

Endocrine-Related Adverse Conditions in Pediatric Patients Treated with Immune Checkpoint Inhibitors: A Position Statement from the Clinical Practice Committee of the European Society for Pediatric Endocrinology.

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New cancer therapies encompass immune-regulatory monoclonal antibodies that inhibit immune checkpoints, also designated as immune checkpoint inhibitors (ICIs). These agents function in one of two ways: either by blocking the interaction between programmed cell death 1 (PD-1) and programmed cell death ligand 1 (PD-L1) or by inhibiting cytotoxic T-lymphocyte antigen 4 (CTLA-4), thereby enhancing existing anti-tumor T-cell responses that have been rendered ineffective by inhibitory pathways. The first checkpoint inhibitor to be approved by the FDA was ipilimumab in 2011 for the treatment of advanced melanoma in adults, and the first phase I trial of ipilimumab in children was published in 2016. The FDA subsequently approved the use of this drug for adolescents in 2017. The utilization of ICIs has improved outcomes for numerous adults affected by advanced, relapsed, or refractory malignancies, and their use continues to expand rapidly. Initial studies in pediatric populations have demonstrated the efficacy of ICIs in Hodgkin's lymphoma and anaplastic large cell lymphoma, pediatric central nervous system tumors, and SMARCB1-deficient tumors [1 – 3]. While ICIs are still mostly in phase I/II trials for resistant cancers in children, concerns have been raised due to common and well-documented immune-related adverse events (irAEs) in adult patients [4]. These conditions may lead to long-term health complications, such as hormone deficiencies and autoimmune manifestations, potentially affecting quality of life and therapeutic outcomes. The current position statement aims to highlight the current knowledge and gaps in ICI irAE on the endocrine system in children.

The most frequently observed endocrine irAEs include adrenal insufficiency (AI), diabetes, thyroid dysfunction, and hypophysitis. In pediatric patients treated with ICIs, the occurrence of hypophysitis and primary AI is very rare. Most endocrine dysfunctions usually occur within the first weeks to months of initiating treatment with ICIs. However, some of the endocrine dysfunctions can emerge more than 1 year after the initiation of ICI treatment. These irAEs often have irreversible effects on endocrine function. Combination therapy is a risk factor for many irAEs. While pediatric-specific data are limited, adult studies provide insight into the frequency, management strategies, and potential links between endocrine irAEs and improved survival [4 – 6]. For the pediatric age group, three reviews on the topic have been published to date [7 – 9]. We completed their references with studies that were published in 2024. For specific endocrine irAEs, recent literature provides the following information.

Hypophysitis is a rare inflammation of the pituitary gland that has become more common since the emergence of ICIs, affecting 1–18% of patients under treatment. ICI-induced hypophysitis (IIH) may present with single or multiple anterior pituitary hormone deficiencies (ACTH>TSH>LH/FSH), with or without pituitary enlargement. The mechanisms of IIH are not fully understood, but it appears that anti-CTLA-4 agents may directly target anterior pituitary tissue, while other ICIs rather induce existing pituitary-reactive immune cells. In adults, the risk of IIH is highest with anti-CTLA-4 agent therapy compared to anti-PD-1 and anti-PD-L1 therapies. Most patients who develop central AI due to IIH have very low cortisol levels, require hormone replacement therapy, and recovery is rare. Yet, IIH is not a contraindication to continue ICI therapy [10].

ICI-induced primary AI occurs in 1–2% of adult patients receiving single-agent (PD-1/PD-L1) or (CTLA-4) therapies and in a higher range of 4–9% when ICIs are used in combinations. Median onset is after 10 weeks of ICI treatment, maybe earlier in children [11 , 12].

The overall incidence of ICI-induced diabetes in adults is 0.45–2%, and 1–9% in children [8]. In adults, preexisting type 2 diabetes, polygenic risk for type 1 diabetes and treatment with combination with ICI are independent significant risk factors. Three primary phenotypes of ICI-induced diabetes can be identified based on C-peptide levels at the time of diagnosis: high, low, or undetectable C-peptide levels. Half of the low-undetectable C-peptide ICI-induced diabetes is antibody negative. Patients with undetectable C-peptide and positive islet-specific autoantibodies had a more fulminant presentation [13].

