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INVITED REVIEW

Nonthyroidal illness syndrome in children

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Abstract Neuroendocrine changes in the hypothalamic–pituitary–thyroid axis during critical illness result in nonthyroidal illness syndrome (NTIS) characterized by abnormal thyrotropin (TSH) and thyroid hormone levels. Studies looking at the natural history of neuroendocrine changes during critical illness have revealed the presence of NTIS. NTIS has been described in a variety of patient settings. Many studies have tried to uncover the pathophysiology behind NTIS and several theories are proposed. Whether NTIS requires treatment or intervention is still controversial and the results of the treatment studies are arguably mixed. Whether implicitly stated or not, the underlying purpose of all the natural history, pathophysiology, or treatment studies is to determine whether NTIS is adaptive or maladaptive. Some studies have illustrated a correlation between illness severity and the degree of NTIS but a cause and effect relationship is still elusive. The human studies can be divided between those with either adult or pediatric subjects, with much less data available in the latter. This review examines the available literature on NTIS with an emphasis on the pediatric literature.

Keywords Nonthyroidal illness · Cardiac surgery · Thyroid · Pediatrics

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Introduction

Neuroendocrine changes in the hypothalamic–pituitary–thyroid axis result in nonthyroidal illness syndrome (NTIS) characterized by abnormal thyrotropin (TSH) and thyroid hormone levels. It is not clear whether, in the setting of critical illness, these changes are beneficial and promote recovery and are therefore adaptive, or if they are rather a direct result or cause of the illness and associated organ failures and are therefore maladaptive [1–4]. Other neuroendocrine changes involving other hypothalamic–pituitary axes can also occur in the setting of critical illness. These include increased serum cortisol levels [5, 6], insulin resistance [7, 8], altered growth hormone (GH) secretion [9–11], altered prolactin (PRL) secretion [11], and decreased serum testosterone [2, 12–16]. Those that suggest that NTIS and other neuroendocrine changes in critical illness may adversely affect outcome propose the use of hormonal intervention to improve outcome. This approach is controversial [4, 17].

Nonthyroidal illness syndrome is also referred to in the literature as sick euthyroid syndrome (SES), euthyroid sick syndrome (ESS), low triiodothyronine (T3) syndrome, and low T3–low thyroxine (T4) syndrome [3]. As discussed by De Groot, while the latter two names are merely descriptive of the biochemistry, SES and ESS convey a controversial assumption that the thyroid status is normal [4].

Nonthyroidal illness syndrome is characterized by low levels of T3, increased reverse T3 (RT3), normal to low T4, and normal to low TSH. There are some inconsistencies among the available studies in the reporting of NTIS, especially with free T4 (FT4) levels, due to differing assays and accepted cut-off levels [3, 18]. The controversy regarding the metabolic status and whether NTIS is adaptive

or maladaptive is essentially centered on the inappropriately normal or low TSH levels in the presence of low levels of T3 and T4. This is not consistent with the feedback mechanisms of the normal hypothalamic–pituitary–thyroid axis or primary thyroid disease. NTIS may also result in the loss of the normal nocturnal surge of TSH [19, 20].

Like other neuroendocrine changes, NTIS can occur with various forms of physiological stress or illness. Other clinical factors that may affect the thyroid function include cardiopulmonary bypass (CPB), dopamine, and corticosteroids.

A review of the literature reveals a list of studies that reveal the presence of NTIS in critical illness. Many studies have also tried to uncover the pathophysiology behind NTIS. Other studies, focused on the treatment of NTIS, show mixed and debatably controversial results. Studies involve both adult and pediatric subjects, but with much less data available in the latter. Whether implicitly stated or not, the underlying purpose of all the natural history, pathophysiology, or treatment studies is to determine whether NTIS is adaptive or maladaptive. This review examines the available literature on NTIS with an emphasis on the pediatric literature.

NTIS in adults

Through many studies, NTIS has been described in various settings in adult patients including starvation, fasting, intensive care, trauma, surgery, sepsis, cardiovascular disease, respiratory disease, burns, malignancy, bone marrow transplant, liver disease, and renal disease [4, 21–26]. One study describes NTIS in 251 of 329 inpatients, with a variety of diagnoses [23]. Many of the natural history and treatment studies of NTIS in adults focus on patients with cardiovascular disease and on those undergoing CPB surgeries [27–30].

Nonthyroidal illness syndrome has been compared to severity of illness in some studies involving adult patients. Rothwell and Lawler [22] illustrated that low levels of T4 and TSH, along with elevated cortisol levels, were superior prognostic indicators of mortality than the APACHE II score in their population of critically ill patients. Slag et al. [31] found that low T4 levels were highly correlated to mortality in critically ill patients. In burn patients, the degree of NTIS is greater in patients with larger burn sizes and in nonsurvivors [26]. However, an abstract by Lalani and Dhuper [32] describes higher mortality in septic shock patients with normal TSH levels compared to those with suppressed levels. These findings may imply that NTIS is an adaptive protection in those patients that survive septic shock.

NTIS in children

The literature on NTIS in children is less vast than that available in adults and the literature that is available on children largely focuses on the population undergoing cardiac surgery for congenital heart lesions. However, there are a handful of publications describing NTIS in children in noncardiac surgery settings [33–38].

Zucker et al.[33] studied 27 children, aged 4 months to 16 years, of which 9 were medical ICU patients and the remaining were cardiac surgery patients. Of the nine medical patients, six had below normal serum T4 and T3 levels, and TSH levels described as <2.5 μU/ml, at 24 h after admission to the ICU. In another study, Hashimoto et al. [36] found low normal T3 levels of less than 1.5 nmol/l, in 13 of 59 outpatients with acute respiratory illnesses. The authors label the three patients with T3 levels below 1.2 nmol/l as having NTIS. While a label of NTIS is debatable since the T3 values were still within the normal range, the possibility that these noncritically ill outpatients may represent a spectrum of thyroid dysfunction with noncritical illness is intriguing.

