When Is it Justified to Treat Symptoms? Measuring Symptom Burden

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Symptom burden is certainly not a new concept in the literature on disease and treatment, but recent developments in our understanding of how to measure symptoms and their impact make it possible to cast symptom burden as a reasonable summary measure of both disease- and treatment-outcome status. We discuss the use of symptom burden as an alternative to quality-of-life measures or as a supplement to these measures.

It is now common for clinicians and patients to face choices among treatments that are highly similar in efficacy and even in prolonging survival. As a result, differences in treatment toxicity and in the patient’s status during the survival period have become critical variables in making treatment choices and in developing new therapies. Paramount in evaluating both toxicity and quality of survival time is the inclusion of patient-reported outcomes as important measures of treatment differences. These outcomes can take a variety of forms, including measures of the differences in symptom severity, perception of daily functioning, feelings of well-being, global impressions of the impact of treatment on daily life, satisfaction with treatment, and health-related quality of life (QOL).

Because these patient-outcome variables are becoming more important relative to "hard" end points such as survival or time to recurrence, decisions about which patient-outcome measures to use and how to interpret them for patients, health-care professionals, and policy makers will need to be made. Almost all of these outcome measures will ultimately depend on the patient's perception of his or her status, before and after becoming ill and receiving treatment. The patient’s representation of this change forms the basis for making practical judgments about how treatment should progress. As treatments that depend on such subjective outcomes emerge, how such treatments will be "valued" becomes a major issue. Will patients, given subjective outcome information about the treatments, opt to pursue them? Will physicians use this outcome information to recommend and prescribe treatments? When such treatments are being developed, will approval agencies decide they are beneficial? Will agencies (public and private health funders) decide that such treatments are worth paying for?

Thus, when a treatment offers little or no survival advantage, yet seems to improve how patients feel, judgments about the worth of the treatment will be made by several audiences who will ultimately determine whether the treatment is effective, should be approved, and will be used. Here we discuss the concept of symptom burden as a way to portray patient status, and offer a definition of symptom burden as an outcome measure.

Symptom Burden: An Operational Definition

We can trace the origin of the word "symptom" from the Greek "symptoma," which means "anything that has befallen one."[1] A more useful definition, however, is provided by Webster,[2] and states that symptom "is the subjective evidence of disease or physical disturbance observed by a patient." Implicit in this definition is the subjective and negative nature of symptoms. Symptoms are an observation by the patient; ie, the person experiencing the evidence of disease or physical disturbance. Symptoms can be the subjective expression of the disease itself, or the products of disease treatment, the latter often referred to as side effects or toxicities. Symptom burden can be thought of as the subjective counterpart of summary expressions of disease such as tumor burden. Patients typically experience multiple concurrent symptoms, due either to the disease or its treatment. We propose that a measure of symptom burden be a summative indicator of

- The severity of the symptoms that are most associated with a disease or treatment
- A summary of the patient’s perception of the impact of these symptoms on daily living,
including activity, mood, ability to work, and ability to relate to others.

Symptom Burden and Quality of Life

Most clinical trials currently include one or more measures of quality of life. In 1996, the American Society of Clinical Oncology stated that quality of life was an end point secondary only to survival.[3] The US Food and Drug Administration (FDA) recommended that quality of life is a more important measure of treatment efficacy than most other traditional end points for drugs that do not have an impact on survival.[4] Clearly, improving a patient’s quality of life is a goal of all medical treatment. Based on the World Health Organization definition of health,[5] quality of life includes psychological and social functioning as well as physical functioning, and incorporates positive aspects of well-being as well as negative aspects of disease and infirmity. Among health researchers, a common consensus is that quality of life is a multidimensional construct composed of at least four dimensions:

- Physical function (ie, daily activities, self-care, etc)
- Psychological function (ie, emotional/mental status, mood)
- Social function (ie, social interactions, family dynamics), and
- Disease/treatment symptoms (ie, pain, nausea, fatigue).

The comprehensive nature of quality of life, however, is both one of its attractions and its difficulties as an outcome measure. Quality of life is best viewed as a subjective evaluation of life as a whole.[6] In this section, we present the potential advantages of symptom-burden measure, highlighting its potential utility as a supplement to QOL measures.

