficult to determine the efficacy of PS in TE. What our analysis does show is that, in TE in AIDS patients, TS and PA appear to be as effective in terms of mortality and complete recovery when compared with PS, and their adverse effect profiles are similar. Thus TS and PA are potential alternatives to treatment with PS. Trimethoprim + sulphamethoxazole in particular is more widely available, especially in resource poor settings, and thus would be an appropriate treatment choice where pyrimethamine is difficult to procure. Nonetheless, further studies are required to evaluate the efficacy of TS. Evidence for the use of azithromycin alone is lacking. Atovoquone could potentially be an alternative to PS, but comparative data does not exist, and in the presence of evidence of efficacy of other drugs, albeit of low quality, it is difficult to justify its routine use; in any case it is not widely available in resource-limited settings.

Assessment of improvement in ocular toxoplasmosis is difficult, due to difficulties in quantifying improvement, and is further confounded by the fact that some studies show no effect on clinical improvement with drug treatment compared to placebo. However these latter studies are small and methodologically poor. As would be expected, side effects were more common with treatment. Improvement with regard to visual acuity, regression in retinal lesion size, sharpening of margins of retinal lesions, and reduction in inflammation has been shown with treatment in comparative studies, and thus, most clinicians would treat ocular toxoplasmosis. The options for treatment are PS, IVCD, TMP-SMX, and PA. Although evidence is of poor quality, all these treatment options appear to be effective. Importantly, IVCD is as safe and effective as oral therapy. There is evidence that treatment helps prevent recurrences, but this finding was heavily influenced by one study where treatment was given for a prolonged period, and the study cohort included patients with a form of toxoplasmosis known to be associated with a high incidence of recurrence.³⁶

We found no RCTs demonstrating the effects of treatment in pregnancy, in terms of preventing mother to child transmission of the disease. Meta-analysis of uncontrolled studies has shown no effect of such treatment. There is no good quality evidence regarding the benefits of treatment for congenital toxoplasmosis.

Although many other drugs are used for treating toxoplasmosis, i.e., spiramycin, dapsone, minocycline, etc, none of these have been evaluated in controlled trials, and current evidence for their use is based on case reports and case series. In the presence of several therapeutic options which have trial

evidence, albeit of poor quality, we cannot recommend their use except in patients who cannot tolerate PS, IVCD, or PA.

Trial evidence for the efficacy of antibiotics for toxoplasmosis is poor, and further well-designed trials are needed. Despite there not being any comparative trials of drugs against placebo in TE, it would be unethical to conduct placebo controlled trials for TE given the serious nature of the disease. Thus, future trials should evaluate the efficacy of other drugs compared with PS. One of the difficulties in determining efficacy in this situation is in differentiating whether mortality is due to TE or other complications of AIDS; thus trials should be adequately powered, and confounding factors carefully controlled for. Whether ocular toxoplasmosis should be treated at all is controversial; hence there is a place for adequately powered trials comparing the different treatment regimens such as PS, TS, and IVCD versus placebo. Importantly, the outcome measures should be standardized in such trials. We suggest the following outcome measures: improvement in visual acuity assessed using a standardized scale; reduction in retinal lesions size, reduction in the degree of inflammation assessed using standardized methods; recurrence rates; and adverse effects. The assessment points should be clearly defined; we suggest assessment of these outcome measures at 1 month and 6 months for recovery, and follow-up for up to 2 years for recurrence. Since there is no clear evidence of benefit for drug treatment of toxoplasmosis in pregnancy, adequately powered trials comparing drugs which are safe in pregnancy against placebo are ethically justifiable, and are recommended. The main outcome measure in these trials would be reduction in the risk of developing congenital toxoplasmosis. While PS is currently used to treat congenital toxoplasmosis, future trials should compare other drugs with PS, with clinical recovery as the main outcome measure.

Limitations

We searched the bibliographies of selected studies to identify any unpublished studies or published studies that might not have been included in the databases; none were found. Nonetheless, we acknowledge that non-indexed studies and unpublished studies may have been missed. We screened all studies which had at least an English abstract; two non-English studies were excluded from the final analysis, as all attempts to obtain the full text failed.

Conclusions

Pyrimethamine + sulfadiazine remains an important drug in the treatment of ocular toxoplasmosis and TE, although precise efficacy is not known. There is little doubt that TE should be treated actively, however the evidence for treating ocular toxoplasmosis is less clear.

In patients who cannot tolerate PS, or where PS is not available, TS appears a reasonable alternative. Patients allergic to sulphonamides could be treated with PA. It seems reasonable to treat patients with active ocular toxoplasmosis, and PS, TS, and IVCD seem appropriate options. For immunocompetent individuals with toxoplasmic lymphadenopathy, TS is an appropriate treatment. Further high quality randomized trials are clearly needed to determine comparative benefits of drugs in patients with toxoplasmosis, especially TE, which has significant mortality. There is a need for rigid methodological quality and identification of clear outcome measures in such trials, as current controversies are a result of the poor quality of previous studies.

Author Contributions:

SR, SDF, NS, and MCS conceptualized the review. SR, MCS, and CR developed the search strategy. MCS, NS, and SR independently read through the abstracts and identified suitable studies. The full papers were read through by SR and SDF. SR extracted and analyzed the data. SDF and SR wrote the first draft. SR, MCS, and CR revised the manuscript, and all authors reviewed and approved the final manuscript.

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Conflict of Interest:

The authors declare no conflict of interest.

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