A few studies in the noncardiac surgery pediatric population have attempted to correlate thyroid hormone levels to outcome or illness severity. Uzel and Neyzi looked at 13 infants, between 1 month and 12 months of age, presenting with sepsis and/or pneumonia [34]. The study population's initial mean T3 was lower and RT3 was higher compared to healthy controls, and therefore consistent with NTIS. Six of the study patients died and their initial T4 levels seemed to be prognostic. These nonsurvivors' initial T4 values were lower than those in the control group, while the initial T4 values in the recovered group did not differ from those in the control group. The survivors group's T3 levels recovered to values comparable to those in the control group, while in the nonsurvivors group the T4 and T3 values remained low and did not recover.

An abstract publication by Mungan et al. [38] further illustrates how the degree of NTIS may be related to illness severity. In this study, total T3 (TT3), free T3 (FT3), total T4 (TT4), and FT4 levels were lower in 21 children with septic shock compared to 51 children with sepsis and 30 controls. In addition, the TT3 and FT3 levels, but not the TT4 or FT4, were lower in the children with sepsis than controls. Twenty-six children died and their TT3, FT3, TT4, and FT4 levels were lower than those in survivors.

However, another study of 26 children with meningococcal sepsis shows some contrasting results to other studies in regard to the possible positive adaptive response of NTIS [35]. In this study by Joosten and colleagues, all patients showed a degree of NTIS but the eight nonsurvivors showed "less" NTIS at initial presentation with lower RT3, higher TSH, and higher T3 levels compared to the

survivors. Within 48 h, the survivors showed decreasing levels of RT3 and increasing levels of TSH and T3 compared to their initial levels, but levels were still outside the normal ranges. Many of the same authors of this study published another study on thyroid function in 44 survivors of meningococcal sepsis [39]. Presumably, this study population is a continuation of the previous study. Again, levels were only measured up to 48 h after admission. All the children showed low TT3 and high RT3 levels, consistent with NTIS. At admission, the TT3 levels were significantly higher in the short versus long stay group. In addition, changes in TT4, FT4, TT3, RT3, and TSH toward normal levels within the first 24 h were prognostic and negatively correlated with duration of stay. A follow-up publication essentially confirmed the results of their previous smaller sample studies [40]. In this study, they now had a total of 69 children with meningococcal sepsis, which they analyzed as two separate groups, 45 who did not receive dopamine and 24 treated with dopamine. In the nondopamine group, TT4 levels were lower with increased disease severity since the nonsurvivors had lower levels than survivors, and the shock survivors had lower levels than the sepsis survivors. TT4 was also found to be negatively correlated with other clinical markers of illness severity such as critical illness scores. RT3 levels were higher in the shock versus sepsis survivors but in contrast they were lower in the nonsurvivors versus survivors leading to a higher TT3/RT3 ratio in the nonsurvivors. This is similar to what the group described in their 2000 publication [35]. The effects of dopamine were similar to their other previous report [39] with dopamine decreasing TSH levels but not affecting TT4, FT4, or TT3 levels. Multivariate analysis showed that higher TT3/RT3 ratios and lower TT4 levels increased the odds for mortality. These two results are somewhat contrasting. When IL-6 was added to the analysis, the thyroid hormone levels were no longer significant and increased IL-6 levels alone greatly increased the odds of mortality. The apparently contrasting results in the nonsurvivors showing "less" NTIS may be a factor of time. The nonsurvivors may have died prior to there being enough time for them to develop NTIS. Alternatively, the inability of this group to adapt to acute critical illness and develop NTIS may be a factor in their mortality.

In the neonatal population, Simpson et al. [37], like others, illustrated that T3 and T4 levels, but not TSH, were inversely correlated to severity of illness in premature infants. However, thyroid supplementation has not been found to be of benefit in this group [41–44].

There have been a good handful of studies that have specifically looked at the presence of NTIS in children undergoing cardiac surgery. The largest study, by Bettendorf et al. [45], studied 132 children undergoing surgery for a variety of congenital heart lesions. The study population was heterogeneous and comprised neonates and older children, aged 2 days to 16 years. Cardiac bypass was required in the large majority, but not all, of the patients, and the patients had a combination of acyanotic and cyanotic cardiac lesions. Thyroid function was measured preoperatively and then every other day for up to 3 weeks, however, median period of measurement was for only 5 days. A degree of NTIS was present in all the patients. The TSH and RT3 changes preceded the T3 and T4 changes. The nadirs of T3 and T4 were below the normal range. The FT4 had a statistically significant decrease but remained within the normal range. TSH, RT3, and FT4 levels recovered on postoperative day (POD) 5, while T3 and T4 levels were rising by POD 5 but were still below the preoperative levels. The degree of NTIS was worse in those patients who underwent CPB or received dopamine infusions. In regards to clinical outcome, this study found that a T3 nadir of less than 0.6 nmol/l was associated with a worse postoperative course. The patients with these lower T3 levels had increased hospital, intensive care, and ventilation days and also required increased inotropic support.

We performed a study at our center in 21 patients, aged 1 to 11 years, undergoing surgery for congenital heart lesions [46]. Patients were followed for 8 days up to POD 7. All children demonstrated NTIS. The mean TSH decreased to the lower limit of normal, the mean TT3, FT4, and FT3 index (FT3I) decreased below the lower limits of normal, and all the postoperative mean RT3 and T3 uptake (T3U) levels were well above normal within hours postoperatively. The TSH recovered back to preoperative levels by POD 4 with a possible rise above preoperative levels starting on POD 7. FT4 and arguably RT3 both recovered to preoperative levels, but TT3, FT3I, and T3U showed no evidence of recovery by POD 7.

Several smaller studies in children undergoing cardiac surgery similarly showed the presence of NTIS [33, 47–57]. As mentioned previously, Zucker et al. [33] followed 27 children of which 18 underwent cardiac surgery. The study period was short and thyroid function was measured for only 24 h postoperatively in the cardiac surgery patients. Evidence of NTIS was present by 24 h postoperatively. One of the cardiac surgery patients in this study died. His biochemistry was consistent with NTIS including a T4 of 3.1 mcg/dl (40 nmol/l). However, five of the surviving patients had even lower T4 levels.