Clinical Condition and Quality of Life

QOL measures may be relatively insensitive to obvious changes in clinical condition. As a multidimensional construct, a measure of quality of life may include aspects that go beyond the impact of cancer or its treatment. Among bone marrow transplant patients, studies have shown patients rating their quality of life as above average despite the persistence of significant physical and psychological symptoms. For example, Bush and colleagues[7] conducted a descriptive study of quality of life, psychological distress, demands of long-term recovery, and health perceptions of 125 bone marrow transplant survivors. They were no different from individuals sampled from the general population with regard to their perceived current health and health outlook. However, 10 or more years posttransplantation, long-term survivors continued to experience a moderate incidence of lingering complications and demands, including emotional and sexual dysfunction, fatigue, eye problems, sleep disturbance, general pain, and cognitive dysfunction.

Molassiotis et al[8] found that long-term autologous bone marrow transplant survivors rated their quality of life as good to excellent, although 20% reported symptoms of anxiety, 10% had signs of clinical depression, and 20% had not returned to full-time employment. McQuellon et al[9] found that quality of life and mood improved slightly in patients following autologous bone marrow transplant, despite the fact that 30% had problems with sexuality, fatigue, and depressive symptoms. These studies show that patients may report their quality of life as improved or unchanged, despite changes or deterioration in health. QOL measures in such situations are liable to yield discrepant results compared with the proposed symptom-burden measure. Further, results indicating that patients’ quality of life did not deteriorate may also imply that intervention need not be undertaken, possibly masking the issue of specific residual symptoms that require intervention.

Symptom-Burden Measures

Symptom burden is correlated with quality of life, and many QOL measures (eg, European Organization for Research and Treatment of Cancer [EORTC], Functional Assessment of Cancer Therapy [FACT]) have components that measure symptoms. Symptom severity is a strong predictor of scores on QOL measures[10] suggesting the potential of symptom-burden measures as an immediate indicator of deteriorating quality of life. For example, Bull and colleagues[11] studied quality of life among women with recurrent breast cancer. Results showed that self-reported physical symptoms were a strong predictor of postrecurrence ratings of overall quality of life. In a study of 206 adult patients with multiple myeloma, Poulos and colleagues[12] looked at the relationship between pain and mood disturbance, and the factors that influence quality of life. They found that pain and mood disturbance scores were significant predictors of quality of life in this group of patients.

Symptom-burden measures may be more informative about true differences in patient status when
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Comparing treatments. A randomized clinical trial compared the quality of life of patients treated with single-agent paclitaxel vs doxorubicin as first-line therapy for advanced breast cancer.[13] Quality of life was measured using the EORTC Quality of Life Questionnaire (QLQ)-C30 and the Rotterdam Symptom Checklist. Results showed that no statistically significant differences were observed in either the functional scales or the global QOL scores during the third cycle of chemotherapy. However, cross-sectional analyses of data at the end of cycle 3 showed that patients in the doxorubicin arm had significantly more nausea/vomiting and loss of appetite than those in the paclitaxel arm. The authors concluded that there is a trend toward greater burden of disease and treatment and lower general health status associated with doxorubicin therapy.

When using QOL measures, components assessing symptom burden are more responsive indicators of changes in patient status. For example, a 1985 randomized phase III study compared patients with low-grade cerebral glioma who received high-dose (59.4 Gy in 6.5 weeks) vs low-dose (45 Gy in 5 weeks) radiotherapy with conventional techniques.[14] A QOL questionnaire, consisting of 47 items that assessed a range of physical, social, psychological, and symptom domains, was included in the trial to measure the impact of treatment over time. No difference in survival was observed between the two treatment strategies.

The authors also report that, in general, the results suggest no major differences in quality of life between the two treatment arms. However, patients who received high-dose radiotherapy reported significantly more fatigue/malaise and insomnia immediately after radiotherapy, and poorer emotional functioning at 7 to 15 months post-randomization. For the remaining QOL domains, no statistically significant differences between the two treatment arms were found. The authors concluded that conventional radiation therapy for low-grade cerebral glioma using an administration schedule of 45 Gy over 5 weeks is at least as good as prolonged treatment in terms of clinical efficacy, survival, and quality of life.

