HHS Public Access

Author manuscript

J Thromb Haemost. Author manuscript; available in PMC 2021 May 03.

Published in final edited form as:

J Thromb Haemost. 2020 October ; 18(10): 2496–2502. doi:10.1111/jth.15010.

ISTH guidelines for treatment of thrombotic thrombocytopenic purpura

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AUTHOR CONTRIBUTIONS

X. L. Zheng, Sara K. Vesely, Spero Cataland, Paul Coppo, Alfonso Iorio, Menaka Pai, and Flora Peyvandi analyzed the data, participated in panel discussion, and wrote manuscript; Brian Geldziler, Masanori Matsumoto, Reem A. Mustafa, Grail Rock, Lene Russell, Rawan Tarawneh, and Julie Valdes analyzed the data, participated in the panel discussion, and revised manuscript. All authors approved the final version of the manuscript.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

CONFLICTS OF INTEREST

Dr. Zheng is a speaker and consultant for Alexion, Sanofi-Genzyme, and Takeda, as well as the co-founder of Clotsolution; Dr. Vesely is a biostatistician for the Oklahoma TTP registry; Dr. Cataland is a consultant for Sanofi-Genzyme and Takeda and served on an advisory board for Alexion; Dr. Coppo is a consultant for Sanofi-Genzyme, Alexion, and Takeda; Dr. Matsumoto has received royalty interest from Alfressa Pharma; Dr. Peyvandi is a speaker for Spark Therapeutics, Sobi, Bioverativ, Grifols, Takeda, and SanofiGenzyme; Dr. Geldziler is an employee of Merck Pharmaceuticals. Dr. Iorio reports that his institution has received project-based funding via research or service agreements from Bayer, CSL, Grifols, NovoNordisk, Octapharma, Pfizer, Roche, Sanofi, Sobi, Spark, and Takeda; Dr. Pai and other authors whose names are not specifically mentioned in this section declare no conflict of interest.

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Abstract

Background: Despite advances in treatment options for thrombotic thrombocytopenic purpura (TTP), there are still limited high quality data to inform clinicians regarding its appropriate treatment.

Methods: In June 2018, the ISTH formed a multidisciplinary guideline panel to issue recommendations about treatment of TTP. The panel discussed 12 treatment questions related to immune-mediated TTP (iTTP) and hereditary or congenital TTP (cTTP). The panel used the Grading of Recommendations Assessment, Development, and Evaluation approach, including evidence-to-decision frameworks, to appraise evidence and formulate recommendations.

Results: The panel agreed on 11 recommendations based on evidence ranging from very low to moderate certainty. For first acute episode and relapses of iTTP, the panel made a strong recommendation for adding corticosteroids to therapeutic plasma exchange (TPE) and a conditional recommendation for adding rituximab and caplacizumab. For asymptomatic iTTP with low plasma ADAMTS13 activity, the panel made a conditional recommendation for the use of rituximab outside of pregnancy, but prophylactic TPE during pregnancy. For asymptomatic cTTP, the panel made a strong recommendation for prophylactic plasma infusion during pregnancy, and a conditional recommendation for plasma infusion or a wait and watch approach outside of pregnancy.

Conclusions: The panel's recommendations are based on all the available evidence for the effects of an individual component of various treatment approaches, including suppressing inflammation, blocking platelet clumping, replacing the missing and/or inhibited ADAMTS13, and suppressing the formation of ADAMTS13 autoantibody. There was insufficient evidence for further comparing different treatment approaches (eg, TPE, corticosteroids, rituximab, and caplacizumab, etc.), for which high quality studies are needed.

Keywords

caplacizumab; guidelines; rituximab; treatment; TTP

1 | INTRODUCTION

Introduction about thrombotic thrombocytopenic purpura (TTP), the reasons why we need the treatment guidelines for TTP, how to use these guidelines, how to develop the treatment guidelines, and the composition and conflicts of interest of the guideline panel and methodology team are all described in detail in the ISTH guidelines for the diagnosis of TTP.[1]

The panel meetings for the development of guidelines for both diagnosis and treatment of TTP were conducted simultaneously.