Another study illustrated the presence of some aspects of NTIS preoperatively in 20 prepubertal children with congenital heart disease [55]. These changes were then worsened by surgery with typical decreases postoperatively in TT4, TT3, and FT3. FT4 and TSH remained normal. This study was unique in that serum binding proteins and thyroid hormone fractions were measured. T4-binding

globulin (TBG) and T4-binding prealbumin (TBPA), also known as transthyretin, were lower in these patients compared to controls. These differences were already evident preoperatively and did not change significantly postoperatively.

Saatvedt et al. [56] found typical changes of NTIS in 10 children, aged 23–68 months. T3, FT4, and T4 were measured frequently perioperatively including after induction of anesthesia, after heparin administration, 10 min after initiation of CPB, every 30 min during CPB, after weaning from CPB, at wound closure, and then at 2, 24, and 48 h postoperatively. TSH was measured once intraoperatively, at wound closure. The authors elected to "correct" the samples for hemodilution using a mathematical equation adjusting for the change in hemoglobin concentration. TSH, T3, FT4, and T4 all dropped below baseline levels to nadirs at 24 h after surgery. FT4 initially increased intraoperatively after initiation of CPB.

Murzi et al. [47] measured thyroid function in 14 patients, aged 18 months to 14 years, during CPB in addition to pre- and postoperatively. The TT3, FT3, and TT4 began to decrease significantly during CPB. NTIS was most severe between 12 and 48 h postoperatively. Two hours after surgery, the TT4 actually began to improve but then began to decrease again before recovering on POD 5. The FT4 remained stable during surgery but then began to decrease at about 6 h after surgery, reached a nadir at 72 h after surgery, and recovered by POD 5. The TSH increased during anesthetic induction, came down to baseline during CPB, and reached a nadir between 6 and 12 h after surgery. The TSH recovered by 72 h after surgery. Similar to the Bettendorf study [45], the TT3 and FT3 still remained below the preoperative values at study end on POD 6. The authors of this study hypothesize as to the possible mechanisms by which CPB itself could affect thyroid function. Based on the nonproportional changes of the TSH, T4, and T3, they conclude that the mechanism is not dilutional. They also noted that the patients had varying degrees of cooling during CPB but this did not seem to be a factor as there was no significant difference in the hormone levels between the normothermic and hypothermic patients. The authors therefore question whether nonpulsatile flow during CPB may blunt the pituitary response to TRH.

A study by Ririe et al. [51] looked further into hypothermia during CPB and its effects on the thyroid axis. The study looked at 23 children undergoing CPB during elective repair of a variety of congenital heart lesions. Twelve of the children underwent CPB with only mild to moderate cooling and the remainder underwent CPB with deep hypothermic circulatory arrest (DHCA) down to a median temperature of 18°C. The degree of cooling was not random but dependent on the age of the patient and type of surgery. Therefore, the two groups differed at baseline in regards to type of cardiac lesion, surgical procedure, age, and weight. Both groups showed similar changes in FT3, FT4, TT3, and TT4 consistent with NTIS. TSH levels remained low throughout the surgery in the group undergoing CPB alone. In contrast, after an initial decrease, the patients undergoing DHCA had a TSH surge during the CPB and surgery period with levels eventually surpassing baseline levels. The authors offer that this TSH surge may be normal and appropriate given the low T3 levels and therefore indicative of an intact hypothalamic–pituitary–thyroid axis preserved by the hypothermia. However, as acknowledged by the authors, the elevated TSH levels could also be a result of pituitary injury. By the morning of POD 1 both groups had similar TSH values.

Mainwaring studied the thyroid effects in a relatively uniform population of 10 neonates undergoing CPB surgery for either transposition of the great arteries or total anomalous pulmonary venous drainage [53]. The CPB prime solution was also analyzed. The FT3 and FT4 were higher in the prime solutions than the preoperative serum values, the TT3 was similar, and the TT4 and TSH were lower in the prime solutions. The exact patterns of the serum hormone changes are difficult to distinguish as there were no samples drawn between 24 h after surgery and POD 5. In other studies, Mainwaring has attempted to differentiate a thyroid response among the various types of congenital cardiac malformations. In one study, he followed the thyroid function in 14 newborns, aged 1–12 days old, all with hypoplastic left heart syndrome undergoing first stage Norwood reconstruction [52]. These children all had decreases in FT3 and TT3 levels starting with the initiation of CPB and reaching a nadir at 24 h after surgery. The levels recovered to preoperative levels on POD 5. In another study, Mainwaring et al. [54] compared thyroid function in one group of eight children undergoing modified Fontan procedures and a control group of six children undergoing various other open heart surgeries. Both groups showed evidence of NTIS postoperatively. However, the FT3, FT4, TT4, and TSH levels returned to baseline levels in the control group by POD 5 but remained below baseline in the Fontan group. The TSH returned to baseline in the Fontan group on POD 8. The FT3, TT3, FT4, TT4 reached nadirs in the Fontan group on POD 5 and were still below baseline on POD 8. The authors conclude that all children undergoing cardiac surgery have suppression of the pituitary–thyroid axis but NTIS is more prolonged in children undergoing the Fontan procedure compared to other surgeries. Our study also showed a more prolonged and greater degree of NTIS in Fontan patients [46].

It is thought that neonates and children of lower weight may respond differently than larger children. Like one of the Mainwaring studies [53], another group specifically looked at infants weighing less than 5 kg [57]. Ten infants

aged 7 days to 5 months, weighing between 2.8 and 4.7 kg, and undergoing surgery for either transposition of the great arteries, ventricular septal defect, or atrioventricular defect were followed. The CPB prime solutions used in six other similar surgeries, but not the specific solutions used with the 10 infants in the study, were analyzed and the TT3, TT4, and TSH levels were much lower than baseline serum levels in the study patients. The authors elected to "correct" the samples taken within 6 h from the start of CPB for hemodilution using a mathematical equation adjusting for the plasma albumin concentration. TSH, TT3, and TT4 levels decreased intraoperatively and then recovered transiently in the first few hours after surgery. After the initial decrease in TSH with the onset of CPB, the levels rapidly surged within 30 min to values much above preoperative levels and lasting for about 3 h. The TT3, TT4, TSH levels then decreased with eventual recoveries following patterns similar to other studies.

