Role of Clofazimine in Treatment of Mycobacterium avium Complex

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Background: Non-tuberculous mycobacteria (NTM), specifically Mycobacterium avium complex (MAC), is an increasingly prevalent cause of pulmonary dysfunction. Clofazimine has been shown to be effective for the treatment of M. avium complex, but there were no published large-scale analyses comparing clofazimine to non-clofazimine regimens in MAC treatment. The objective of this large-scale meta-analysis was to evaluate patient characteristics and treatment outcomes of individuals diagnosed with MAC and treated with a clofazimine-based regimen.

Methods: We used Pubmed/Medline, Embase, Web of Science, and the Cochrane Library to search for studies published from January 1, 1990 to February 9, 2020. Two reviewers (SSH and NY) extracted the data from all eligible studies and differences were resolved by consensus. Statistical analyses were performed with STATA (version 14, IC; Stata Corporation, College Station, TX, USA).

Results: The pooled success treatment rate with 95% confidence intervals (CI) was assessed using random effect model. The estimated pooled treatment success rates were 56.8% in clofazimine and 67.9% in non-clofazimine groups. Notably, success rates were higher (58.7%) in treatment of HIV patients with disseminated infection.

Conclusions: Treatment was more successful in the non-clofazimine group overall. However, HIV patients with disseminated infection had higher treatment response rates than non-HIV patients within the clofazimine group.

Keywords: clofazimine, Mycobacterium avium complex, pulmonary disease, mycobacteria, MAC

INTRODUCTION

Non-tuberculous Mycobacteria

Non-tuberculous mycobacteria (NTM) are found ubiquitously in the environment and serve as a common cause of pulmonary infection associated with increasing prevalence and significantly impaired health-related quality of life (HRQL). Symptoms of pulmonary NTM (PNTM) are non-specific (cough, fever, malaise) and severity is dependent on presence of baseline lung comorbidities (1). The majority (80%) of PNTM infections are caused by Mycobacterium avium complex (MAC) (2–5).
Current Treatment Approaches
There are limited data to guide the treatment of pulmonary non-tuberculous mycobacterial infection in patients without HIV. Current strategies involve multimodal drug therapy, drug susceptibility testing, and extended courses of antimicrobials which can often be unsuccessful. Extended courses of targeted drug therapy for slow versus rapid growing NTM are selected with the assistance of drug susceptibility testing (DST) (4). The American Thoracic Society/Infectious Diseases Society of America guidelines recommend a three-drug macrolide combination therapy containing rifamycin (rifampin, rifapentine, or rifabutin), ethambutol, with a macrolide (clarithromycin or azithromycin) for at least 12 months after culture conversion. The addition of aminoglycoside therapy (amikacin or streptomycin) is recommended in the first 3–6 months of therapy for severe disease (6).

Role of Clofazimine
Continued discovery is crucial to streamline a treatment regimen for PNTM in attempt to lower costs, target treatment-resistant isolates, and increase health-related quality of life for patients. Clofazimine is a lipophilic antibiotic FDA approved for the treatment of *Mycobacterium leprae*, the bacteria causing Hansen's disease. Clofazimine inhibits mycobacterial respiratory chain and ion transporters in the outer membrane; the phenazine molecule acts as an artificial electron acceptor. Clofazimine is oxidized in place of NADH, leading to reduced cellular ATP and presence of damaging reactive oxygen species (7). The role of clofazimine in the treatment of MAC has not been elucidated. Its efficacy has been shown in several studies, but a comprehensive analysis has not been published. The objective of this large-scale meta-analysis was to evaluate patient characteristics and treatment outcomes of individuals diagnosed with MAC who were treated with a clofazimine based regimen.

EXPERIMENTAL SECTION
Search Strategy
We searched Pubmed/Medline, Embase, Web of science and the Cochrane Library for studies published from January 1, 1990 to February 9, 2020. The search strategy was based on the following key words: *M. avium* complex, *Mycobacterium avium-intracellulare* complex, MAC, macrolides, aminoglycosides, and clofazimine. Lists of references of selected articles and relevant review articles were hand-searched to identify further studies.