‘Response Shift’

Why might more general QOL measures fail to reflect increasing or persistent symptoms and associated distress? This paradox has been addressed by several investigators. For example, it has been proposed that such findings may be due to the phenomenon of “response shift.”[15] Response shift is described as occurring because of changes in patients’ internal standards and conceptualization of quality of life over the course of disease, which is an inherent process of adjusting to the illness. Several attempts have been made to suggest ways of correcting for this response shift. The studies cited above, however, suggest that simple symptom measures may be less sensitive to this attempt to redefine standards by which patients judge their overall quality of life.

Symptom burden may have advantages compared with QOL measures when interpreting potential outcomes for patients. In clinical practice, it may be difficult to make sense of improvement in QOL scores. For example, the finding that a treatment is associated with a 10-point improvement in quality of life as opposed to a 15-point improvement is not intuitive to either clinician or patient. Because of this, interpreting findings presented as improvements in quality of life for patients brings with it challenges when discussing treatment options. In contrast, both patient and clinician should have an easier decision to make when given the information that, although two treatments produce a similar survival benefit, one is associated with significantly less pain, fatigue, and sleep disturbance.

Prevalence and Adverse Impact of Multiple Symptoms

Studies have assessed the prevalence of symptoms at different stages of the disease. Among cancer patients, symptoms may be the result of the disease itself or side effects from cancer therapies. For example, even when their disease is in remission or cured, cancer survivors continue to experience physical, affective, or cognitive symptoms. These symptoms may be due to the physiologic changes associated with prior treatments, delayed side effects of treatment, or the long-term consequences of the disease.

Most symptoms and side effects (pain, vomiting, fatigue) have been studied in isolation, with the possible crude ratings of "toxicities" associated with new therapies. The study of the prevalence and severity of sets of symptoms (sometimes referred to as symptom clusters[16]) is relatively new, even though the co-occurrence of multiple symptoms is obvious to both cancer patients and clinicians. Understanding the impact of symptoms acting together is critical for the construct of symptom burden.

Portenoy et al assessed multiple symptoms in a random sample of inpatients and outpatients with
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The most frequently reported symptoms were lack of energy, worry, sadness, and pain. In a prospective study of 1,000 patients with advanced cancer, Donnelly et al.[18] found that pain, fatigue, and anorexia were among the 10 most prevalent symptoms in all 17 primary sites studied. When pain, anorexia, weakness, anxiety, lack of energy, easy fatigue, early satiety, constipation, and dyspnea were present, a majority of patients rated them as moderate or severe. A second prospective study evaluated 1,635 cancer patients referred to a pain clinic[19]. In addition to pain, patients reported an average of more than three additional symptoms. The most common were insomnia, anorexia, and constipation. One in five patients also reported sweating, nausea and vomiting, dyspnea, dysphagia, and neuropsychiatric symptoms. Similarly, a prospective study of cancer patients in palliative care centers in Europe, Australia, and the United States found that pain (57%) and weakness (51%) were the most frequently reported symptoms.[20] Weight loss, anorexia, constipation, nausea, and dyspnea were also common. These studies suggest the high prevalence of symptom burden among patients with a given disease or treatment.

Common symptoms of cancer and cancer treatment have also been found to adversely affect patients’ daily functioning, and have become a major health problem in their own right. The adverse impact of pain, for example, on health outcomes such as function,[21-23] affective status,[24-26] and quality of life[27,28] among patient populations is well documented. Symptoms that are unrecognized by treatment teams may also become so severe that emergency room visits or hospitalization are required for management, adding substantially to the cost of treatment and to disruption of the patients’ routines and those of their families. Untreated symptoms may also negatively influence treatment efficacy by interrupting therapy.[29] Multiple and severe symptoms present a significant challenge to the resources of those who care for and manage cancer patients. For example, intensive cancer therapies produce severe and sometimes life-threatening side effects, resulting in the inability of patients to care for themselves and in total dependence on caregivers.[30]

Measuring Symptoms and Symptom Burden

Patient outcome measures, especially when they must be repeated several times, need to be easy to use and intuitive. Symptom scales easily meet these requirements. An ideal tool for measuring symptom burden should focus on the most prevalent and distressing symptoms for the group of patients who will use the scale. Long scales with exhaustive symptom lists tire patients and reduce their interest in completing them. Symptom scales should also assess the patient’s perspective of the collective impact of symptoms on different activities.

