

Review Article

THYROID FAILURE BEHIND NON-THYROIDAL ILLNESS IN OLDER PATIENTS RECOVERING FROM SEPSIS: A NARRATIVE REVIEW AND HYPOTHESIS

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ABSTRACT

Background: The objective is to examine whether primary hypothyroidism can be missed behind non-thyroidal illness syndrome (NTIS) in older patients recovering from sepsis, and to propose a testable hypothesis and a practical bedside approach. **Materials and Methods:** Study Design Narrative review with an explicit hypothesis (SANRA framework). Data Sources and Search Period PubMed, Semantic Scholar, and Google Scholar from January 2018 to July 2026, plus foundational earlier papers. **Result:** NTIS was present in 37% to 58% of the ICU and septic cohorts reviewed. Upper TSH limits in healthy older adults ranged from 3.75 to 5.28 mIU/L, and one cohort calculated a rise from 4.74 to 6.28 mU/L over eight years. In trials of adults aged 65 years or older with subclinical hypothyroidism, levothyroxine did not improve symptoms or tiredness, so an age-related shift in TSH is unlikely to hide a failure severe enough to stall recovery. In a 32-ICU French cohort, severe hypothyroidism was previously unknown in 54% of patients, and levothyroxine discontinuation (28%), sepsis (15%) and amiodarone (11%) were the commonest triggers. We found no serial-testing study of older septic patients aimed at missed primary failure. Observational data and small trials argue against empirical thyroid hormone. **Conclusion:** Masked primary hypothyroidism in older septic patients is an untested hypothesis and is probably uncommon. Pending a serial-testing cohort, we suggest a thyroid history on admission, joint reading of TSH and FT4, no thyroid hormone for an NTIS pattern, repeat tests after recovery when the cause is unclear, and prompt treatment if myxedema coma is suspected.

INTRODUCTION

Older patients who survive sepsis do not always recover at the pace their numbers suggest. Cultures clear and vasopressors stop, yet the patient stays drowsy, bradycardic and weak, and the bedside team is left asking what else is holding recovery back. The problem is common enough to matter. In a scoping review of 99 studies, persistent or chronic critical illness affected a pooled 28% of patients with sepsis, and pooled one-year mortality among patients with persistent critical illness was 45%.^[1] Frailty, present in about 30% of ICU admissions, adds to the burden: hospital mortality was higher in frail than in non-frail patients (relative risk 1.71).^[2]

Thyroid tests are often part of the work-up, and they are usually abnormal. Non-thyroidal illness syndrome (NTIS) is characterised by low triiodothyronine (T3), low or low-normal thyroxine (T4) and a thyroid-stimulating hormone (TSH) that is normal or low rather than raised.^[3,4] It was present in 665 of 1,790 ICU patients (37%) in a German cohort,^[5] and in 520 of 1,226 septic patients (42.4%) in a Chinese two-centre study.^[6] A meta-analysis of 25 studies reported a median prevalence of 58%.^[7] The standard teaching is that NTIS reflects adaptation to illness, so it is observed rather than treated. That teaching leaves a narrow but uncomfortable question. Distinguishing NTIS from severe hypothyroidism can be difficult in some patients.^[4] If an older patient has an unrecognised primary thyroid

failure, could sepsis, the age-related rise in TSH, and the overlap between hypothyroid features and frailty or delirium combine to make it look like NTIS and delay the diagnosis? We found no study that tests this directly. The aim of this review was to bring together what is known about each element, to state the idea as a testable hypothesis, and to set out a practical bedside approach in the meantime.

MATERIALS AND METHODS

This is a narrative review written to the SANRA quality framework [8]. We searched PubMed, Semantic Scholar, and Google Scholar for English-language articles published between January 2018 and July 2026 on four topics: NTIS in sepsis and critical illness, hypothyroidism and myxedema coma in critically ill patients, TSH reference limits in older adults, and thyroid hormone treatment in sepsis. We also used Consensus, an AI-assisted search tool, to find papers that the PubMed strings might miss. The authors added foundational earlier papers where no recent study answered the same question. Search strings and record counts are given in Supplementary File S1; the three main PubMed strings returned 134, 330 and 178 records.

The authors selected papers by relevance to the question. There was no dual screening and no formal risk-of-bias appraisal, so the review is open to selection bias. Every cited paper was checked against its PubMed record for authors, title, journal, year and DOI, and the numbers quoted here were checked against the PubMed abstract (Supplementary File S4). Where a practical step rests on physiology or expert opinion rather than trial evidence, we say so.

