Worldwide Expert Agreement on Updated Recommendations for the Treatment of Systemic Sclerosis

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ABSTRACT. ***Objective.*** To evaluate agreement of the updated European League Against Rheumatism and European Scleroderma Trials and Research group (EUSTAR) recommendations for treatment of systemic sclerosis (SSc) among international experts. In addition, to determine factors that might influence agreement.

Methods. Level of agreement (10-point scale: 0 = not at all, 10 = completely agree) and local drug availability (yes/no) were assessed using an online survey. The Web link to the survey was shared with 481 unique e-mail addresses and SSc networks (Scleroderma Clinical Trials Consortium, Australian Scleroderma Interest Group, International Systemic Sclerosis Inception Cohort). Level of agreement was compared between subgroups stratified for participant characteristics.

Results. In total, 263 experts participated, of whom n = 209 (79%) completed each single item. The majority were rheumatologists (n = 200, 76%) working in Europe (n = 185; 71%); 59% (n = 156) were EUSTAR members; and 57% (n = 151) had > 10 years of clinical experience. Overall level of agreement was high (mean 8.0, SD 2.5). The 3 highest mean agreements included (1) angiotensin-converting enzyme inhibitors for scleroderma renal crisis (9.2, SD 2.1); (2) blood pressure control in SSc-patients treated with corticosteroids (9.0, SD 2.2); (3) proton pump inhibitors to prevent reflux complications (9.0, SD 2.2). The 3 lowest mean agreements included (1) fluoxetine for Raynaud phenomenon (RP; 4.6, SD 2.8); (2) hematopoietic stem cell transplantation (HSCT) for severe SSc (7.1, SD 2.9); (3) phosphodiesterase inhibitors 5 for RP (7.3, SD 2.7). Agreement differed between Europe and non-Europe for the use of iloprost, bosentan, methotrexate, HSCT, and cyclophosphamide. Treatment availability could partially explain differential agreement for iloprost, bosentan, and HSCT.

Conclusion. In general, worldwide expert agreement on updated recommendations for treatment of SSc is high, supporting their value. Differences in agreement are partially explained by geographical area and treatment availability. (J Rheumatol First Release October 1 2019; doi:10.3899/jrheum.181173)

Key Indexing Terms:
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In systemic sclerosis (SSc), the complex pathophysiology and multiple organ involvement require, in most cases, a multidisciplinary therapeutic approach. Therefore, because of the disease heterogeneity, the physician needs clear guidance in the choice of drugs that are supported by the best clinical evidence and that may be used in practice[1,2].

The European League Against Rheumatism (EULAR) and the European Scleroderma Trials and Research group (EUSTAR) have updated their recommendations on SSc treatment[3]. When compared to previous recommendations, the vascular area has been expanded to include phosphodiesterase type 5 (PDE-5) inhibitors for the treatment of SSc-related Raynaud phenomenon (RP) and digital ulcers (DU), and riociguat for the treatment of pulmonary arterial hypertension (PAH). Also in this area, the recommendations for the use of endothelin receptor antagonists (ERA), prostanoids, and PDE-5 inhibitors for SSc-related PAH have been defined more precisely. In the area of systemic treatment, hematopoietic stem cell transplant (HSCT) is proposed for patients with a rapidly progressive SSc course[3,4].

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There is great interest in how and to what extent these guidelines are considered useful and applicable in everyday clinical practice[5]. Apart from newly added recommendations, there has been wider clinical experience regarding the drugs also highlighted in the previous set of recommendations, which may have changed physicians' perceptions of these recommendations[6,7].

In general, it has been shown that guidelines are not always followed for different reasons: lack of awareness, lack of familiarity, lack of agreement, outcome expectancy, and inertia toward changing previous practice[5,8,9]. Years of clinical experience, especially in a narrow area of specialization, and lack of medical resources have also been suggested[1] as possibly influencing guidelines/recommendations application. Previous evaluation of agreement on the 2009 EULAR/EUSTAR recommendations on SSc treatment among 66 experts in the field showed that agreement, although in general high, differed significantly between areas[10]. Specifically, among experts from North America, the agreement on iloprost treatment of active DU was low, and was significantly lower than for experts from Europe. In the same report, the agreement on the use of methotrexate (MTX) for skin involvement in early diffuse SSc, and bosentan for recurrent DU despite treatment with iloprost and calcium antagonists were low, with more than 50% of participants scoring < 7 (scale 1–9).