![Flow chart of study selection for inclusion in the systematic review and meta-analysis.](image)
| References         | Country   | Type of study       | HIV prevalence (%) | Mean age | MAC disease      | Sample size | Treatment regimen                  | Median length of treatment (months) | Definition of cure |
|-------------------|-----------|---------------------|--------------------|----------|------------------|-------------|------------------------------------|------------------------------------|-------------------|
| Aznar et al. (10) | Canada    | Retrospective       | NR                 | 61       | MAC pulmonary disease | 35          | CFZ+RFP+EMB+AMK+FQ+macinolide      | 26                   | Culture conversion |
| Martiniano et al. (11) | USA | Prospective cohort | 0                  | 67       | MAC pulmonary disease | 26          | CFZ+RFP+EMB+AMK+FQ+macinolide      | 12                   | Culture conversion |
| Jarand et al. (12) | Canada    | Retrospective       | 0                  | 67       | MAC pulmonary disease | 107         | CFZ+EMB+macinolide                  | 14                   | Culture conversion |
| Jo et al. (13)    | South Korea | Retrospective    | 0                  | 59       | MAC pulmonary disease | 51          | CFZ+MXF+RFB                          | 5                    | Culture conversion |
| Field and Cowie (14) | Canada | Retrospective       | 0                  | 70       | MAC pulmonary disease | 30          | CFZ+CLR+AZM+EMB                     | 12                   | Culture conversion |
| Singer et al. (15) | Canada    | Randomized trial    | 100                | 16<     | Disseminate d MAC disease | 90          | CFZ+RFP+EMB+CPX                      | 4                    | Symptom improvement |
| Cohn et al. (16)  | USA       | Randomized trial    | 100                | 38       | Disseminate d MAC disease | 28          | CFZ or RFB+CLR 500 mg+EMB             | 2                    | Culture conversion |
| Fournier et al. (17) | France | Randomized trial    | 100                | 39       | Disseminate d MAC disease | 16          | CFZ+CLR+EMB                          | 2                    | Culture conversion |
| Haefner et al. (18) | Switzerland | Randomized trial | 100                | 40       | Disseminate d MAC disease | 23          | CFZ+CLR+RFB                          | 4.5                  | Symptom improvement |
| Burman et al. (19) | USA       | Retrospective cohort | 100               | 35       | Disseminate d MAC disease | 117         | CFZ+CLR+EMB                          | 3                    | Symptom improvement |
| Parenti et al. (20) | USA | Randomized trial     | 100                | 36       | Disseminate d MAC disease | 37          | CFZ+RFP+CPX+EMB+AMK                  | 3                    | Culture conversion |
| Roussel and Igual (21) | France | Retrospective       | NR                 | 41       | MAC pulmonary disease | 22          | CFZ+CLR+Mino                         | 15                   | Culture conversion |
| Chaisson et al. (22) | USA | Randomized trial    | 100                | 37       | Disseminate d MAC disease | 51          | CFZ+CLR+EMB                          | 3                    | Culture conversion |
| Dube et al. (23)  | USA       | Randomized trial    | 100                | 37       | Disseminate d MAC disease | 21          | CFZ+CLR+EMB                          | 2                    | Culture conversion |
| May et al. (24)   | France    | Randomized trial    | 100                | 35       | Disseminate d MAC disease | 59          | CFZ+CLR+EMB                          | 2                    | Culture conversion |
| Shafran et al. (25) | Canada | Randomized trial    | 100                | 38       | Disseminate d MAC disease | 90          | CFZ+RFP+EMB+CPX                      | 3                    | Culture conversion |
| Dautzenberg et al. (26) | France | Randomized trial  | 100                | 37       | Disseminate d MAC disease | 55          | CFZ+RFB+EMB+INH                      | 3                    | Culture conversion |
| Kissingen et al. (27) | USA  | Randomized trial    | 100                | 33       | Disseminate d MAC disease | 29          | CFZ+RFB+EMB+INH                      | 3                    | Culture conversion |
| Kemper et al. (28) | USA       | Randomized trial    | 100                | 35       | Disseminate d MAC disease | 31          | CFZ+RFP+EMB+CPX+AMK                  | 3                    | Culture conversion |