RESULTS

Thyroid tests during sepsis and during recovery

In the early phase of critical illness, the changes of NTIS follow the acute-phase response and macronutrient restriction, and part of the pattern appears adaptive.^[3] In prolonged critical illness the picture changes. Suppressed hypothalamic thyrotropin-releasing hormone expression accounts for a persistently reduced TSH despite low thyroid hormone concentrations.^[3,4] Whether low hormone levels in sepsis are only a marker of severity or also contribute to harm remains disputed. A meta-analysis of 6,869 patients found NTIS independently associated with mortality (OR 2.21, 95% CI 1.64 to

2.97).^[7] In the two-centre septic cohort the association held at 30 days (OR 1.759, 95% CI 1.009 to 3.104) but not at 60 or 90 days,^[6] and in the German ICU cohort NTIS was not an independent predictor of ICU mortality after adjustment.^[5] A more recent cohort of 2,391 septic patients linked lower FT3, lower TSH and several thyroid hormone sensitivity indices to higher 90-day mortality.^[9]

These studies sampled patients during illness and asked a prognostic question. None of them was designed to detect underlying primary thyroid disease.

What happens to TSH during recovery matters for our question. In a prospective series of 60 critically ill patients with burns, septicaemia or acute renal failure, serum T4 fell below 35 nmol/L in 24 patients and 14 of them survived with T4 returning to normal.^[10] All 13 episodes of rapid T4 rise were accompanied by a marked rise in TSH, TSH was transiently above the reference range in 8 of them, and in the 6 episodes sampled less than 6 hours apart the TSH rise came first.^[10] In the 4 patients given dopamine, TSH and T4 stayed low until the infusion stopped.^[10] Spencer drew the practical lesson. In a hospitalised patient, hypothyroidism should be diagnosed on a high TSH together with a low free T4, because an isolated high TSH may merely reflect the recovery phase, and a definitive assessment can wait until recovery and discharge.^[11] Abnormal results may also reflect glucocorticoid or dopamine treatment.^[11] These studies date from the 1980s, used older assays and did not focus on older adults. We found no study that charted the recovery of TSH and FT4 in older septic patients.

Does age change the TSH threshold?

Four studies of older people report different upper limits for TSH [Table 1]. Among 10,995 healthy community-dwelling Australians aged 70 years or older, the reference interval was 0.34 to 3.75 mU/L, and TSH did not differ by age or sex.^[12] An indirect analysis of 3,835 laboratory records from people aged 65 or older in eastern Türkiye gave 0.41 to 3.94 mIU/L, with no consistent difference across age subgroups.^[13] In 349 Chinese adults aged 90 years or older, the interval was 0.29 to 5.28 μ U/mL.^[14] In the Whickham cohort, 204 survivors with a mean age of 77 years were tested twice, a median of 7.8 years apart. The calculated upper limit of TSH rose from 4.74 to 6.28 mU/L, and the prevalence of subclinical hypothyroidism by standard ranges rose from 3.5% to 9.0%, but it was 2.0% at both visits when visit-specific ranges were used.^[15]

Table 1: TSH limits reported in studies of older adults.

Study	Population	Method	TSH limits as reported	Comment
Tran et al. ^[12] (ASPREE, Australia)	Healthy, community-dwelling, age ≥ 70 y; n = 10,995	Direct; middle 95% of log-transformed baseline TSH	0.34 to 3.75 mU/L	TSH did not differ by age or sex
Çatak et al. ^[13] (Eastern Anatolia, Türkiye)	Age ≥ 65 y; n = 3,835 laboratory records	Indirect; nonparametric percentiles, CLSI approach	0.41 to 3.94 mIU/L	No consistent difference across age subgroups; sex-specific intervals advised

Liu et al. ^[14] (Guangxi, China)	Oldest-old, age ≥ 90 y; n = 349	Direct; nonparametric 2.5th to 97.5th percentile	0.29 to 5.28 μ IU/mL	FT4 correlated with age
Razvi et al. ^[15] (Whickham, UK)	Survivors, mean age 77.0 y; n = 204; same people at two visits, median 7.8 y apart; known thyroid disease excluded	Longitudinal; calculated upper limit	Upper limit 4.74 mU/L at visit 1, 6.28 mU/L at visit 2	Subclinical hypothyroidism 3.5% to 9.0% by standard range; 2.0% at both visits by visit-specific range

TSH units are equivalent: 1 mU/L = 1 mIU/L = 1 μ IU/mL. Assay platforms differ between studies and are not harmonised. y, years.

The studies differ in method (direct sampling of healthy volunteers, indirect laboratory-database estimation, longitudinal calculation), in age band and in assay, so they do not combine into a single ceiling. Read together, they are compatible with an upper limit that rises at the extremes of old age. That fits the view that TSH rises with age in people without thyroid disease and that standard ranges overestimate subclinical hypothyroidism after 70.^[16] We therefore do not propose an age-adjusted ceiling for septic patients.