Several symptom scales have been developed for use with cancer patients. Any of these scales, if the salient symptoms and the degree to which these symptoms interfere with patient functioning are represented, could serve as the basis for measuring symptom burden. Such scales include the Symptom Distress Scale,[31] the Memorial Symptom Assessment Scale,[32] and the Rotterdam Symptom Checklist.[33]

The M. D. Anderson Symptom Inventory

We have developed the M. D. Anderson Symptom Inventory, a brief measure of the severity and impact of cancer-related symptoms.[34] It is based on our previous efforts in assessing the severity and interference of single symptoms, including the Brief Pain Inventory and the Brief Fatigue Inventory.[35] The "core" M. D. Anderson Symptom Inventory (see appendix 1) is a 19-item scale consisting of 13 symptoms frequently reported by cancer patients: pain, fatigue, nausea, disturbed sleep, emotional distress, shortness of breath, lack of appetite, drowsiness, dry mouth, sadness, vomiting, remembering, and numbness or tingling. It also contains six items that describe how much the symptoms have interfered with different aspects of the patient’s life over the past 24 hours: general activity, mood, walking ability, normal work (including both work outside the home and housework), relations with other people, and enjoyment of life.

Both the symptom and interference items are rated on an 11-point scale, with 0 indicating "does not interfere" and 10 indicating "completely interferes." The validation process for the M. D. Anderson Symptom Inventory has been reported elsewhere.[34]

Interpreting Symptom Scale Results

The use of any of the measurement scales described above should facilitate and improve the symptom-assessment process, help direct treatment choices, and supply information about the effectiveness of treatment. Providing patients and clinicians with additional information to help them interpret the relative severity of a score should be helpful. Based on our experience with pain, we have found that the relationship between symptom severity and the degree of the symptom’s
interference in functions such as activity and mood may help determine the level of symptom severity, which may, in turn, direct treatment. In particular, we have found that pain intensity ratings have a corresponding degree of interference with function. Mild, moderate, and severe pain differentially affect the function of cancer patients[22]: A rating of 1-4 on a 0-10 scale corresponded to mild pain, 5-6 to moderate pain, and 7-10 to severe pain. Cut-off points such as these are now incorporated into several guidelines for the management of pain. Recent studies also indicate that the severity of cancer-related fatigue can be classified in the same fashion, suggesting that a patient’s report of fatigue severity might directly contribute to treatment recommendations.[35] A similar methodology might be applied to other cancer-related symptoms (ie, sleep disturbance, negative affect, cognitive impairment) to help determine levels of severity that may help guide treatment decisions.

Studies of Symptom Burden

Symptom burden is not a new concept in studies of disease and treatment. Desbiens and colleagues[36] report the "symptom burden" and associated factors in a cohort of 1,582 seriously ill patients admitted at five tertiary care academic centers in the United States. They found that pain, dyspnea, anxiety, and depression caused the greatest symptom burden. Accounting for 67.3% of all symptoms that were at least moderately severe at least half of the time were

- Dyspnea (19.2%)
- Pain (17.6%)
- Pain/dyspnea (7.6%)
- Anxiety (5.9%)
- Depression (5.0%)
- Anxiety/depression (4.4%)
- Anxiety/depression/pain/dyspnea (3.9%), and
- Nausea (3.7%).

Hospital, male gender, disease category, more comorbidities, more dependencies in activities of daily living prior to illness, and poorer quality of life were associated with greater symptom burden. In their evaluation of the prevalence of and the QOL factors associated with self-reported depression in 987 patients with inoperable lung cancer, Hopwood and Stephens found that depression was self-rated in 322 patients (33%) before treatment and persisted in more than 50% of patients.[37] Pretreatment physical symptom burden and clinician-rated physical symptoms were independent predictors. Physical symptom burden was measured as the number of physical items reported in the Rotterdam Symptom Checklist.