EMB, etambutol; RFP, Rifampicin; RFB, Rifabutin; INH, Isoniazid; STM, streptomycin; CFZ, clofazimine; CPX, ciprofloxacin; CLR, clarithromycin; AZM, azithromycin; AMK, amikacin; Mino, minocycline; FQ, fluoroquinolone.
| References            | Country     | Type of study | HIV prevalence (%) | Mean age | MAC disease                        | Sample size | Treatment regimens                  | Median length of treatment (months) | Definition of cure                                           |
|-----------------------|-------------|---------------|--------------------|----------|-----------------------------------|-------------|-------------------------------------|-----------------------------------|-------------------------------------------------------------|
| Asakura et al. (29)   | Japan       | Retrospective | 0                  | 68       | Refractory MAC pulmonary disease  | 31          | STFX+CLR+EMB+RFP                    | 12                                | Culture conversion, Radiologic improvement, Symptom improvement |
| Jhun et al. (30)      | South Korea | Prospective cohort | NR                | 63       | MAC pulmonary disease             | 26          | EMB+RFP+macrolide                  | 23.2                              | Culture conversion, Radiologic improvement, Symptom improvement |
| Cadelis et al. (31)   | France      | Retrospective | 17                 | 50       | MAC pulmonary disease             | 34          | CLR+RFP+EMB                        | 8.4                               | Culture conversion                                           |
| Zweijpfenning et al. (32) | Netherlands | Retrospective | NR                | 61       | MAC pulmonary disease             | 34          | RFP+EMB+macrolide                  | 15.7                              | Culture conversion, Radiologic improvement, Symptom improvement |
| Ellender et al. (33)  | Australia   | Retrospective cohort | NR                | 61       | MAC pulmonary disease             | 31          | CLR+RFP+EMB+AMK                    | NR                                | Culture conversion, Symptom improvement                     |
| Griffith et al. (34)  | USA         | Retrospective | NR                | 75       | MAC pulmonary disease             | 180         | CLR+RFP+EMB                        | >12                               | Culture conversion                                           |
| Shimomura et al. (35) | Japan       | Retrospective cohort | NR                | 71       | MAC pulmonary disease             | 42          | CLR+RFP+EMB                        | 12                                | Culture conversion                                           |
| Ito et al. (36)       | Japan       | Retrospective | 0                  | 61       | MAC pulmonary disease             | 72          | CLR+RFP+EMB                        | >12                               | Culture conversion                                           |
| Miwa et al. (37)      | Japan       | Randomized trial | 0                  | 68       | MAC pulmonary disease             | 32          | CLR+RFP+EMB                        | 12                                | Culture conversion                                           |
| Fujita et al. (38)    | Japan       | Randomized trial | 0                 | 69       | MAC pulmonary disease             | 14          | CLR+RFP+EMB                        | 12                                | Culture conversion, Radiologic improvement, Symptom improvement |
| Kim et al. (39)       | South Korea | Retrospective | NR                | 65       | MAC pulmonary disease             | 21          | CLR+RFP+EMB                        | 18                                | Culture conversion, Radiologic improvement, Symptom improvement |
| Sim et al. (40)       | South Korea | Retrospective | 0                  | 59       | MAC pulmonary disease             | 96          | CLR+RFP+EMB                        | >12                               | Culture conversion, Radiologic improvement, Symptom improvement |
| Hasegawa et al. (41)  | Japan       | Retrospective | NR                | 62       | MAC pulmonary disease             | 13          | CLR+RFP+EMB                        | 18                                | Culture conversion                                           |
| Jenkins et al. (42)   | UK          | Randomized trial | 0                 | 67       | MAC pulmonary disease             | 66          | CLR+EMB+RFB                        | 24                                | Culture conversion                                           |
| Kobashi et al. (43)   | Japan       | Randomized trial | 0                 | 63       | MAC pulmonary disease             | 73          | CLR+RFB+EMB                        | 24                                | Culture conversion, Symptom improvement                    |
| Lam et al. (44)       | USA         | Randomized trial | 0                 | 60       | MAC pulmonary disease             | 91          | CLR+RFP/RFB+EMB                    | >12                               | Culture conversion, Radiologic improvement, Symptom improvement |
| Benson et al. (45)    | USA         | Randomized trial | 100                | 35       | Disseminated MAC disease         | 57          | CLR+RFP+EMB                        | 16 week                           | Culture conversion                                           |

(Continued)
Only studies written in English were selected. This study was conducted and reported according to the PRISMA guidelines (8).