Among the endocrine adverse events, thyroid dysfunction is one of the most frequent both in adults and pediatric patients. The incidence of anti-CTLA-4 mAb-induced thyropathy, for instance, due to tremelimumab and ipilimumab, varies but remains relatively low, while pembrolizumab and nivolumab (targeting PD-1 inhibition)-treated patients have higher rates of thyropathy [7]. In pediatric patients, hypothyroidism can occur in 1–20% of patients and hyperthyroidism in 1–15% of patients [8]; mostly occurring a few weeks after treatment starts. Thyroid dysfunctions are immune-mediated thyrotoxicosis (mostly due to anti-PD-1 antibodies) that can be followed by hypothyroidism [14]. The presence of anti-thyroglobulin autoantibodies and anti-thyroperoxidase autoantibodies during the thyrotoxicosis phase is a risk factor for developing hypothyroidism. Subclinical hypothyroidism has also been described.

All ICI can induce new-onset hypothyroidism or exacerbate preexisting thyroid dysfunction. The recovery rate is poor. However, ICI treatment is usually not discontinued if it is effective against tumors, but thyroid replacement therapy is a manageable option.

Pediatric literature on endocrine irAEs of ICIs is scarce. Most information, therefore, comes from adults, and this has the following consequences. Pediatric-specific guidelines: a paucity of standardized protocols exists for the monitoring, diagnosis, and management of endocrine irAEs in children. Emphasis is required regarding aspects of growth and pubertal development, and metabolic effects in the pediatric age group.

Long-term outcomes: the lifelong implications of pediatric endocrine irAEs and their interaction with cancer survivorship remain unclear.

Biomarkers and screening: identifying predictive biomarkers (e.g., a combination of genetic predispositions and baseline autoantibody profiles) for irAEs in pediatric populations is an unmet need. Such studies have been very recently published in adults [13].

Therapeutic optimization: the endocrine irAEs are mostly irreversible, but hormone replacement therapies are efficient. However, the balance between managing irAEs and maintaining effective cancer immunotherapy requires further exploration in pediatric cancer therapy.

In view of the available evidence mainly based on adult reports, four actions may be implemented in children undergoing treatment with ICIs. 1. Enhance monitoring: diagnosis of irAEs can be challenging since subtle, non-specific symptoms at presentation may be diagnosed as the natural course of cancer progression or cancer therapy-associated side effects. Therefore, close monitoring of symptoms is important, and biochemical surveillance of hormone levels is essential for a correct diagnosis. Regular assessments of pituitary hormones, with special attention to thyroid, adrenal function, and glucose homeostasis should be conducted before, during, and after ICI treatment.

Collaboration between pediatric oncology and endocrinology/diabetes teams is crucial for early recognition and management of endocrine toxicities.

Hormone replacement therapies should be initiated promptly when deficiencies are diagnosed.

Prioritize pediatric-specific clinical trials and observational studies on ICI safety and efficacy.

Develop a database specifically related to pediatric anti-cancer drug-related endocrinopathies that will help develop guidelines based on age, tumor type, and underlying biology for risk management.

Patients and families should receive education about the potential endocrine risks of ICIs and the importance of timely symptom reporting.

An emergency card for AI should be given, especially in combination treatments with ICIs.

By addressing these gaps, we can ensure safer and more effective integration of ICIs into pediatric cancer care, with a focus on minimizing irAEs.

Prof. Dr. med. Christa E. Flück and Prof. Shlomit Shalitin were members of the journal's Editorial Board at the time of submission.

C.E.F., D.K., S.S., and K.B. performed literature review and wrote the manuscript. K.B. wrote the original draft and edited it. F.C. reviewed and validated the manuscript.