Both Mitchell and Mainwaring deliberate as to the effect that the CPB prime solution may have on intraoperative thyroid hormone levels. The prime solutions may have concentrations of TSH, T4, and T3 below or above the normal or preoperative baseline serum levels. Theoretically this could at least transiently alter patient serum levels following priming. Mitchell attempts to at least partially explain the thyroid hormone changes in his patients on the dilutional effect of the prime solutions [58]. In response to Mitchell, Mainwaring states that while some changes like the FT4 levels may be dilutional, the FT3 changes in his study patients cannot be a result of hemodilution based on analysis of the hormone levels in the prime solution used in the study [53].

One previous small study in pediatric patients attempts to compare thyroid function and illness severity. In this study, Allen et al. [50] followed the thyroid function in 12 children, aged 1 month to 9 years, undergoing cardiac surgery. Thyroid function was measured preoperatively and then on five more occasions up to 72 h after surgery. All the patients had evidence of NTIS. Illness severity was measured in this study using a modified Therapeutic Intervention Scoring System (TISS) score [59]. Through regression analysis, TISS scores had a correlation coefficient of -0.63 ± 0.17 with T3 levels, and 0.51 ± 0.18 with RT3 levels. Changes in illness severity preceded changes in thyroid function. This time frame relation led the authors to conclude that the thyroid function changes were not the cause of increased illness severity, but rather resulted from the critical illness.

Like Allen, we also correlated thyroid function with clinical outcome [46]. In our study, greater NTIS changes, especially changes in the triiodothyronine measures of TT3, FT3I, and T3U, were correlated to prolonged hospital stays with increased PICU and mechanical ventilation requirements. The hormone levels on POD 0 in the PM, drawn within 6–14 h from surgery, seemed predictive of clinical outcome. These early hormone measurements may be a valuable clinical tool in predicting clinical course. We also found that thyroid levels were related to the clinical status, as measured by the PELOD scores, of the preceding 24 h. Similar to the Allen study, this may suggest that alterations in illness precede changes in thyroid hormones.

All the studies illustrate that children undergoing cardiac surgery and some children with other critical illnesses have the biochemical changes consistent with NTIS. There is some minor variation in the natural history and time course depicted among the studies. The TSH nadir is usually early in the postoperative period with a range from POD 0 to 1 in the various studies. The timing of the TSH recovery is quite varied between the studies and ranged from POD 2 to 5, and was on POD 8 in the small study with eight patients undergoing the Fontan procedure [54]. The timing of the T3, T4, FT3, and FT4 nadirs were either on POD 1 or 2 for most of the studies. However, Fontan patients show later T3, T4, FT3, and FT4 nadirs and later recovery [46, 54]. Some studies showed thyroid hormone recovery on POD 5 or 6 while some others showed levels still below baseline at that time. Many studies did not follow the hormone levels long enough to comment on this. A few of the studies did nicely illustrate that the TSH and RT3 recoveries preceded the recoveries of the other thyroid hormones [45, 57]. Only a few of the studies followed FT3 levels. RT3 was also only followed by a few studies. Some studies that did follow RT3 found a peak on either POD 0 or 1 and a recovery on POD 3 or 5. In our study, RT3 rose immediately postoperatively and remained elevated up to POD 7, the end of the observation period. Our study also looked at T3U levels. T3U increased immediately postoperatively and remained high throughout the study period. It was strongly correlated to clinical outcomes [46]. T3U is rarely measured in previous NTIS studies. However, one study in adults found elevated T3U in NTIS [31]. To the best of our knowledge, no previous NTIS natural history study in children has measured T3U. T3U reflects the quantity of unoccupied TBG and TBPA sites. Higher T3U indicates less available sites. Increased T3U in our study was coupled with decreased TT3, FT3I, and FT4. Therefore, this likely reflects decreased levels of TBG and TBPA themselves, which would result in lower total hormone levels. It is theoretically not reflective of a binding inhibitor implicated in previous studies [60, 61], or to decreased binding secondary to severe illness as these should result in elevated free hormone levels. Low TBG and TBPA have been found in a previous study in pediatric cardiac surgery patients [55]. The low levels were already present preoperatively in that study. TBG has also been shown to be low in other examples of acute illness [62].

The available data on NTIS in children are still rather limited. There is the one large study of 132 patients although 48 of these patients were under 1 year of age and not all the patients required CPB making it a nonhomogeneous population [45]. The remaining studies' sample sizes are quite small. In addition, there are some wide time gaps between hormone measurements in some of the studies. Therefore, a detailed description of the natural course is arguably difficult. Only our study and two other studies compared the course of NTIS to clinical markers of illness severity [45, 46, 50]. Only ours and Allen's studies used a critical illness scoring scale.

Pathophysiology of NTIS

Patients with NTIS have decreased serum levels of TT3 and FT3 along with increased RT3 within hours of illness onset or surgery. With severe illness, the serum T4 level also decreases. These serum changes have been correlated with peripheral tissue hormone levels [63].

Altered activity of the iodothyronine deiodinases, D1, D2, and D3, has long been described as a major contributor in the pathophysiology of NTIS [64]. In the healthy individual, D1 is thought to be the major deiodinase and converts T4 to T3 and metabolizes RT3 to T2. In NTIS, it is believed that D1 activity is decreased while D3 activity is increased. This would neatly explain the elevated RT3 and low T4 and T3 levels found in NTIS. This theory was supported in a study by Peeters et al. [65] looking at post mortem blood, liver, and skeletal samples of 80 ICU patients. Their findings showed that D1 activity in the liver was downregulated, and D3 activity in the liver and skeletal muscle, areas where D3 is usually not present in healthy individuals, was upregulated. The D1 activity was positively correlated with the T3/RT3 ratios. An in vivo study in rabbits confirmed the downregulation of D1 and the upregulation of D3 in NTIS [66]. This study also found that D1 activity improved with TRH infusion. The D3 activity also normalized with TRH infusion but the addition of GH-releasing peptide-2 was required in order to normalize the RT3 levels. The authors conclude that these findings imply that D1 is suppressed by changes in the thyrotropic axis only but D3 is upregulated by changes in both the thyrotropic and somatotropic axes. Others have suggested that downregulation of D2 activity in peripheral tissue is a major factor causing decreased T3 levels in NTIS [67]. However, in a recent publication, Mebis et al. [68] found that D2 was not altered in acute critical illness compared to controls and in fact was upregulated in prolonged illness and inversely correlated to T3 levels.