Twelve Population, Intervention, Comparison, and Outcome treatment questions (PICO) (Appendix S1C) relating to the treatment of acute immune-mediated TTP (iTTP) and hereditary/congenital TTP (cTTP) (the first event, the relapse, and during remission without and with pregnancy) were fully appraised and recommendations were provided.

The targeted audience for the treatment guidelines of TTP include primarily hematologists, clinical pathologists over seeing trans- fusion medicine, intensive care physicians, and other health care providers who treat TTP at relatively regular basis.

2 | RECOMMENDATIONS

2.1 | iTTP, first event

2.1.1 | Recommendation 1—For patients with iTTP experiencing a first acute event, the panel recommends the addition of corticosteroids to therapeutic plasma exchange (TPE) over TPE alone. (A strong recommendation in the context of very low certainty evidence.)

The panel made a strong recommendation, despite very low certainty evidence, because the recommended intervention may moderately reduce the mortality in a life-threatening situation, whereas adverse events for short-term use of corticosteroids are not severe. The panel placed a high value on the uncertain but potentially life-saving benefit by adding corticosteroids. The panel also felt that a small increment of cost and resource usage, relative to the potential benefits, justified the addition of corticosteroids to TPE in the treatment of first acute event of iTTP. Overall, the quality of evidence is very low, supported by only small studies with a heterogenous population and varied interventions (Appendix S1G–1).

The panel was unable to make a more detailed recommendation on a preferred dosage and type of corticosteroids (eg, prednisone, or methylprednisolone). Given the known cardiac, endocrine, and neuropsychiatric adverse effects of corticosteroids, the panel felt that special attention to adverse effects should be paid to the susceptible populations, such as those with hypertension, diabetes mellitus, psychiatric comorbidities, and advanced age, etc.

2.1.2 | Recommendation 2—For patients with iTTP experiencing their first acute event, the panel suggests the addition of rituximab to corticosteroids and TPE over corticosteroids and TPE alone. (A conditional recommendation in the context of very low certainty evidence.)

The data informing this recommendation are from nonrandomized trials; this raises the concern of selection bias, where patients receiving rituximab may have had a more severe disease, a bias that may have blunted beneficial effects of adding rituximab to the treatment with corticosteroids and TPE, however. The panel notes that the primary effect of rituximab appears to be the prevention of relapses; however, many patients with iTTP may not experience a relapse, regardless of the initial treatment regimen. Given such low certainty evidence, a fairly narrowed range of outcomes affected by rituximab, and issues related to drug cost, the panel choose to make conditional recommendation for the use of rituximab.

Practitioners may consider among the conditions in favor of rituximab use, the presence of a known comorbid autoimmune disorder, albeit with scant supportive evidence (Appendix S1G–2).

2.2 | iTTP, relapsing episode

2.2.1 | Recommendation 3—For patients with iTTP experiencing a relapse, the panel recommends addition of corticosteroids to TPE over TPE alone. (A strong recommendation in the context of very low certainty evidence.)

The panel made a strong recommendation despite very low certainty evidence because the recommended intervention may moderately reduce the mortality in a life-threatening situation, and its adverse events are not prohibitive over a short term. The panel placed high value on the uncertain yet potentially life-saving benefits of adding corticosteroids. This recommendation was largely informed by indirect evidence on the effects of corticosteroids in the setting of the first acute event of iTTP. There is little evidence (often single-arm and registry data) exclusively informing the treatment of iTTP patients with relapses.

The panel considered that the prognosis and severity of the relapsed episode may be different from the first episode.[2,3] The panel also considered the adverse effects associated with multiple courses of high-dose corticosteroids. Pulse corticosteroids used repeatedly (even in a short duration) may be associated with serious morbidities. Patients may be less willing to tolerate adverse effects with each of the subsequent relapses. Nevertheless, the panel still felt that, given the high mortality rate associated with the relapsing iTTP, the small increment of cost associated to adding corticosteroids, relative to the potential benefit, justifies the addition of corticosteroids to TPE in the treatment of iTTP patients with relapses. The panel also emphasized that corticosteroid-sparing ancillary therapy (eg, use of rituximab) may be more acceptable to patients after the first acute event. However, this recommendation remains relevant because not all patients in all jurisdictions are able to access these ancillary therapies.