Clinical Benefit Response

Changes in the severity and impact of single symptoms, such as pain, vomiting, and sleep disturbance, are often primary outcome measures for clinical trials targeted at reducing or preventing these symptoms. Recently, some trials have used combinations of symptoms and other outcomes in an attempt to approximate ecologically valid clinical outcomes. One such attempt is the clinical benefit response developed by Burris et al.[38] Clinical benefit response has been used in trials of agents in cancers with an extremely poor prognosis, such as pancreatic and lung cancer. In a study of gemcitabine (Gemzar) for pancreatic cancer, Burris et al[38] used clinical benefit response as a primary outcome measure. Clinical benefit response was defined as a dichotomous outcome, with a positive response being defined as (1) an improvement in one or more symptoms, (2) a reduction in analgesic usage, and (3) a specified improvement in performance status. In order to be counted as a positive responder, improvement had to be sustained for at least 4 weeks. A specified weight gain could be added as a secondary measure.[38] In the first major trial using clinical benefit response, the measure was presented as a synopsis of expected palliative changes from previous trials. Clinical benefit response was used as a primary outcome measure even though the investigators acknowledged that no prospective evaluation (or validation) of the clinical benefit outcome had been undertaken. Gemcitabine was approved by the FDA as well as in the United Kingdom, based primarily on a modest survival advantage. The clinical benefit response was not recognized as a validated outcome.[39] Patients with lung cancer also receive only a modest survival benefit from cancer therapies, so palliation of symptoms becomes a major therapeutic goal. A recent trial comparing gemcitabine and
cisplatin/vindesine in advanced non-small-cell lung cancer illustrates an even more symptom-focused outcome.[40] The primary outcome measure for this trial was also a combined clinical benefit measure, this time composed of (1) the mean of weekly symptom ratings of six symptoms from the Lung Cancer Symptom Scale,[41] (2) improved, stable, or worsening Karnofsky performance status, and (3) weight. The time to worsening of clinical status was defined as the time from randomization to the first evidence of worsening postbaseline.

**Symptom-Specific Measures**

The effects of a treatment may occasionally be reflected in both global measures of quality of life as well as symptom-specific measures. For example, recent large phase IV community trials of erythropoietin in anemic cancer patients have shown that an increase in hemoglobin has been associated with improvements in ratings on measures of quality of life. These improvements were noted on both linear analog scales[42,43] and the FACT-Anemia subscale (FACT-An, see Appendix).[43] One of the scales demonstrating improvement was a linear analog rating of energy, suggesting that patients were less fatigued.

A recent incremental analysis[44] of the second data set suggested that there was a nonlinear relationship between increasing hemoglobin and quality of life. An incremental analysis is a regression technique that attempts to identify maximum benefit (in this case improvement in quality of life) as it relates to another variable (in this case hemoglobin). This analysis indicated that the relationship was nonlinear, with the maximum benefit occurring when hemoglobin levels reached 12 g/dL.

The FACT-An contains several symptom-specific items, and it would be interesting to identify other areas of symptom improvement that may have benefited from the correction of anemia. The literature on the treatment of anemia in dialysis patients has documented the association between the resolution of anemia and the relief of several symptoms, including sleep disturbance, depressed affect, and appetite[45] as well as improved daytime alertness[46] and cognitive test performance.[47,48] In the anemia of cancer studies, supplementing QOL measures with multiple symptom scales could yield information about specific symptom areas that might be expected to improve, and how much symptomatic improvement might be expected. Such information would be useful to patients, physicians, and those who make decisions about funding or approving therapies.

**Treating Symptom Burden: When Is it Justified?**

The development of treatments that produce symptom relief or a QOL outcome as their primary focus generates the need to consider how these therapies might be deployed and accepted by the audiences who will be the target of clinical data concerning these treatments. Symptom burden may provide a conceptual focus for decisions about treatment allocations, research prioritization, and health policy.

The treatment of symptoms, such as fatigue, emotional distress, sleep disturbance, and cognitive slowing, presents a challenge from both assessment and interpretation perspectives. Just how much symptom improvement is worth the effort, in terms of research, development of new agents, the approval process, establishing practice, and reimbursement standards?

Over the last 20 years, changes in the treatment of cancer-related pain have been significant. Although several issues still lead to undertreatment of pain, the treatment of cancer-related pain presents a model for how to think of the evolution and acceptance of the treatment of other symptoms.