The inappropriately normal TSH levels in the presence of low thyroid hormones in NTIS point to a possible central etiology of NTIS with an alteration in the hypothalamic–pituitary axis. This altered feedback loop between the hypothalamus, pituitary, and thyroid in NTIS is viewed by some as an appropriate adaptive mechanism to preserve energy. Post-mortem studies do show small thyroid glands in previously chronically ill patients [69]. Alteration in the axis is also evident by the decrease in TSH pulsatility and loss of the nocturnal TSH surge and circadian rhythm [27, 28]. Bartalena illustrated the loss of the nocturnal TSH surge for five nights in 10 surgical patients with NTIS [70]. Romijn and Wiersinga [20] found an absent nocturnal TSH surge in 15 of 26 medical patients with NTIS. A post-mortem study by Fliers et al. [71] further implicates a central etiology in the pathophysiology of NTIS. In this interesting study, they measured in situ TRH mRNA in the paraventricular nuclei of deceased subjects. TRH levels were low in those with chronic versus acute illness. Low TRH levels correlated with low T3 and TSH levels. This is in contrast to rat models of hypothyroidism with low T3 levels, where the TRH was elevated. Other studies have shown the possible benefit of TRH infusion in the treatment of NTIS [66, 72–74]. The alteration of the hypothalamic–pituitary axis as a major factor in NTIS is further supported by the fact that the other central axes are also affected in critical illness, such as the suppression of the gonadotropins.

Cytokines, such as interleukin-1 (IL-1), IL-6, and tumor necrosis factor (TNF) are elevated in NTIS in correlation to severity of illness and have therefore been implicated in its pathogenesis. One could argue, however, that NTIS occurs in severe illness and cytokines are merely a marker of severe illness. Cytokine levels, especially IL-6, and cytokine receptor protein levels have been shown to be negatively correlated to T3 and T4 levels in adults with NTIS [75–78]. These findings have been replicated in children undergoing cardiac surgery, and in children with acute respiratory infections [36, 79]. Bacterial endotoxin administered to mice induced elevated cytokine production, decreased 5′- deiodinase mRNA, and decreased T3, T4, FT4, and FT3 levels [80]. IL-6 or TNF infusions can result in biochemical alterations of thyroid hormones similar to those found in NTIS [81, 82]. However, attempts at neutralizing endogenous IL-6 have not prevented these NTIS hormone changes [83]. A complete explanation as to a mechanism of the cytokines' role in NTIS is unclear. However, a study by Yu and Koenig using rat hepatocyte cultures illustrated that IL-1 and IL-6, but not TNF-alpha, decrease the T3 induction of D1 [84]. The authors theorize that the increasing levels of cytokines successfully compete for gene transcription co-activators and therefore limit the supply for the deiodinase gene.

Leptin, a protein secreted by adipocytes, has also been studied as a possible factor in the pathogenesis of NTIS.

Leptin levels are decreased during starvation and fasting, two clinical states classically associated with NTIS. Exogenous leptin provided during fasting can prevent the usual hormone changes seen in NTIS [85, 86]. Legradi et al. [86] illustrated that leptin administration normalized the previously suppressed proTRH mRNA in the hypothalamic paraventricular nucleus. However, the leptin levels in surgery patients appear to differ from those seen in fasting and starvation. One study of pediatric cardiac surgery patients showed a decrease in leptin levels intraoperatively, an increase to above normal levels postoperatively, and then a return to normal levels about 24 h after surgery [87]. A similar triphasic leptin response has been shown in adult surgery patients [88].

Decreased levels of thyroid binding proteins and inhibition of binding and transport of T4 and T3 have been suggested as a possible factor in the low thyroid hormone levels in NTIS. Increased levels of free fatty acids and bilirubin have been implicated in this [60, 89, 90].

The role of the elevated RT3 itself has also been studied. Infusions of pharmacological doses of RT3 in rats decreased the levels of T3 and impaired conversion of T4 to T3 [91]. However, a study in which RT3 was given orally to humans resulted in no changes in T4, T3, or TSH levels [92]. RT3 is generally considered to have no significant biological effects, however, some have suggested that it may have a role in the detrimental clinical and physiological activity in NTIS [93].

Several clinical factors have been implicated as triggers of the thyroid hormone changes in NTIS. Intraoperative factors cited as triggers for NTIS in CPB patients include hemodilution by the CPB prime solution [53, 58], thyroid binding inhibitory effects of heparin [90], hypothermia [51], and pulsatile versus nonpulsatile flow [47]. However, one would expect that any effect of these intraoperative factors should be short lived and therefore not necessarily explain any prolonged changes. As described earlier, the type of cardiac lesion may also be a factor in the degree of NTIS [46, 54]. One study specifically attempted to identify distinct clinical factors that put children at most risk of developing NTIS following cardiac surgery [94]. Plumpton and Haas studied 36 infants less than 12 months of age following cardiac surgery for a variety of congenital heart lesions. Increased CPB time, decreased weight, and age less than 3 months were associated with decreased FT3 levels immediately after surgery. Increased cross-clamp time and intraoperative hypothermia resulted in lower TSH levels on POD 1, while interestingly, and in contrast to many other studies, dopamine use resulted in higher TSH levels. These associations did not continue on POD 2. Prolonged ventilation beyond 48 h was associated with lower FT3 and TSH levels on POD 2. Arguably this study does not identify risk factors but rather associations as it is a relatively short-term study and the sequential timing of the appearance of the various parameters in relation to the thyroid biochemistry changes cannot be elucidated. Our study showed similar prognostic qualities of early TT3, FT3I, and T3U on clinical outcome [46].