Several factors might account for differences in the level of agreement for the EULAR/EUSTAR recommendations, such as access to drugs, national insurance policy, familiarity with treatment regimen, geographical area, and years of clinical experience in the field. EUSTAR educational activity including oral presentations during EULAR and American College of Rheumatology meetings, EUSTAR online and educational scleroderma courses, and the growing number of EUSTAR members and centers may influence the expertise and recommendation adherence[11]; one might expect that members of EUSTAR in general would show a higher agreement level with EULAR/EUSTAR guidelines than non-EUSTAR members.

To improve usefulness of treatment recommendations and to enable their effective implementation in everyday clinical practice worldwide, deeper insight into factors that contribute to the level of agreement is needed. We performed a Web-based survey among SSc experts around the world to determine the level of agreement with 2017 updated recommendations on the treatment of SSc, and assessed factors that might account for differences in agreement between experts.

MATERIALS AND METHODS

After publication of the updated EULAR/EUSTAR recommendations on the treatment of SSc in 2017, an online survey was designed using Survey Monkey; the survey contained the 17 EULAR/EUSTAR updated recommendations[3] (Supplementary Data 1, available with the online version of this article). Based on the 17 recommendations, 20 specific items were derived and evaluated. An e-mail containing a Web link to the survey and to the original article was sent out to international SSc networks [Scleroderma Clinical Trials Consortium (SCTC), Australian Scleroderma Interest Group (ASIG), International Systemic Sclerosis Inception Cohort (INSYNC)] and to 481 unique e-mail addresses of known SSc experts, including experts from South America and Asia. In total, 5 e-mails were sent between June 8, and August 5, 2017; the survey was closed on October 1, 2017. The participating authors had access to e-mail addresses of possible participants through membership of organizations in the field or based on personal contact. Responses were analyzed anonymously; responses could not be traced back to individual participants. In line with this, necessity for ethics approval was waived by the Medical Ethics Committee of The Leiden University Medical Center, the Netherlands.

The following characteristics of the participants were registered: geographical area, specialty, EUSTAR affiliation or membership, membership to other (national) networks, years of clinical experience in the SSc field, approximate number of patients with SSc under followup, and participation in clinical trials in the SSc field.

For each recommendation, the level of agreement was determined on a 10-point scale (0 = not at all; 10 = completely agree). Specifically, regarding the treatment guidelines for PAH, the number of responders prescribing PAH drugs and the number of responders referring their patients to a cardiologist and/or pulmonologist for treatment of PAH was registered. Participants were asked whether they felt comfortable in answering the questions regarding treatment of PAH and were offered the possibility to skip the part of the survey concerning guidelines for PAH treatment. Local drug availability (yes/no) was assessed. The usefulness of the recommendations was assessed by a score on a 10-point scale (0 = not at all; 10 = very useful).

Statistical analyses. General characteristics of participants were summarized. Mean level of agreement, mean level of usefulness, and drug availability were reported for the 20 items. Mean level of agreement was compared between different subgroups stratified according to EUSTAR membership, geographical area, drug availability, specialty (rheumatologist vs non-rheumatologist), number of patients with SSc in active followup (≤ 50 or > 50 during the past 6 months) and years of experience.

Stratification for drug availability was performed only in cases where availability was < 90% in either Europe, outside Europe, or both. Differences between subgroups were tested for significance using 2-tailed and 2-sample t test, with a p value < 0.05 indicating statistical significance.

RESULTS

Characteristics of participants. Of the 481 unique e-mail addresses contacted, a response was retrieved from n = 228 (response rate for unique e-mail addresses = 47%). Through the Web link that was shared with 3 SSc networks (SCTC, ASIG, INSYNC), an additional 35 responses were acquired. In total, 263 unique persons participated in the survey, of whom 209 (79%) completed every single item. General characteristics were compared between the completers and the noncompleters and did not differ for any of the items (data not shown). Therefore, for each question in the survey, all available measurements were taken into account.