**Study Selection**

The records found through database searching were merged and the duplicates were removed using EndNote X7 (Thomson Reuters, New York, NY, USA). Two reviewers (SSH and NY) independently screened the records by title and abstract to exclude those not related to the current study. The full-text of potentially eligible records was retrieved and evaluated by a third reviewer (MJN). Included studies met the following inclusion criteria: (i) patients were diagnosed with MAC using the criteria suggested by ATS/IDSA; (ii) all study patients were treated with clofazimine or macrolide and/or aminoglycoside-containing regimens, with companion drugs; and (iii) the treatment outcomes were addressed. We defined treatment success as achievement of culture conversion and completion of the planned treatment without relapse while on treatment. Studies with insufficient information about patients’ characteristics and treatment outcomes were excluded. Conference abstracts, editorials, and reviews were also excluded.

**Data Extraction and Quality Assessment**

A data extraction form was designed by two reviewers (SSH and NY). These reviewers extracted the data from all eligible studies and differences were resolved by consensus. The following data were extracted: first author name; year of publication; study duration, type of study, country/ies where the study was conducted; number of patients with MAC; age; HIV/AIDS status; treatment protocols (treatment regimens and duration of treatment), and treatment outcome. The methodological quality of the eligible studies was assessed according to the Cochrane-based criteria (9).

**Data Synthesis and Analysis**

Statistical analyses were performed with STATA (version 14, IC; Stata Corporation, College Station, TX, USA). The pooled success treatment rate with 95% confidence intervals (CI) was assessed using random effect model. The between-study heterogeneity was assessed by Cochran’s Q and the I² statistic. Publication bias was assessed statistically by using Begg’s and Egger’s tests ($p < 0.05$) was considered indicative of statistically significant publication bias). To explore sources of studies’ heterogeneity, sensitivity analyses were carried out with meta-regression and subgroup analysis.

**RESULTS**

Figure 1 summarizes the study selection process. Briefly, we retrieved data from 40 selected articles comprising data for 19 studies with clofazimine in their regimens (clofazimine group) and 21 studies without clofazimine in their regimens (Non-clofazimine group). Characteristics of the included studies are described in Tables 1, 2.
| Studies with clofazimine in their regimens | First author | Sampling methods | Blinded | Cross sectional design | Prospective | Incomplete outcome data addressed |
|------------------------------------------|--------------|-----------------|---------|------------------------|-------------|----------------------------------|
| Aznar                                    | Consecutive  | No              | Yes     | No                     | No          | No                               |
| Martiniano                               | Consecutive  | No              | Yes     | No                     | No          | No                               |
| Jarand                                   | Consecutive  | No              | Yes     | No                     | No          | No                               |
| Jo                                       | Consecutive  | No              | Yes     | No                     | No          | No                               |
| Field                                    | Consecutive  | No              | Yes     | No                     | No          | No                               |
| Singer                                   | Randomized   | No              | Yes     | Yes                    | Yes         | No                               |
| Cohn                                     | Randomized   | No              | Yes     | Yes                    | Yes         | No                               |
| Fournier                                 | Randomized   | No              | Yes     | Yes                    | Yes         | No                               |
| Haefern                                  | Consecutive  | NR              | Yes     | Yes                    | No          | No                               |
| Burman                                   | Consecutive  | No              | Yes     | No                     | No          | No                               |
| Parenti                                  | Randomized   | NR              | Yes     | Yes                    | Yes         | No                               |
| Roussel                                  | Consecutive  | No              | Yes     | Yes                    | Yes         | No                               |
| Chaisson                                 | Randomized   | No              | Yes     | Yes                    | No          | No                               |
| Dube                                     | Randomized   | No              | Yes     | Yes                    | No          | No                               |
| May                                      | Randomized   | No              | Yes     | Yes                    | Yes         | No                               |
| Shafran                                  | Randomized   | No              | Yes     | Yes                    | No          | No                               |
| Dautzenberg                              | Randomized   | Yes             | Yes     | Yes                    | Yes         | No                               |
| Kissinger                                | Randomized   | No              | Yes     | Yes                    | No          | No                               |
| Kemper                                   | Randomized   | No              | Yes     | Yes                    | No          | No                               |
| Studies                                  | Consecutive  | No              | Yes     | No                     | No          | No                               |
| Asakura                                  | Consecutive  | No              | Yes     | No                     | No          | No                               |
| Jhun                                     | Consecutive  | No              | Yes     | Yes                    | Yes         | No                               |
| Cadelis                                  | Consecutive  | No              | Yes     | No                     | No          | No                               |
| Zweijpfenning                            | Consecutive  | No              | Yes     | No                     | No          | No                               |
| Ellender                                 | Consecutive  | No              | Yes     | No                     | No          | No                               |
| Griffith                                 | Consecutive  | No              | Yes     | No                     | No          | No                               |
| Shimomura                                | Consecutive  | No              | Yes     | No                     | No          | No                               |
| Ito                                      | Consecutive  | No              | Yes     | No                     | No          | No                               |
| Miwa                                     | Randomized   | No              | Yes     | Yes                    | Yes         | No                               |
| Fujita                                   | Randomized   | No              | Yes     | Yes                    | Yes         | No                               |
| Kim                                      | Consecutive  | No              | Yes     | No                     | No          | No                               |
| Sim                                      | Consecutive  | No              | Yes     | No                     | No          | No                               |
| Hasegawa                                 | Consecutive  | No              | Yes     | No                     | No          | No                               |
| Jenkins                                  | Randomized   | No              | Yes     | Yes                    | Yes         | No                               |
| Kobashi                                  | Randomized   | Yes             | Yes     | Yes                    | Yes         | No                               |
| Lam                                      | Randomized   | Yes             | Yes     | Yes                    | No          | No                               |
| Benson                                   | Randomized   | No              | Yes     | Yes                    | Yes         | No                               |
| Dunne                                    | Randomized   | Yes             | Yes     | Yes                    | Yes         | No                               |
| Gordin                                   | Randomized   | No              | Yes     | Yes                    | Yes         | No                               |
| Tanaka                                   | Consecutive  | No              | No      | No                     | No          | No                               |
| Wallace                                  | Consecutive  | No              | Yes     | No                     | No          | No                               |

