PEDIATRICS PERSPECTIVES

Opportunities to Treat Toxic Stress

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The American Academy of Pediatrics publications on trauma-informed care and toxic stress[1–3] are timely as our children face an increased risk of toxic stress from the myriad adversities heightened by the coronavirus disease 2019 pandemic. The American Academy of Pediatrics, like much of the medical field, has done tremendous work on the primary prevention of toxic stress: preventing child abuse, boosting relational health, and addressing social determinants of health and unmet social needs.[1–3] However, through our work on California's Adverse Childhood Experiences (ACEs) Aware Initiative, and observing rising mental and physical health needs in our patients through the pandemic, we worry that primary prevention and addressing social needs are not enough.

Although it is imperative to focus on preventing toxic stress altogether, primary prevention efforts will not prevent all childhood adversity, and some children will still experience the negative effects of the toxic stress response. In these cases, we believe that the pediatric community has a vital opportunity to advance secondary and tertiary prevention by addressing the toxic stress response as a health condition that is amenable to treatment.[4,5] In addition to promoting primary prevention and nurturing relationships and environments (external factors), pediatric clinicians could also provide early detection and treatment of the neuro–endocrine–immune–metabolic physiologic disruptions that characterize the toxic stress response (internal factors). (Fig 1)

TOXIC STRESS AS A TREATABLE HEALTH CONDITION

Emerging evidence indicates that the toxic stress response may be a treatable physiologic link between ACEs and an increased risk for a wide variety of mental and physical health conditions. Exposure to 4 or more ACEs is associated with numerous pediatric health conditions, including, but not limited to, asthma (odds ratio [OR] 1.7–2.8), allergies (OR 2.5), headaches (OR 3.0), overweight and obesity (OR 2.0), poor dental health (OR 2.8), learning and/or behavioral problems (OR 32.6), depression (OR 3.9), attention-deficit/hyperactivity disorder (OR 5.0), first use of alcohol before age 14 (OR 6.2), and early sexual debut (OR 3.7).[4,6]

The toxic stress response is defined as the prolonged activation of the stress response when a child experiences strong, frequent, and/or

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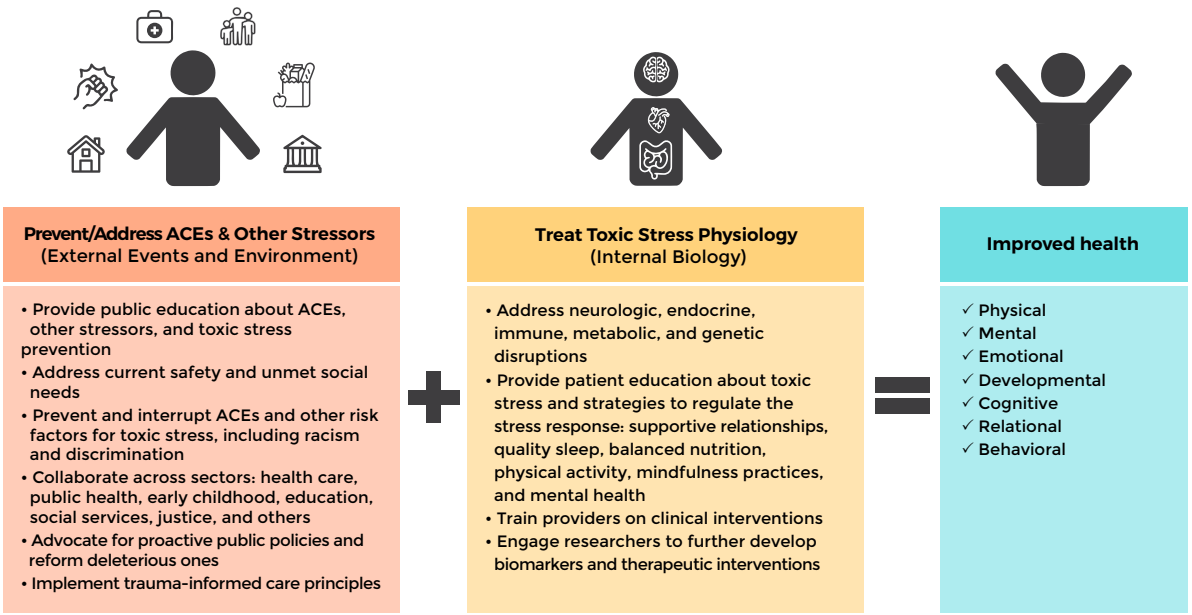

FIGURE 1
Pediatric clinicians are in a unique position to prevent and address our patients' ACEs and other stressors, as well as to treat their toxic stress physiology through evidence-based and evidence-informed stress mitigation strategies. Doing both can lead to improved health and well-being for our patients. Adapted with permission from Ortiz et al[14]

prolonged adversity in childhood without adequate buffering factors, leading to disruptions in neurologic, endocrine, immune, metabolic, and/or genetic systems.[7] Childhood adversities could include experiences such as abuse, neglect, caregiver substance misuse/dependence or undertreated mental illness, racism and discrimination, and/or exposure to violence.[1,3–7] The subsequent neurodevelopmental and physiologic disruptions can "increase the risk for stress-related disease and cognitive impairment, well into the adult years."[7] After children have the neurodevelopmental, endocrine, metabolic, and/or immune disruptions characterizing the toxic stress response and are at risk for, or develop, health conditions associated with ACEs, ensuring safety and resolving the current stressors alone may not be enough to treat the underlying disruptions in physiology.