The majority of participants were rheumatologists (n = 200, 76%), currently working in Europe (n = 185, 71%); 59% (n = 156) were EUSTAR members, 68% (n = 183) were working in a center affiliated with EUSTAR, and 151 (57%) reported > 10 years of experience in the SSc field. Of all participants, 22% (n = 58) were not involved in any of the official networks. Non-European geographical areas were also represented (29%): Africa, n = 2 (1%); Asia, n = 18 (7%); Australia, n = 13 (5%); North America, n = 27 (10%);

South America, n = 17 (6%). Other specialties that participated in the survey included internal medicine specialists (n = 25), dermatologists (n = 9), immunologists (n = 22), and other (n = 7). Forty-eight percent of participants reported to have seen up to 50 patients with SSc during the past 6 months, 19% had seen 50–100 patients, and 31% had seen > 100 patients with SSc during the past 6 months. Eighty-one percent of participants saw 0–10 patients with early SSc (diagnosis < 1 yr) during the past 6 months, 12% saw 11–25 patients with early SSc, and 7% saw > 25 patients with early SSc during the past 6 months. Regarding treatment of SSc-related PAH, 208 responders completed these questions: 51% of responders prescribed PAH drugs themselves, 69% needed to refer the patient with PAH to a pulmonologist/cardiologist/another rheumatologist (e.g., from a tertiary center) for treatments as well, and 21% felt uncomfortable in answering the questions regarding guidelines on treatment of SSc-related PAH.

General agreement and usefulness. The mean level of agreement was 8.0 (median 9, SD 2.5). The 3 highest mean agreements were reported for angiotensin-converting enzyme (ACE) inhibitors for scleroderma renal crisis (SRC), blood pressure and renal function control in SSc patients treated with corticosteroids, and treatment with proton pump inhibitors (PPI) to prevent esophageal reflux complications (Table 1). The 3 lowest mean agreements included the use of fluoxetine for RP, HSCT for rapidly progressive SSc, and PDE-5 inhibitors for RP (Table 1).

The mean score for usefulness of the recommendations was in line with the level of agreement for the majority of recommendations. The top 3 levels of usefulness consisted of (1) the use of ACE inhibitors for SRC (9.2, SD 2.1; (2) treatment with PPI to prevent esophageal reflux complications (8.9, SD 2.2); and (3) blood pressure/renal function control in SSc patients treated with corticosteroids (8.8, SD 2.4). The 3 lowest levels of usefulness included the use of (1) fluoxetine (4.6, SD 3.0), and (2) PDE-5 inhibitors for RP (6.7, SD 3.0); and (3) HSCT for rapidly progressive SSc (6.6, SD 3.2). Supplementary Table 1 (available with the online version of this article) provides a complete overview of mean scores for agreement and usefulness for all evaluated items.

Agreement stratified for subgroups. When comparing experts from Europe to experts from other geographical areas, the level of agreement differed significantly ($p < 0.05$) for the following recommendations: iloprost for RP, iloprost and bosentan for DU, MTX for early diffuse SSc, cyclophosphamide for SSc-related lung disease, and HSCT for severe SSc (Table 2).

Comparison of agreement between SSc experts for whom the particular drug/treatment option was available with agreement among experts for whom this particular drug/treatment option was not available showed significant differences for the use of PDE-5 inhibitors, fluoxetine for RP, iloprost for DU and for RP, and riociguat for PAH and HSCT (Table 3).

Only for use of bosentan to prevent DU was there a signifi-

Table 1. Recommendations for treatment of systemic sclerosis; mean level of agreement among SSc experts (n = 209).