**Quality Assessment**

Based on Cochrane tool (Table 3), the included studies had a low risk of bias. In clofazimine group, 12 studies were randomized controlled trials and the rest were non-randomized controlled trials (i.e., cohort or retrospective observational studies). In this group, the statistical analysis methodology was well-described in 17 studies but was not reported in the other two studies.

**Treatment Success**

The estimated pooled treatment success rates were found to be 56.8% (95% CI 47.0–66.5%) and 67.9% (95% CI 62.0–73.8%) in clofazimine and non-clofazimine groups, respectively (Figures 2, 3). The heterogeneity in the study characteristics led to significant variation in the reported treatment outcomes. Varying treatment success rates caused heterogeneity in the pooled results. Thus, we ran a meta-regression to understand the source of heterogeneity.
Based on meta-regression, different treatment success rates resulted as a significant source of heterogeneity ($P$-value = 0.000) in both clofazimine and non-clofazimine groups. In clofazimine group, there was some evidence of publication bias (Begg's and tests $P$-value was 0.01).

**Subgroup Analysis**

Table 4 shows the subgroup analysis of the studies based on treatment regimens, length of treatment, type of patients, number of drugs used, definition of cure, type of study and year of publication.

**DISCUSSION**

**Summary**

This study found that the estimated pooled treatment success rates were 56.8% in clofazimine and 67.9% in non-clofazimine groups. The duration of treatment above 1...
year after did not show any improvement in success rates. The success rate was higher (58.7%) in treatment of HIV patients with disseminated MAC compared to treatment of Non-HIV patients with MAC pulmonary disease (51.0%). Counterintuitively, treatment regimens containing more than three drugs were less successful (47.6% compared to 64.5%). The success rates were higher in studies which defined cure by symptomatic improvement rather than culture conversion.