Medications can alter thyroid metabolism. Dopamine is classically implicated in exacerbating NTIS with the suppression of TSH, T4, and T3 [95, 96]. This suppression resolves within hours of stopping the dopamine. RT3 is not elevated by dopamine as it is in classic NTIS. Glucocorticoids can also transiently affect thyroid metabolism through suppression of TSH. Brabant et al. [97] describe the suppression of TSH levels and TSH pulses but a normal response to TRH stimulation following dexamethasone administration. The authors conclude that this implies a supra-pituitary site of the glucocorticoid action. Iodine exposure through topical iodinated antiseptics has also been implicated in exacerbating NTIS [98]. However, studies have shown that the effect of this iodine exposure appears to be minimal [99, 100]. In addition, if there is an effect, it tends to be a rise in the TSH level in response to a state of hypothyroidism, which is contrary and easily differentiated from the TSH response seen with NTIS [28].

A recent study indicates that in an optimal ICU setting nutrition does not affect thyroid hormone levels. No relation was found between thyroid hormone changes and the adequacy of protein and energy intake in 84 critically ill neonates and children followed for 6 days [101]. As selenium is important for deiodinase enzyme function, it has also been identified as a possible factor in NTIS [102, 103]. The serum concentration of selenium decreases following CPB surgery [102]. A Cochrane review on selenium supplementation in critically ill adults concluded that there was no evidence for any benefit although the reviewed studies were described as limited in regards to their availability of outcome measures, sample size, and quality [104].

Treatment of NTIS

Various studies have looked at treatment in NTIS. While the concept of treating or supplementing critically ill patients with hormones may appear to be a risk free proposal, past GH studies provide a cautionary note. Early studies of GH supplementation in critical illness showed perceived benefit with decreased catabolism and improved nitrogen balance [105, 106]. Some studies also showed clinical improvement including a study in children with burns that showed improved healing time and decreased hospital time in those that received GH [107]. However, a later large randomized placebo controlled multinational study showed increased mortality in critically ill adults receiving GH [108].

Treatment of NTIS in adults

Treatment of NTIS with T4 or T3 has been attempted in various clinical scenarios although most commonly in adults undergoing CPB surgery. Generally, T4 therapy has not been successful. This should be expected given the suspected underlying endogenous defect in the conversion of T4 to the metabolically active T3 in patients with NTIS. T3 therapy has resulted in arguably mixed results.

Some animal studies in CPB have shown improved survival and inotropic effects with T3 supplementation [109–111]. A basic science model with pig myocytes illustrated that pre-treatment with T3 improves myocyte velocity of shortening after hypothermic arrest and rewarming [112].

Much of what is described in the human studies is dependent on the outcome measures and how their importance is interpreted. In a small study, Novitzky et al. [30] randomized adults undergoing coronary artery bypass to intraoperative and postoperative T3 therapy or placebo. As expected, the treatment group showed increased FT3 levels. In those patients with preoperative ejection fractions less than 30%, the treatment group showed decreased inotropic and diuretic requirements compared to the placebo group. There was no difference in any of the hemodynamic measures or mortality between the treatment and placebo group. In those patients with preoperative ejection fractions greater than 40%, there was no difference in the required inotropic or diuretic requirements between the two groups. However, in this subset, the treatment group did have increased stroke volume and cardiac output, and decreased vascular resistance. In a nonrandomized study, these same authors have also described beneficial outcomes using T3 as a rescue therapy in postoperative cardiac surgery patients who either had difficulty weaning from CPB support or had ongoing poor myocardial function [113]. A larger randomized study with 170 CPB surgery patients found similar results with improved ventricular function, lower inotropic requirements, less need for mechanical device intervention, and decreased ischemia in the group treated with intraoperative and postoperative T3 compared to placebo. Differences in mortality did not reach statistical significance [114]. Others have found less positive results or have chosen to interpret the results differently. Similar to the other studies, Klemperer et al. [115] found that CPB surgery patients treated with T3 had improved cardiac output and stroke volume and decreased vascular resistance in a randomized study of 142 patients. However, they stress that the more important clinical outcomes such as the time to wean from CPB, inotrope requirements, duration of mechanical ventilation, length of ICU stay, length of hospital stay, incidence of major postoperative complications, and mortality did not differ between the treatment and placebo group. Therefore, they conclude that T3 therapy is not warranted despite its positive inotropic effects.

There have also been some therapy studies in adults with NTIS and not cardiovascular disease. Brent and Hershman randomized 23 critically ill men with very low T4 levels to either intravenous T4 therapy for 14 days or placebo. Not surprisingly, the treated group had normal TT4 and FT4 levels earlier, on day 3 compared to day 13 in the control group. The control group had an earlier improvement in the T3 and FT3 levels compared to the treated group. In addition, the treated group had a greater elevation of RT3 levels and suppression of the TSH levels compared to the control group. This may indicate that the exogenous T4 was not able to be converted to T3 and in fact was being metabolized to RT3. The inability of patients with NTIS to convert exogenous T4 to T3 has been shown in other studies [24]. Overall, there was a high mortality in this study with 17 of the 23 patients dying. A low T4 level was an inclusion criterion for the study, so the high mortality rate merely confirms previous studies that illustrated that a low T4 level was predictive of mortality [31]. The deaths were distributed evenly between the treatment and control groups but there was an increased mortality from days 5 to 17 in the treated group, which did not reach statistical significance. The baseline T3 level and the T3/T4 ratio were significantly higher in the survivors of both groups.

In another randomized study, T3 therapy did not affect mortality or the resting metabolic rates in a cohort of burn patients [26].