The size of the shift also limits how much it can explain. The reported upper limits span about 3.75 to 6.28 mIU/L, which is the range in which treatment has been tested in older adults. In the TRUST trial, 737 adults aged 65 or older with persistent subclinical hypothyroidism (TSH 4.60 to 19.99 mIU/L, FT4 within the reference range) were randomised to levothyroxine or placebo, and neither the hypothyroid symptom score nor the tiredness score differed at one year.^[17] A combined analysis of 251 participants aged 80 or older reached the same conclusion.^[18] These were stable community-dwelling adults, not septic patients, so the result cannot be transferred directly. It does suggest that a modest age-related rise in TSH is an unlikely hiding place for a failure large enough to stall recovery.

How common is severe hypothyroidism in the ICU? The best ICU data come from a retrospective study of 82 patients with severe hypothyroidism treated over 18 years in 32 French ICUs.^[19] Hypothyroidism had not been known before admission in 44 patients (54%). The commonest triggers were levothyroxine discontinuation (28%), sepsis (15%) and amiodarone-related hypothyroidism (11%), and the main causes were thyroiditis (29%) and thyroidectomy (19%). Hypothermia (66%), haemodynamic failure (57%) and coma (52%) dominated the presentation. In-ICU mortality was 26% and six-month mortality 39%, and age over 70 years was independently associated with death in the ICU (OR 6.01, 95% CI 1.75 to 24.1).^[19] Inclusion required biochemical hypothyroidism plus a cardinal sign and an organ failure, so this cohort describes the severe end of the spectrum, not mild or masked disease.

Population estimates are low. A systematic survey of 584 published and 114 unpublished cases of myxedema coma from 2004 to 2024 estimated an incidence of 0.12 per million per year, with mortality of 38.8%, a precipitating factor in 77.6%, altered

mental status in 88.9%, hypothermia in 71.9% and a heart rate below 60 beats/min in 66.2%.^[20] A Japanese national inpatient database identified 149 patients among about 19 million admissions, with a mean age of 77 years, in-hospital mortality of 29.5% and an estimated incidence of 1.08 per million per year.^[21] The ninefold difference in incidence may reflect case definition, data source and setting, and we could not establish the reason. The two sources agree that myxedema coma is rare, often precipitated, and fatal in roughly three to four of every ten patients. A single case report shows the diagnostic difficulty when both conditions coexist: a 36-year-old woman with septic shock developed NTIS and then features of myxedema coma.^[22] One case in a younger patient cannot indicate how often this happens in older adults.

Why the picture is hard to read at the bedside

In an older patient whose recovery has stalled, thyroid failure competes with more common explanations: hypoactive delirium, accumulation of sedatives and analgesics when renal or hepatic function is poor, ongoing infection, metabolic or structural brain causes, adrenal insufficiency and persistent critical illness. The PADIS guideline sets out recommendations for assessing and managing pain, agitation and sedation, and delirium in adult ICU patients.^[23]

Hypothyroidism itself often presents with fewer or less specific symptoms in older adults.^[24] The cardinal features of myxedema coma (altered mental status, hypothermia and bradycardia),^[20] also occur in sepsis, so they discriminate poorly unless a thyroid history raises the pre-test probability. The link between thyroid status and cognition is also less firm than often assumed. In an individual participant analysis of 74,565 adults, subclinical hypothyroidism and hyperthyroidism were not associated with cognitive function, cognitive decline or dementia, and no firm conclusion could be drawn for overt disease.^[25] Those are community data. None of them tells us how much thyroid failure adds to delirium or frailty in the ICU.

Thyroid hormone treatment for an NTIS pattern

The evidence for treating NTIS is weak and partly points to harm. A recent review found conflicting trial results and no robust trial showing better survival or recovery.^[26] In a MIMIC-IV analysis of 20,231 septic patients, early levothyroxine within seven days was associated with higher 28-day mortality (HR 2.48, 95% CI 1.96 to 3.15; matched

cohort HR 2.38, 95% CI 1.75 to 3.23).^[27] The abstract does not say whether recipients included patients with known hypothyroidism continuing home treatment, and confounding by indication is likely in any database of this kind. In two pilot placebo-controlled trials of oral T3 in 95 patients with septic shock and NTIS, 28-day mortality in the low-T3 group (n = 48) was 18 of 24 (75%) with T3 and 8 of 24 (33.3%) with placebo (p = 0.004). In the low-T3 and low-T4 group (n = 47) it was 6 of 24 (25%) with T3 and 12 of 23 (52.1%) with placebo (p = 0.039).^[28] The trials were small, used T3 rather than levothyroxine, and the authors advised caution. Taken together, the evidence supports not giving thyroid hormone for an NTIS pattern alone. It does not argue against treating confirmed primary hypothyroidism.