The panel was again unable to make a more detailed recommendation on the dosage and type of corticosteroids. Given the known cardiac, endocrine, and neuropsychiatric adverse effects of corticosteroids, the panel felt that special attention to adverse effects be paid to the susceptible populations, including those with hypertension, diabetes, psychiatric comorbidities, and advanced age (Appendix S1G–3).

2.2.2 | Recommendation 4—For patients with iTTP experiencing a relapse, the panel suggests the addition of rituximab to corticosteroids and TPE over corticosteroids and TPE alone. (A conditional recommendation in the context of very low certainty evidence.)

The data informing this recommendation are sparse, with very low certainty. However, the panel noted that indirect data from the use of rituximab in addition to corticosteroids and TPE in individuals with the first acute event of iTTP suggest that rituximab use has a beneficial effect in preventing disease relapse. Moreover, they also noticed that the risk of a subsequent relapse may be higher in patients who have previously relapsed. The panel thus chose to make a conditional recommendation for the use of rituximab in this clinical setting.

Though there is little subgroup evidence available, practitioners may more strongly consider adding rituximab to treatment with corticosteroids and TPE in those with known comorbid autoimmune disorders (Appendix S1G–4).

2.3 | iTTP, first or relapsing episode

2.3.1 | Recommendation 5—For patients with iTTP experiencing an acute event (first event or relapse), the panel suggests using caplacizumab over not using caplacizumab. (A conditional recommendation in the context of moderate certainty evidence.)

The data informing this recommendation were of moderate certainty, based on two published randomized controlled trials (one of which is double-blinded). Data were not available to differentiate the caplacizumab's effect on the first and relapsed events, so these patients are considered together. The panel noted that the mortality rate was low in both control and caplacizumab arms in both randomized controlled trials. This might not be reflective of the true mortality rates in other TTP studies or patient populations, suggesting the possibility of selection bias. It means that the patients participating in these clinical trials may have had less severe disease. Patients receiving caplacizumab showed a clinically and statistically significant reduction in the number of exacerbations (defined as disease recurrence during therapy or within 30 days of stopping TPE); however, these patients also had a clinically and statistically significant increase in the number of relapses (defined as disease recurrence after 30 or more days since stopping TPE) at 12 months. This indiates that caplacizumab may have staved off recurrence within 30 days after stopping TPE. Caplacizumab may leave patients prone to experience a later recurrence owing to the unresolved ADAMTS13 deficiency and inhibitors. The panel also noted that patients on caplacizumab experienced clinically important bleeding side effects (Appendix S1G–5).

At the time of the panel deliberations, specific information on cost was not available; this uncertainty around cost was important to the panel's decision to make a conditional recommendation. Drug acceptability would likely be reasonable because caplacizumab can be administered subcutaneously in an outpatient or home setting via self-administration. The panel was mindful of the potential cost and accessibility issues in various parts of the world around the use of caplacizumab, and the urgent need for further studies of the cost-effectiveness.

Mechanistically, caplacizumab targets at the A1 domain of von Willebrand factor that interacts with platelet glycoprotein 1b, which immediately blocks platelet-von Willebrand factor interactions and prevents the formation of microvascular thrombosis in small arterioles and capillaries. Microvascular thrombosis may result in organ ischemia and long-term neurocognitive decline in patients with iTTP.[4,5] The panel also believed that the greatest benefit of caplacizumab is accrued if it is started in the early phase of an acute TTP event (i.e., at the time when a diagnosis is confirmed). Therefore, caplacizumab use is conditional on the capacity to rapidly identify patients with high likelihood of iTTP (eg, high clinical suspicion with evidence of severe deficiency of plasma ADAMTS13 activity and presence of inhibitors or anti-ADAMTS13 IgG). Practically, when treating physicians are considering caplacizumab, they should consider administration of the drug even before the results of plasma ADAMTS13 activity become available (Recommendations 1–3 in the

Guidelines for the Diagnosis of TTP)[1]; this raises the possibility of overuse in patients who do not actually have the diagnosis of TTP.