- First, the adverse impact of pain on patient comfort and function is now well established. Several studies have demonstrated that cancer pain is pervasive, especially when patients have metastatic disease, and that moderate-to-severe pain impairs function. Studies have also documented pain that was undertreated with available methods, and that oncologists recognized that it was undertreated. The positive effects of treating pain on patient comfort and function have now been so clearly demonstrated that few would deny that patients are entitled to treatment for cancer-related pain.
- Second, in the case of pain, a variety of effective treatment strategies are available, many with acceptable side-effect profiles.
- Third, several consensus-based and evidence-based guidelines that provide treatment recommendations for pain management have become available.
- Fourth, effective pain treatment is valued not only by patients and their families but also by health-care professionals, policy makers, and the general public.
Finally, in recognition of the need to manage pain, accrediting bodies such as the Joint Commission for the Accreditation of Hospital Organizations have developed standards for both the assessment and management of pain.[49]

The approach to the treatment of other symptoms in cancer, such as fatigue, depression, and sleep disturbance is less systematically developed than the treatment of pain. For further development in this area, researchers must first establish that a single symptom or combined set of symptoms is prevalent and severe enough to cause distress as well as loss of function to significant numbers of patients. Second, evidence that supports the effectiveness of treatment for these symptoms must be demonstrated. Third, effective symptomatic treatments, since they can be viewed as elective, need to minimize negative side effects. For example, a treatment for fatigue that causes significant sleep disturbance would be unacceptable. Guidelines for both the assessment of these symptoms (when to treat) and treatment (how to treat) need to be in place, and established as standards. Finally, data describing the cost and benefit of symptom reduction need to be available for public debate and the consideration of approval and funding agencies; how much is an improvement (small, medium, large) in symptom burden worth?

Future Development of Symptom Burden as an Outcome Measure

The acceptance of symptom burden as a patient outcome measure for clinical trials, clinical treatment, and policy decisions will require further conceptual elaboration and clinical research. The evolution of research in cancer-related pain suggests how symptom-burden research might evolve. For example, as seen above, studies that describe the prevalence and severity of multiple symptoms among cancer patients are relatively new. These studies have depended on the development of scales that can reliably capture differences (in quality, severity, and impact) between cancer-related symptoms and symptoms experienced by others who do not have cancer (eg, Mendoza et al[35]).

In terms of symptom burden, the development of methods for its measurement will give us the tools necessary to conduct the descriptive and epidemiologic studies that define who will experience severe symptom burden, what symptoms contribute most to symptom distress, and what factors correlate with its development. This should lead to a subset of symptoms (such as pain, cognitive problems, fatigue, depression, and sleep disturbance) that account for the bulk of symptom burden and become the target of the most aggressive therapeutic development and testing. An additional need is to determine the chronicity of both disease and treatment-related symptoms. As with pain, we need to determine the prevalence, severity, and impact of symptom burden throughout the course of disease: at diagnosis, during treatment, when cancer is in remission or cured, and, for some patients, near the end of life. More chronic symptoms will obviously have greater weight in overall symptom burden.

Now that we have scales that successfully capture multiple symptoms and the distress they cause, we are very much in need of longitudinal studies of symptom clusters or patterns in large numbers of patients. We need to be able to specify risk factors (disease, stage, type of treatment) that are associated with increased symptom burden, as well as "host" factors (such as gender, age, ethnicity) that may influence symptom-burden status. We need to continue to look at potential causes, both through clinical studies that examine correlates of symptom burden and those that examine what might improve symptoms.

Data on potential biologic correlates of the mechanisms underlying symptoms (such as hemoglobin, albumin, and the inflammatory process) might be collected at the same intervals as symptom-burden measures. These data could be a rich source of hypotheses about potential new therapeutic approaches to symptom management. It would be helpful to standardize symptom-burden measures, cognitive and affective assessments, and measures of potentially correlated biological variables across institutions in order to develop large databases that would best yield common patterns, enabling the identification of therapies that benefit more than one symptom at the same time.

With further development, symptom burden has many potential benefits as a patient-outcome summary measure. Symptom burden should be responsive to appropriate treatment. It should be sensitive to differences in treatment toxicities. It should be easy for patients, health-care professionals, and policy makers to understand and use as the basis for treatment choices and priorities. Finally, if symptom-burden data are collected along with biologic markers of potential mechanisms that may cause symptoms, measures of symptom burden have the potential for identifying new treatment strategies.
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