**Clofazimine**

The need for novel therapies to combat MAC infection is high due to drug resistance, disease recurrence, and current suboptimal efficacy. Even though there is a lack of robust data supporting its efficacy, clofazimine has been used in combination therapies for the treatment of MAC. In this study we found lower treatment success rates when using clofazimine-based regimens, especially for the treatment of non-HIV related MAC pulmonary disease.
Resistance to clofazimine may have contributed to lower treatment success rates. In *vitro* isolates of NTM have been shown to be susceptible to clofazimine. Luo et al. tested 209 isolates containing rapid and slow growing NTM for *in vitro* susceptibility to clofazimine. Most slow growing clinical isolates were sensitive to clofazimine with MICs < 1 µg/ml and 17 out of 30 rapid growing clinical isolates showed sensitivity with MICs below <1 µg/ml (50). However, Chen et al. found mutations in genes coding for transcriptional regulatory proteins of Mycobacterium which confer resistance to clofazimine (51).

In addition to its antimicrobial activity, clofazimine displays immune modulating effects which may alter patient response to therapy. Clofazimine increases humoral immune response by increasing major histocompatibility complex class II expression in monocytes and decreasing suppressor T-cell activity. However, it negatively modulates innate immune activity by inducing apoptosis in macrophages (52). It is possible that the clofazimine decreases cure rates through death of macrophages, however this decrease may be offset by the beneficial T-cell modulation in immunocompromised HIV patients.

Lower treatment success rates in the clofazimine group could be attributed to a clinically significant drug interaction with rifampin. Pooled treatment success rates were lower in regimens containing more than three drugs compared to regimens containing three or less drugs. Interestingly, every clofazimine study using a greater than three-drug regimen contained rifampin as part its regimen. Whereas, rifampin was only used in a minority of drug regimens containing ≤ 3 drugs (2/11). Rifamycin antimicrobials induce many hepatic cytochrome P450 enzymes as well as glucuronidation pathways. Clofazimine undergoes glucuronidation prior to excretion as it transitions out of its pharmacologically active state. Clinically noticeable drug-interactions have been reported between clofazimine and rifampin (53). This finding could be secondary to rifampin-induced glucuronidation and subsequent excretion of clofazimine.

### Previous Data
Clofazimine based treatment regimens have been shown to be efficacious for the treatment on MAC in several previous studies, but data is scant, and treatments were never compared prospectively in a head-to-head fashion. Field et al. conducted a single-arm prospective study looking at the efficacy of macrolide/ethambutol/clofazimine regimen in MAC lung disease in 33 patients. Treatment for an average of 10 months converted sputum findings to negative in 87% of patients. However, relapse occurs in 19% of patients (14). Jarand et al. retrospectively reviewed patients with MAC lung disease being treated with regimens including clofazimine or rifampin (100 vs. 71%; *P* = 0.0002). However, relapse and re-treatment rates did not differ between groups (12). Martiniano et al. retrospectively found 50% of patients with pulmonary disease converted to negative cultures with the treatment of clofazimine regimens. However, only 48% of patient had *M. avium* complex, 21% of patients were diagnosed with cystic fibrosis, and most patients (78%) had failed previous treatment attempts (11).
Strengths/Limitations
This study was the first comprehensive review comparing clofazimine and non-clofazimine treatment regimens for the treatment of MAC. Our sample size of studies (19) and controls (21) is robust. External validity of this paper is strong; we were able to include studies treating HIV related disseminated MAC and non-HIV related pulmonary MAC. However, there are some limitations to address. Our study did not characterize MAC and non-HIV related pulmonary MAC. However, there were able to include studies treating HIV related disseminated MAC. Our sample size of studies (19) and controls 10

Future Directions
Our findings will help in assigning a role to clofazimine in the treatment of MAC. Based on our results, clofazimine should be considered a last-line agent. It is possible that its only role is in the treated of disseminated HIV disease. Future clinical trials need to be done to assess the efficacy in disseminated MAC. Furthermore, we need novel therapeutic agents to target non-HIV pulmonary MAC as current therapies are long in duration and often result in relapse of disease process (54).

DATA AVAILABILITY STATEMENT
The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

AUTHOR CONTRIBUTIONS
MN performed the literature review, conducted data analysis, and manuscript preparation. TC performed the literature review and manuscript preparation. SH, AH, NN, and MK-Y helped in the literature review and data analysis. MM conducted literature review, designed the study, and performed data analysis and manuscript preparation. All authors contributed to the article and approved the submitted version.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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