The panel emphasized that caplacizumab may not yet be available worldwide. Few clinicians are familiar with its use and the monitoring protocol. The panel stressed that caplacizumab should only be given under the guidance of an experienced clinician, who has the required level of knowledge about the use of this dru; ideally, the treating physician would be a TTP expert (eg, a hematologist or pathologist specialied in transfusion medicine who has previous experience in treating the disease). Clinicians using caplacizumab and patients who receive it must understand its unique mechanism of action as caplacizumab does not correct the underlying ADAMTS13 deficiency nor does it eliminate autoantibodies against ADAMTS13, the primary cause of iTTP. Discontinuation of caplacizumab treatment after platelet count normalization but with persistently low ADAMTS13 activity(<10 U/dL) may result in disease exacerbation.[6] Therefore, the immunosuppressive therapies such as rituximab and corticosteroids are still required to control the underlying disease process (Recommendations 1–4 in the ISTH Guidelines for Treatment of TTP).

Experienced physicians can provide guidance on how to start the caplacizumab, how to monitor patients, how to incorporate other ancillary therapies, and, finally, when to stop the drug. An appropriate use of caplacizumab depends on the accessibility to timely and reliable ADAMTS13 testing, either for the initiation of therapy or continued therapy once it has been started). (See Figure 1 in the ISTH Guidelines for the Diagnosis of TTP).[2] Finally, the panel highlighted the need to continue gathering data on the optimal use of this new drug.

2.4 | iTTP in remission

2.4.1 | Recommendation 6—For patients with iTTP who are in remission, but still have low plasma ADAMTS13 activity with no clinical signs/symptoms, the panel suggests the use of rituximab over nonuse of rituximab for prophylaxis. (A conditional recommendation in the context of very low certainty evidence.)

The data informing this recommendation do not clearly differentiate patients in the first remission from those in the subsequent remissions. Rituximab does not appear to affect survival; however, a small nonrandomized study suggests that patients receiving rituximab have fewer relapses and require a longer time for iTTP to relapse. The panel raised practical issues around the cost, resource utilization, and patient commitment necessary for monitoring during remission, such as continued monitoring of plasma ADAMTS13 activity and starting rituximab in a timely fashion.[7] The panel also noted that this strategy may not be feasible in all centers or acceptable to all patients. There is also no evidence on the appropriate interval for performing ADAMTS13 activity testing. The panel cautioned that implementation of rituximab prophylaxis during remission without access to ADAMTS13 testing is not an evidence-based strategy, which may lead to the potential overuse of this drug (Appendix S1G–6).

2.5 | cTTP in remission

2.5.1 | Recommendation 7—For patients with cTTP who are in remission, the panel suggests either plasma infusion or a watch and wait strategy. (A conditional recommendation in the context of very low certainty evidence)

The evidence to address this question is sparse with very low certainty. The panel felt that the balance between benefits and harms is unclear from the evidence available. Regular plasma infusions (eg, 10–15 mL/kg body weight, every 1–3 weeks) involve the use of substantial infrastructure resources and a large volume of plasma, and impose a burden on patients who must travel to a hospital or an infusion center to receive such a treatment. Repeated vascular access and transfusion reactions were also a concern. The panel believed, after weighing the evidence and practical considerations, that a recommendation for one strategy over another could not be issued. Individual patient preferences and clinical circumstance should be used to guide the decision-making process (Appendix S1G–7).

2.5.2 | Recommendation 8—For patients with cTTP who are in remission, the panel suggests against the use of factor VIII (FVIII) concentrate vs. a watch and wait strategy. (A conditional recommendation in the context of very low certainty evidence)

There is no clear evidence on the benefits or harms of using intermediate purity plasma-derived FVIII concentrates in this patient population. FVIII is a shelf-stable product that can be self-administered at home, which would be acceptable to many patients. However, the panel raised concerns about the variability of ADAMTS13 concentrations across various FVIII concentrate products with intermediate purity, and felt that in some cases, low ADAMTS13 concentration in the FVIII concentrate may not be sufficient to have the desired effect. To date, how FVIII works in the treatment of cTTP remains unclear. Given the absence of reliable data and lack of understanding the mechanism of action, the panel did not recommend the use of FVIII concentrate for most patients with cTTP in remission (Appendix S1G–8).