Recommendations	Agreement, Mean (SD)
CCB should be considered as first-line therapy for SSc-RP	8.2 (2.7)
PDE-5 inhibitors should be considered in treatment of SSc-RP	7.3 (2.7)
Fluoxetine might be considered in treatment of SSc-RP attacks	4.6 (2.8)
Intravenous iloprost should be considered for severe SSc-RP	7.9 (2.7)
Intravenous iloprost should be considered in the treatment of DU in patients with SSc	8.7 (2.3)
PDE-5 inhibitors should be considered in the treatment of DU in patients with SSc	8.0 (2.5)
Bosentan should be considered for reduction of number of new DU in patients with SSc	7.9 (2.8)
ERA should be considered to treat SSc-related PAH*	8.8 (2.4)
PDE-5 inhibitors should be considered to treat SSc-related PAH*	8.9 (2.3)
Riociguat should be considered to treat SSc-related PAH*	7.4 (2.8)
Intravenous epoprostenol should be considered for treatment of patients with severe SSc-related PAH*	8.3 (2.5)
Prostacyclin analogs should be considered to treat SSc-related PAH*	8.0 (2.7)
MTX may be considered for skin manifestations of early diffuse SSc	7.4 (2.8)
Cyclophosphamide should be considered for treatment of SSc-ILD, in particular for patients with progressive ILD	8.0 (2.6)
HSCT should be considered for treatment of selected patients with rapidly progressive SSc at risk of organ failure	7.1 (2.9)
Experts recommend immediate use of ACE inhibitors in the treatment of SRC	9.2 (2.1)
Blood pressure and renal function should be carefully monitored in SSc patients treated with glucocorticoids	9.0 (2.2)
PPI should be used for the treatment of SSc-related GERD, and prevention of esophageal ulcers and strictures	9.0 (2.2)
Prokinetic drugs should be used for the management of SSc-related symptomatic motility disturbances	8.0 (2.4)
Intermittent or rotating use of antibiotics may be useful to treat symptomatic bacterial overgrowth in patients with SSc	8.5 (2.1)

* N = 166: of n = 209 complete responders, 21% did not complete the questions regarding PAH-specific drugs because they stated that they felt uncomfortable answering questions regarding guidelines on treatment of SSc-related PAH. SSc: systemic sclerosis; CCB: dihydropyridine-type calcium channel blockers; PDE-5: phosphodiestherase type 5; ACE: angiotensin-converting enzyme; PPI: proton pump inhibitors; RP: Raynaud phenomenon; DU: digital ulcers; ERA: endothelin receptor antagonists; PAH: pulmonary arterial hypertension; MTX: methotrexate; ILD: interstitial lung disease; HSCT: hematopoietic stem cells transplant; SRC: scleroderma renal crises; GERD: gastroesophageal reflux disease (nonsignificant).

Table 2. Treatment recommendations with different agreements between European SSc experts and non-European SSc experts.

Recommendations	European Experts, n = 157	Non-European Experts, n = 63	p
Intravenous iloprost should be considered for severe SSc-RP	8.5 (2.2)	6.5 (3.1)	< 0.0001
Availability, %	90	55	
Intravenous iloprost should be considered in the treatment of DU in patients with SSc	9.0 (1.9)	7.4 (2.7)	< 0.0001
Availability, %	93	59	
Bosentan should be considered for reduction of number of new DU in patients with SSc	8.5 (2.3)	6.3 (3.2)	< 0.0001
Availability, %	86	57	
MTX may be considered for skin manifestations of early diffuse SSc	7.9 (2.7)	6.8 (3.0)	< 0.05
Availability, %	95	92	
Cyclophosphamide should be considered for treatment of SSc-ILD, in particular for patients with progressive ILD	8.3 (2.4)	7.4 (2.9)	< 0.05
Availability, %	99	100	
HSCT should be considered for treatment of selected patients with rapidly progressive SSc at risk of organ failure	7.3 (2.7)	6.4 (3.2)	< 0.05
Availability, %	66	66	

Values are mean (SD) unless otherwise specified. SSc: systemic sclerosis; RP: Raynaud phenomenon; DU: digital ulcers; MTX: methotrexate; ILD: interstitial lung disease; HSCT: hematopoietic stem cell transplant.

Table 3. Treatment recommendations with different agreements between experts stratified according to drug/treatment option availability.