There is a vital opportunity to push the research and clinical practice of trauma-informed, toxic stress-responsive care forward to include the explicit treatment of the toxic stress response (ie, its root neurodevelopmental and physiologic disruptions) as a core component of addressing health conditions associated with ACEs.[4,5] Although the specific causal pathways between ACEs, toxic stress, and health outcomes are still being investigated, the Office of the California Surgeon General's *Roadmap for Resilience* report[4] summarizes growing evidence that toxic stress-responsive clinical interventions (supportive relationships, physical activity, nutritional strategies, quality sleep, mindfulness practices, experiencing nature, and trauma-specific mental health interventions) could regulate autonomic and hypothalamic–pituitary–adrenal axis systems and improve the neurologic, endocrine, metabolic, and immune dysfunctions that are the hallmarks of toxic stress physiology.[4,5,8] These strategies could be implemented through patient education, additions to usual treatment plans, and referrals to cross-sector networks of care.

These strategies can also be integrated with primary prevention and social needs efforts. While addressing current safety, increasing access to basic needs such as food and shelter, and advocating for antiracist and antipoverty public health and government policies, clinicians could simultaneously connect patients to positive experiences and interventions aimed at regulating the stress response system. (Fig 1)

For example, mindfulness practices reduce stress-related neuroendocrine, immune, and metabolic markers such as cortisol, C-reactive protein, tumor necrosis factor α, blood pressure, heart rate, and triglycerides.[9] Research suggests these mindfulness practices may be especially beneficial for patients at risk for elevated cortisol levels, including those with cardiovascular disease, type 2 diabetes, depression, posttraumatic stress disorder, and those living under stressful life circumstances.[10] Thus, connecting families to mindfulness-based interventions can be an

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additional treatment modality for health conditions associated with ACEs. Patient-centered, strengths-based, and motivational interviewing strategies can be used to partner with patients to identify which stress mitigation strategy to start with, and providers can use improvement of the ACE-associated health condition as a potential indicator of intervention effectiveness. More research is needed to establish effective doses of these interventions and their utility in specific subpopulations, as well as clinically useful diagnostic and prognostic biomarkers for toxic stress.[11]

Pediatric clinicians could, therefore, be at the forefront of testing and translating the science into clinical practice.[11] For example, emerging research reveals that early life stress may be associated with decreased glucocorticoid and β-adrenergic receptor expression.[12] This could have significant implications for treating children with early adversity and conditions like asthma, who may not be responding well to traditional steroid and β-adrenergic medications. Medical providers have a unique role in addressing these underlying physiologic links between adversity and health as part of the larger bio–psycho–social efforts to address trauma.

Although there are additional interventions being studied in the mental health and neuroscience fields, clinicians can start now by integrating clinical interventions that are both safe and potentially effective.[13] In addition to promoting relational health,[1] clinicians can supplement usual care with additional trauma-responsive strategies for mindfulness, sleep, nutrition, physical activity, experiencing nature, and mental health referrals.[4,5,8]

A CALL TO ACTION

The field of ACEs and toxic stress has advanced beyond "What is wrong with you?" to "What happened to you?" and "What is right with you?" We believe we need to go one step further and also ask, "What is healing for you?" The answer is multifactorial and can include evidence-based interventions that specifically target an individual's underlying neurologic, endocrine, metabolic, immune, and genetic dysregulation if they have toxic stress. We believe the field of pediatrics has a vital opportunity to advance a multidisciplinary approach to treatment and healing from toxic stress by taking the following actions:

1. Help patients understand the potential links between childhood adversity, stress physiology, and their health condition(s) or risks.
2. Assess patients for clinical risk of toxic stress by assessing for adversity, health conditions potentially associated with adversity (eg, asthma, obesity, attention-deficit/hyperactivity disorder, and mental health conditions),[4–7] and protective factors.
3. For patients with clinical signs of toxic stress, consider supplementing standard care with evidence-based and evidence-informed toxic stress mitigation interventions that could specifically regulate the underlying neuro–endocrine–immune–metabolic disruptions.[4,5,8–10]
4. Partner with cross-sector community networks of care, such as home visiting programs, 2-1-1 call centers, and Boys and Girls Clubs to offer toxic stress-responsive interventions; clinicians do not have to do this work alone.
5. Develop resources and referral networks for trauma-specific mental health interventions and approaches for those exhibiting neuropsychiatric symptoms that address toxic stress neurobiology, such as eye-movement desensitization and reprocessing, neurofeedback, child-parent psychotherapy, and the Neurosequential Model of Therapeutics.[4,8]
6. Create policies and systems that provide clinicians with the time, resources, and support to implement assessment and intervention strategies for adversity and toxic stress into routine workflows.
7. Create training, continuing education opportunities, models of care, and quality improvement tools that incorporate the growing research on adversity and toxic stress as a core competency for trainees in medical schools, residencies, and fellowships.
8. Advocate to expand funding and incentives for toxic stress research into more precise biomarker-based diagnostics, tracking of treatment response, and therapeutic targets.

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ABBREVIATIONS

ACE: adverse childhood experiences
OR: odds ratio

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