Some recent studies have focussed on therapy with releasing factors as opposed to peripheral hormones such as T3. It is thought that this approach may be more physiological by respecting the usual feedback loops and therefore possibly allowing for easier less exact dosing. Studies with TRH, GH releasing peptide-2, and gonadotropin-releasing factor (GnRH) have shown some promise. Infusions of these releasing factors lead to increased secretion and pulsatility of TSH, GH, and LH, and increased levels of T4, T3, insulin growth factors-I, insulin growth factor-binding protein 3, and testosterone [72–74]. Generally, the administration of a combination of the releasing factors leads to better results than when they are used alone [72]. Clinical outcome studies in this area are still lacking.

Treatment of NTIS in children

Despite the arguable lack of clear clinical evidence that NTIS causes harm in children, and therefore requires intervention, there have been some attempts with small studies, including some randomized controlled trials (Table 1), to investigate the possible benefits of perioperative thyroid supplementation in children. The NTIS

Table 1 Randomized studies of treatment in children with NTIS

Authors	Sample size	Patient description	Treatment	Outcomes
Chowdhury et al. [117]	28 (14 control)	0–18 years old Congenital heart disease surgery TT3 < 40 ng/dl (0.6 nmol/l) Or <60 ng/dl (0.9 nmol/l) in neonates	T3 infusion 0.05–0.15 mcg/kg/h	Increased TT3 in treatment group No difference in treatment score (TISS), inotrope score, mechanical ventilation days, or hospital days Subanalysis of 9 neonates (4 control) showed improved TISS score and inotrope score in treatment group Mixed venous oxygen saturation, mechanical ventilation and hospital days trended to improvement but were not statistically significant in this subanalysis
Portman et al. [119]	14 (7 control)	<1 year old VSD or tetralogy of Fallot repair	T3 0.4 mcg/kg pre-bypass and at reperfusion	Increased FT3 and T3 in first 24 h in treatment group then equivalent at 72 h No difference in inotrope use Increased HR and peak pressure rate product in treatment group Supraventricular tachycardia in one patient in treatment group
Mackie et al. [122]	42 (20 control)	Neonates Norwood or two-ventricle repair	T3 infusion 0.05 mcg/kg/h for 72 h	Increased T3 and FT3 in first 72 h in treatment group then equivalent by 7 days Half day quicker achievement of negative fluid balance in treatment group Increased systolic and mean BP in treatment group No difference in cardiac index at 48 h, inotrope score, ICU, and hospital days Study stopped in two patients in treatment group with hypertension and ectopic atrial tachycardia
Bettendorf et al. [124]	40 (20 control)	2 days–10 years old Congenital heart disease surgery All received dopamine	T3 2 mcg/kg on day 1, 1 mcg/kg until dopamine stopped, up to maximum of 12 days (median 5 days)	Increased T3 in treatment group with both groups having normal T3 at discharge Better cardiac index, systolic function, and treatment score (TISS) in treatment group No difference in ICU, hospital, and ventilation days

changes, specifically the decreases in T3 and TSH, may be greater in children than adults and therefore the possible physiological effects may also be greater [116]. As with many treatment studies, the difficulties in the analysis and comparison of these studies include their heterogeneous choice of outcome measures, treatment protocols, and patient populations. In addition, as perioperative mortality is fortunately rare in this pediatric population, the relevance of the clinical benefits outlined in many of these studies seems open to discussion.

Chowdhury et al. [117] conducted a prospective study randomizing children to treatment with continuous T3 infusion to maintain T3 levels within the normal range or no treatment. Twenty-eight eligible children were randomized with 14 in each group. Not surprisingly, the TT3 levels rose in the treatment group within 24 h of initiation of the T3 infusions. There was no difference between the two groups in the assessed outcome measures of illness severity measured by TISS score, inotrope score, mechanical ventilation days, or hospital days. A subanalysis of a small cohort of the nine neonates did show significant improvements in the TISS and inotrope scores in the treatment group. The mixed venous oxygen saturations, mechanical ventilation days, and hospital stay days trended toward improvement in the treatment group but none of these differences reached statistical difference. There was no difference in adverse events including changes in blood pressure, heart rate, or dysrythmia between the two groups. This study is reportedly ongoing under the direction of one of the original authors [118].

An infant population was also specifically studied by Portman et al. [119] in a randomized prospective study of 14 children less than 1 year of age undergoing surgical repair of perimembranous ventricular septal defects, some of whom had underlying tetralogy of Fallot. The seven patients in the treatment group received intravenous T3 before initiation of CPB and intraoperatively after the release of the aortic cross clamp. Inotrope requirements, including the use of dopamine, were equivalent in both groups. Serum FT3 and TT3 levels increased in the

treatment group in the first 24 h but then decreased and were equivalent to the control group at 72 h, the end of the observation period. TT4 levels declined equally in both groups. The heart rate was transiently higher at 1 and 6 h after surgery in the treatment group. Systolic and diastolic blood pressures were not different between the two groups. One patient in the treatment group had an episode of supraventricular tachycardia and it appears from the published graphs that some patients had heart rates greater than 160 beats per min within a few hours after surgery [118]. There were no other adverse events reported. Other clinical outcomes, such as ventilation and hospital days, were not assessed in this study. To the best of my knowledge, this group is currently involved with a Food and Drug Administration (FDA) funded trial looking at perioperative thyroid hormone supplementation in children less than 2 years of age with congenital heart disease with an enrollment goal of 225 patients [118, 120, 121]. The Portman and Chowdhury [118] studies were the only two included studies in a Cochrane review assessing perioperative thyroid supplementation in infants undergoing cardiac surgery. The review concluded that there is not sufficient evidence from randomized trials as to the harm or benefit of thyroid supplementation in this population. The review highlights the lack of standard measured outcomes and dosing methods.