Recommendations	Drug Available	Drug Not Available	p
PDE-5 inhibitors should be considered in treatment of SSc-RP	7.9 (2.5), n = 129	6.4 (2.7), n = 88	< 0.0001
Fluoxetine might be considered in treatment of SSc-RP attacks	4.9 (2.9), n = 138	4.1 (2.5), n = 81	< 0.05
Intravenous iloprost should be considered for severe SSc-RP	8.3 (2.6), n = 170	6.8 (2.7), n = 44	< 0.001
Intravenous iloprost should be considered in the treatment of DU in patients with SSc	8.8 (2.2), n = 176	7.5 (2.6), n = 37	< 0.0001
Bosentan should be considered for reduction of number of new DU in patients with SSc	8.3 (2.4), n = 165	6.5 (3.0), n = 48	< 0.0001
Riociguat should be considered to treat SSc-related PAH	8.1 (2.4), n = 99	6.6 (3.0), n = 66	< 0.0001
HSCT should be considered for treatment of selected patients with rapidly progressive SSc at risk of organ failure	7.4 (2.8), n = 136	6.5 (2.8), n = 71	< 0.05

Values are mean (SD) unless otherwise specified. PDE-5: phosphodiestherase type 5; SSc: systemic sclerosis; RP: Raynaud phenomenon; DU: digital ulcers; PAH: pulmonary arterial hypertension; HSCT: hematopoietic stem cell transplant.

cant difference in agreement between EUSTAR members and EUSTAR non-members. For all other items, the level of agreement was comparable between EUSTAR members and non-members. There were no significant differences in the subgroups when stratified for years of clinical experience. A complete overview of all stratified analyses is provided in Supplementary Tables 2–5 (available with the online version of this article).

Physicians who saw ≤ 50 patients with SSc during the past 6 months (n = 126) were significantly more often European (79%) and EUSTAR members (82%), and less often participated in clinical trials (50%), compared to physicians who saw > 50 patients with SSc during the past 6 months (total n = 137; 62% European; 72% EUSTAR member; 86% participants in trials). Of those with lower patient numbers, 53% had been involved in SSc treatment > 10 years versus 74% of physicians who saw > 50 SSc patients during the past 6 months. However, mean agreement with the recommendations did not differ for any of the items between these 2 groups (data not shown).

Finally, rheumatologists were compared with non-rheumatologists. Non-rheumatologists with complete data on agreement (n = 36) were more often European (85%), and more often EUSTAR members (90%). Mean level of agreement with recommendations was in general higher among rheumatologists (n = 173 with complete data), and significantly higher for the following recommendations: PDE-5 inhibitors for DU [mean 8.3 (SD 2.3) vs 6.7 (3.2)], ERA for PAH [9.0 (2.1) vs 7.6 (3.2)], prostacyclin analogs for PAH [8.3 (2.5) vs 6.6 (3.1)], MTX for skin manifestations in early diffuse SSc [7.7 (2.5) vs 5.7 (3.6)], and HSCT for selected patients with rapidly progressive SSc [7.3 (2.8) vs 6.0 (3.0)].

DISCUSSION

In general, agreement among SSc experts on updated recommendations for treatment of SSc is high. Perception of the usefulness mirrors this high level of agreement. Because the majority of responders is European, mean agreement for different recommendations largely represents European SSc experts. However, by specifically comparing non-European with European physicians, the data do provide insight into agreement outside Europe as well, and show that differences

in the level of agreement between continents may be partially explained by local drug or treatment option availability.

Of note, it is hard to define when a physician fulfills criteria for "expert in the field." When arbitrarily using the cutoff of > 50 patients in active care during the past 6 months, we did not see a difference in level of agreement with recommendations. Possibly, this observation might be explained by the rarity and complex features of SSc itself: physicians involved in care for these patients might more often rely on existing guidelines. In addition, by reaching out to participants through personal contacts and e-mail addresses available through SSc networks, physicians with special interest in the field were contacted and they participated: the majority of responders (78%) is involved in at least 1 of the currently existing official SSc networks.

Interestingly, in general, agreement was higher among rheumatologists compared to other specialties represented in the survey. However, these data should be interpreted with caution, because the number of physicians of other specialties was relatively low (n = 36 with complete data).