2.6 | TTP during pregnancy

2.6.1 | Recommendation 9—For patients with iTTP who are pregnant and have decreased plasma ADAMTS13 activity but with no clinical signs/symptoms, the panel recommends prophylactic treatment over no prophylactic treatment. (A strong recommendation in the context of very low certainty evidence)

The panel felt that pregnant women with decrease in plasma ADAMTS13 activity (eg, <30 U/dL or <30% of normal) may have poor clinical outcomes. However, there was a paucity of data on the effect of available treatment regimens. The panel elected to make a strong recommendation for prophylactic treatment despite the absence of moderate to high-certainty evidence. The panel believed that any intervention may help reduce maternal and infant mortality and morbidity rates in a life-threatening situation like TTP. The risks and benefits of prophylactic treatment and immunosuppressive strategies during pregancy merit further study. However, the panel placed a high value on the uncertain yet potentially life-

saving benefit of prophylactic treatment, and believed that the benefits of prophylactic treatment likely outweigh its risks (Appendix S1G–9).

2.6.2 | Recommendation 10a—For patients with cTTP who are pregnant, the panel recommends prophylactic treatment over no prophylactic treatment. (A strong recommendation in the context of very low certainty evidence)

The panel believed that pregnant women with cTTP had poor clinical outcomes, but there was unfortunately a paucity of data on the effects of available treatment regimens. The panel elected to make a strong recommendation, despite the absence of moderate to high-certainty evidence, because the panelists believed that any intervention may help reduce maternal and infant mortality and morbidity rates in patients with a life-threatening situation like TTP. The risks and benefits of prophylactic treatment merit further study, but the panel placed a high value on the uncertain but potentially life-saving benefit of prophylactic treatment, and believed that the benefits of prophylactic treatment likely outweigh its risks (Appendix S1G–10.1).

2.6.3 | Recommendation 10b—For patients with cTTP who are pregnant, the panel suggests prophylactic treatment with plasma infusion over FVIII products. (A conditional recommendation in the context of very low certainty evidence)

Recommendation 10b explores what *type* of prophylactic treatment might be appropriate to implement in Recommendation 10a. As explained in the Recommendation 8, there is no clear evidence on the benefits or harms of using plasma-derived intermediate-purity FVIII concentrate infusions in cTTP. There is also no direct evidence on the use of regular plasma infusions in this patient population. FVIII is a stable product that can be self-administered at home, which makes it more acceptable to many patients than plasma infusion. Plasma infusions require substantial infrastructure resources and a large volume of plasma, which imposes a burden on patients who must travel to a hospital or infusion center to receive the treatment. Repeated vascular access and transfusion reactions are also a concern with plasma infusions. However, the panel raised concerns about the variability in ADAMTS13 concentration across various FVIII products with intermediate purity, and believed that in some cases, the ADAMTS13 concentration in a FVIII product may be too low to have a beneficial effect. Given the absence of data, the panel believed that FVIII product infusion is not an appropriate treatment for most patients with cTTP who are pregnant. Comparatively, plasma infusion appears to be a preferred option in this setting (Appendix S1G–10.2).

3 | DISCUSSION

Remarkable advances have been made in recent years toward our understanding of the pathophysiology of TTP,[8,9] which has led to advancements in novel therapies.[6,10] However, there are relatively limited data from prospective, randomized, and controlled clinical trials to direct the most appropriate use of these treatments. For these reasons, the ISTH guidelines for the treatment of TTP, along with guidelines for the diagnosis of TTP[1] and Good Practice Statements,[11] will be helpful to health care professionals who manage these patients. The guidelines are intended to help clinicians as they determine the treatment options and follow

up the patients, with the understanding that the guidelines provided are not intended to replace the discussions between treating physician and patient, regarding to the relative risks and benefits of each treatment. With the knowledge of the mechanism of each treatment and expansion of treatment options-, guidelines will evolve. Future research should focus on high-quality randomized clinical trials to evaluate the role of TPE in conjunction with various pharmacologic regimens for the treatment of TTP.