In 2005, following the publication of the Cochrane review, Mackie and colleagues [122, 123] published a randomized controlled study looking at 72 h postoperative continuous T3 infusion treatment in 42 neonates undergoing either a Norwood procedure or a two ventricle repair of an interrupted aortic arch and VSD soon after birth. As expected, the T3 and FT3 levels were higher in the treatment group at 24, 48, and 72 h postoperatively. At the next scheduled measurement, 7 days postoperatively, the levels were equal between the two groups. Other thyroid hormone measures including TT4, FT4, TSH, and T3U did not differ between the two groups. Cardiac index values, inotrope scores, ICU days, hospital days, heart rate, and diastolic blood pressure did not differ between the two groups. The clinical outcome score was 2.0 (range 0–4) in the treatment group and 2.0 (range 0–7) in the placebo group. The difference in the outcome scores' ranges did result in a statistically significant difference between the two groups ($P = 0.046$). The clinical outcome score was a composite of three variables including days to negative fluid balance, sternal closure, and extubation with a possible range of total score of 0 to 7. When assessed individually, the only variable found to differ between the two groups was days to negative fluid balance. The treatment group achieved negative fluid balance a half day quicker than the control group, a difference of questionable clinical significance. The treatment group also had higher systolic and mean blood pressures. Two adverse events requiring discontinuation from the study were reported in the treatment group. One patient was hypertensive and the other developed ectopic atrial tachycardia. Of note, the tachycardia also recurred days after discontinuation of the T3. One patient in the placebo group, who was withdrawn from the study because extracorpeal membrane oxygenation support was required intraoperatively, died.

Another randomized study of NTIS treatment in children studied 40 children, aged 2 days to 10 years, undergoing various types of cardiac surgeries, and therefore not as homogeneous a population as in the previously described studies [124]. All patients in this study received dopamine. Therefore, comparison to other studies may be somewhat blurred. Patients were randomized to either a daily T3 bolus or placebo for up to a maximum of 12 days postoperatively, with a median treatment period of 5 days. The treatment group reached above normal levels of T3 soon after receiving the first dose of T3. Yet, both groups had normal T3 levels by the time of discharge from hospital. The treatment group had better cardiac index scores, systolic function, and treatment scores. The cardiac function improvement was most evident in patients who had longer operation and CPB times. A close look at the study shows that other important clinical indicators including ICU, hospital, and ventilation days did not differ statistically between the two groups.

There have been other nonrandomized studies and reports that have looked at NTIS treatment in children undergoing cardiac surgery [125–129]. Mainwaring administered one bolus of T3 intraoperatively followed by one bolus postoperatively to 10 children, aged 19 to 42 months, undergoing modified Fontan procedures [125]. These children were then compared to eight historical controls. The treated group had statistically shorter ventilation hours and hospital days compared to the historical controls. Prior to his group's randomized study, Chowdhury et al.[128] published a report describing improved cardiorespiratory status in an index case of a child undergoing a Fontan procedure, along with five additional cases. Carrel et al. [129] also described improved cardiorespiratory function in five children undergoing cardiac surgery for congenital heart defects who received T3 infusions during their postoperative courses. In an abstract publication, Rosen et al. [127] described improved hemodynamics in four children receiving T3 following surgeries for complex congenital heart diseases. In a short communication, Bialkowski [126] also conveys success using T3 supplementation in children following cardiac surgery, but he also describes a complication of persistent hypotension in one such patient.

Thyroid supplementation has also been attempted in the noncardiac surgery neonatal population. Cochrane Collaboration reviews have shown no benefit of prophylactic

thyroid hormone therapy in preterm infants with low-thyroid hormone levels in regard to improving neonatal mortality, morbidity, respiratory distress syndrome, or neurodevelopment [41–44].

In conclusion, the published treatment studies do arguably show some improvement in selected outcomes, mostly physiological cardiac function, in children undergoing cardiac surgery and receiving T3 supplementation. The adverse events described to date appear to be minimal although the number of patients studied is still relatively small. However, the results of arguably more important measures of clinical outcome still seem to be unclear. Perhaps, the ongoing larger trials will better be able to clarify this. It could also be argued that the underlying basic question of whether NTIS is harmful is still not clear. While the biochemical thyroid hormone changes of NTIS unquestionably occur in critically ill children, especially those undergoing cardiac surgery, one must still ponder whether NTIS is a cause or merely a marker of critical illness? T3, both endogenous and exogenous, does have what appears to be a positive inotropic physiological effect on cardiac function. But does supplemental T3 truly translate to improved clinical outcomes?

Summary

Are the changes in NTIS adaptive or maladaptive? All the studies on the neuroendocrine changes in critical illness, and NTIS in particular, are essentially trying to answer this same question. Some still believe that NTIS may be an adaptive response to decrease the catabolic effects of critical illness. Conversely, NTIS may be maladaptive with the decreased thyroid hormone levels leading to, or at least associated with, physiological and clinical deterioration. As evident in this review, there are studies that support both these theories. Studies have shown that nonsurvivors of critical illness may in fact show less NTIS changes [35] and that treatment may delay normal biochemical recovery [25]. Other evidence in support of NTIS being adaptive, or perhaps more correctly "not maladaptive", is that many of the treatment studies do not show relevant clinical improvement. However, there are studies outlined in this review that show possible physiological, biochemical, and arguably clinical improvement with treatment, lending support to the possible maladaptive effects of NTIS. In addition, several studies do show an association of NTIS with severity of illness or mortality. However, these studies do not necessarily prove a causal relationship. It is not clear whether NTIS causes illness or whether illness causes NTIS. Only a few studies have attempted to assess this further in children by comparing NTIS to illness severity [45, 46, 50]. These studies seem to indicate that severe illness leads to NTIS and not vice versa.

Based on the limited data, the conflicting results among studies, and the still small patient numbers the question of the adaptive or maladaptive role of NTIS in children is still arguably unclear. However, it is this author's opinion that NTIS is not adaptive, but rather a result of critical illness. Specifically, illness severity seems to be the "chicken before the egg", and changes in illness severity precede NTIS changes. The degree of illness severity appears to be linked to the degree of NTIS. However, since greater NTIS biochemistry changes may be predictive of worse clinical outcome, it is difficult to label these changes as adaptive. In addition, the treatment studies do not convincingly demonstrate positive clinical outcomes. Therefore, perhaps the most effective therapies for NTIS may be advancements and improvements in surgical and postoperative care in these patients as opposed to hormone replacement.

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