When comparing our results to the results of the survey evaluating the agreement with the previous version of the EULAR/EUSTAR recommendations, the same areas of controversy were identified: the use of iloprost for RP and DU, and the use of bosentan for DU. Our data demonstrate that regarding iloprost and bosentan, local drug availability might at least partially account for the differences in level of agreement. In addition, for iloprost, lack of evidence and variation in regimens might result in a lower level of agreement[12]. We could observe the growing level of agreement for the use of bosentan for DU over time, specifically in the European region. Among the 5 newly added recommendations — PDE-5 inhibitors and fluoxetine for RP, PDE-5 inhibitors for DU, riociguat for PAH, and HSCT for rapidly progressive SSc — 4 were ranked among the recommendations with the lowest agreement in general. This could not be explained by the reported strength of the recommendation[3,13]. Still, only limited evidence is available to support use of fluoxetine for RP[14]. In addition, the fear of possible side effects or complications might also contribute to this ranking, specifically regarding use of HSCT for rapidly progressive SSc, for which high clinical efficacy is partially counterbalanced by treatment-related mortality[15]. Finally, one should acknowledge that data regarding availability could also reflect whether the drug is prescribed off-label. We suggest that these factors, together with low familiarity with new treatment options as a single or combined factor, might explain our observation. Also, drug availability might partially account for it (Supplementary Tables 1–5, available with the online version of this article). Interestingly, the use of MTX for skin involvement in early diffuse SSc gets a lower level of agreement in both European and non-European responders. Clearly, this cannot be explained by a difference in drug availability or lack of familiarity.

In this survey we could assess the level of agreement, which was actually high in general, but the study did not evaluate the actual adherence to treatment recommendations, which might differ significantly from the agreement. This was, for example, shown in a study on agreement and adherence to treatment guidelines in patients with knee osteoarthritis[16]: while the level of agreement with guidelines was high (97–99%), the adherence was acceptable but significantly lower (74–75%). Older patients' age and longer symptoms duration resulted in a lower chance for guideline adherence; the chance for better guideline adherence increased among physicians who participated in educational events regularly and who had longer clinical experience. Interestingly, in our study, we did not observe an association between years of clinical experience with SSc and recommendation agreement.

This study has a few disadvantages that should be taken into account. First, the exact number of physicians who received the link to the survey is not known, because a Web link was shared with SCTC, INSYNC, and ASIG, who shared the survey with their members and yielded an additional 35 responders. By reaching out to personal contacts of the authors as well as using all e-mail addresses available through SSc networks, we tried to extend the group of responders beyond the networks themselves. Still, the majority of responders (78%) was involved in any of the official SSc networks, indicating that practicing rheumatologists outside SSc networks are underrepresented. Because responders participated anonymously, no comparison between responders and nonresponders could be made. Nevertheless, 79% of responders fully completed the survey and general characteristics did not differ between completers and noncompleters. Also, owing to anonymous participation, authors of the guidelines might have participated but could not be identified and compared to the remainder of the responders; this is a limitation of the study. However, the original article included 37 authors, which indicates a maximum of 14% of responders being authors on the guideline manuscript. Also, the comparison of agreement between EUSTAR members and EUSTAR non-members did not show large differences. Unfortunately, rheumatologists from Europe were overrepresented in our survey despite all our efforts to recruit specialists from other geographical areas and specialists from other backgrounds. Results of the current study show that specific geographical area and local drug availability are of importance, and probably as a consequence, adherence to treatment recommendations is influenced by these factors. It could be suggested that increased EULAR/EUSTAR educational activity and advocacy of newly published clinical trial results or observational studies may significantly improve recommendation availability and adherence; we can assume that close contact with local regulatory authorities may influence the promotion of needed drugs or treatment options and justify their use.

Still, in the treatment of SSc, areas remain that need to be clarified such as the correct use of corticosteroids, treatment of calcinosis, treatment of severe gastrointestinal motility dysfunction and gastric antral vascular ectasia, and use of biological therapies[17,18]. Given a lack of evidence in these areas, these complications were not addressed in the recommendations and consequently were not part of the survey.

The level of agreement on EULAR/EUSTAR recommendations for treatment of SSc worldwide is, in general, high. Differences in agreement are partially explained by geographical area and local drug/treatment option availability. To ensure the effective implementation of treatment recommendations for SSc worldwide, it is necessary to expand the network of educational efforts in the field of SSc, to learn more about local drug/treatment option availability, and to put more effort into the improvement of treatment by recruiting decision makers who will merge real treatment options and existing recommendations. More steps should be taken to implement recommendations for treatment of SSc in everyday clinical practice, in particular looking at the new wave of drugs and expanding drug indications that are now under investigation in clinical trials and that may enter into clinical practice in the near future[19].

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ONLINE SUPPLEMENT

Supplementary material accompanies the online version of this article.

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