The strong recommendation for the addition of corticosteroids to TPE in patients with iTTP is a good example of a recommendation in the context very low certainty of evidence. The presumptive rationales for the use of corticosteroids are to reduce acute inflammation and inhibit the production of ADAMTS13 autoantibodies, although high-quality data are not available. The potential benefits and clinical experience with the use of corticosteroids outweigh the relatively low risks for serious adverse events.[12,13] The use of rituximab as an adjunctive therapy to TPE has also gained its momentum in recent years, especially in patients presenting with a recurrent or relapsed iTTP.[14–17] While published data to date have suggested that rituximab is effective in preventing or delaying iTTP relapse, the lack of high-quality data, the need for parenteral administration, and concern for drug cost were all important factors for the panel to issue a conditional (rather than a strong) recommendation for the use of rituximab in addition to TPE and corticosteroids for the first and relapsed TTP events.

The panel gave caplacizumab a similar conditional recommendation for patients with the first and relapsed TTP episodes despite a more robust study design used to assess its efficacy and safety, compared with corticosteroids and rituximab. Although caplacizumab represents the first drug to receive a regulatory approval for the treatment of iTTP,[6,10] the panel recognized that the benefit with caplacizumab is greatest when given earlier in the course of disease. Caplacizumab is associated with side effects, significant cost, and requiring cotreatments to remove the underlying autoantibody. The panel placed a greater emphasis on the clinical expertise and access for ADAMTS13 tests for rapid diagnosis, and also have a readily access to the measurement of the ADAMTS13 activity to both confirm the diagnosis and monitor patients to determine when caplacizumab can be safely discontinued.

Patients with a history of iTTP in remission that are pregnant with reduced levels of ADAMTS13 activity have more recently been recognized to have poor clinical outcomes with close monitoring alone.[18–20] Although no specific prophylactic immune suppressive or plasma treatment regimen is recommended, the panel made a strong recommendation for the use of prophylactic treatment to increase the ADAMTS13 activity to prevent both maternal and fetal mortality and morbidity. Similarly, it is strongly recommended that pregnant patients with cTTP receive prophylactic plasma therapy;[2,21–24] plasma is conditionally recommended over FVIII concentrates in this scenario. The panel felt that the amount of ADAMTS13 in FVIII concentrates is quite minimal[25]; thus, the mechanism of action remains unclear.

Although clinicians may find the treatment guidelines, in conjunction with the guidelines for the diagnosis of TTP and the good practice statement, useful aiding in the management of patients with TTP, these guidelines are not the replacement for ongoing dialogs and

discussions between treating physicians and patients, which determines the most appropriate treatment option. It is such a shared decision-making process that is most appropriate in the case of a rare disease like TTP, where the quality of the published data is limited. The field of TTP is rapidly evolving with the development of novel therapeutic approaches, which will undoubtedly lead to the accumulation of additional knowledge and likely the revisions of these guidelines in the near future.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGMENTS

This work was supported by ISTH. The authors thank the entire McMaster Research Team for their tireless effort and guidance for developing these guidelines. The authors also acknowledge Federico Germini and Cindy Yeung for their support in systematic review and panel meetings. Special thanks to Samantha Craigie for her work on the systematic review and Elisabetta Trinari for review and coordination of all registry data submitted from the participating registries. Barbara Ferrari, James N. George, Junshik Hong, Nedaa Husainat, Mohamad Kalot, Nicole Kocher, Ilaria Mancini, Danijela Mikovic, Doyeun Oh, Kazuya Sakai, Deirdra R. Terrell, and Erica Wood all contributed registry data from their institutions. The authors also thank Cary Clark and Lacey Schmeidler from ISTH headquarters for their administrative support and review throughout the process.

Funding information

Educational Fund from International Society of Thrombosis and Haemostasis

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Foreword

- The treatment guidelines honor the memories of Mrs. Lauren Chapman Ruiz and Dr. J. Evan Sadler who were part of the Guidelines panel and attended the first meeting, June 21–22, 2018. Mrs. Chapman Ruiz was a patient representative and Dr Sadler served as a cochair.
- Mrs. Chapman Ruiz was diagnosed with TTP in early adulthood and died from complications of TTP on September 29, 2018.
- Dr. Sadler was a Professor and Divisino Director of Hematology at Washington University in St. Louis, Missouri, USA, and a world-renowned physician scientist who pioneered the studies of several blood coagulation factors, including von Willebrand factor, prothrombin, thrombomodulin, and ADAMTS13. Dr. Sadler died on December 13, 2018 following a brief illness.