A bounded hypothesis

We propose the following, and no more. In a minority of older patients recovering from sepsis, previously unrecognised or inadequately treated primary hypothyroidism is labelled as NTIS because TSH is blunted by acute illness or by drugs such as dopamine and glucocorticoids,^[10,11] because its features overlap with delirium and frailty,^[24] and because thyroid tests are not repeated after recovery.

To be testable, the hypothesis needs an operational definition. We suggest the following sequence: low or low-normal FT4 with a TSH that is not raised during sepsis, which is an NTIS-compatible pattern, followed after clinical recovery by persistently low FT4 with a raised TSH, supported by a prior thyroid history, TPO antibodies, or both. Any other sequence, including a transient TSH overshoot that settles, is recovery from NTIS. Patients with known hypothyroidism whose levothyroxine was interrupted would be analysed as a separate group, because their route to the same biochemical picture is different and better understood.^[19]

Three observations make the hypothesis plausible. Severe hypothyroidism had been unknown before

admission in more than half of the French ICU patients, and sepsis was a recognised trigger.^[19] The recovery phase can mimic hypothyroidism for a time.^[10,11] And thyroid dysfunction is under-recognised in older adults because it presents quietly.^[24] Three others argue for caution. The age-related shift in TSH is too small to hide a clinically important failure.^[17,18] Severe disease is rare.^[19-21] And no study has followed older septic survivors serially to look for it. On this evidence we expect the absolute yield to be low.

A more likely route to the same bedside problem is known hypothyroidism in which levothyroxine is stopped or not absorbed during the ICU stay, or in which a drug such as amiodarone tips a vulnerable thyroid into failure. These accounted for 28% and 11% of triggers in the French cohort.^[19] That cohort captured only severe cases, so the frequency of milder forms is unknown. The hypothesis is therefore not a reason to give levothyroxine empirically, and it should not be read as one.

A practical approach in the meantime

Until better data exist, the steps below are a reasonable way to avoid two opposite errors: treating NTIS as thyroid failure, and overlooking thyroid failure as NTIS. Figure 1 summarises them. They are the authors' expert opinion, built on the evidence above, and none has been validated in older septic patients.

On admission, record thyroid history, levothyroxine and amiodarone use, and any earlier TSH result, because most of the risk identified in the French cohort lay in known disease, stopped treatment and drugs.^[19] Stopping established levothyroxine should be a deliberate decision. When recovery stalls, look first for the common causes.^[23] TSH and FT4 are most informative when read together,^[11] and [Table 2] shows how we would read the common patterns. A single raised TSH during illness should not be labelled subclinical hypothyroidism.^[11]

Table 2: Reading common thyroid function patterns in older patients with sepsis (expert opinion supported by the cited sources).

Pattern	Usual interpretation	Suggested action (expert opinion)	Basis
Low FT3; low or low-normal FT4; TSH normal, low or slightly low	NTIS: acute adaptation, later reduced hypothalamic drive	Observe. No thyroid hormone. Review drugs.	[3,4]
Low FT4 with TSH low during dopamine or glucocorticoid exposure	Drug-related suppression of TSH	Repeat after the drug is stopped.	[10,11]
Isolated raised TSH, FT4 normal or rising, during recovery	Recovery-phase TSH overshoot	Repeat after recovery. Do not label from one value.	[10,11]
Raised TSH with low FT4 that persists after recovery	Probable primary hypothyroidism	Add TPO antibodies, take endocrine advice, treat once confirmed.	[11]
Low FT4 with TSH not raised, persisting after recovery	Persistent NTIS, drug effect, or hypothalamic-pituitary disease	Endocrine review; consider pituitary causes.	[4]
Low FT4 or FT3 with hypothermia, bradycardia and altered mentation	Possible myxedema coma	Urgent endocrine advice; treat under local protocol without waiting for results.	[19,20]

FT3, free triiodothyronine; FT4, free thyroxine; NTIS, non-thyroidal illness syndrome; TPO, thyroid peroxidase; TSH, thyroid-stimulating hormone.

If the picture remains unexplained once the patient is clinically stable, repeat TSH and FT4 and add TPO antibodies. No study defines the right interval. The TSH rebound occurs while T4 is rising,^[10] so a test taken too early may catch the overshoot. We suggest waiting until the acute illness has settled, and propose several weeks as a pragmatic interval, which is opinion. Someone must own that test after ICU discharge, and we suggest recording it in the discharge summary.

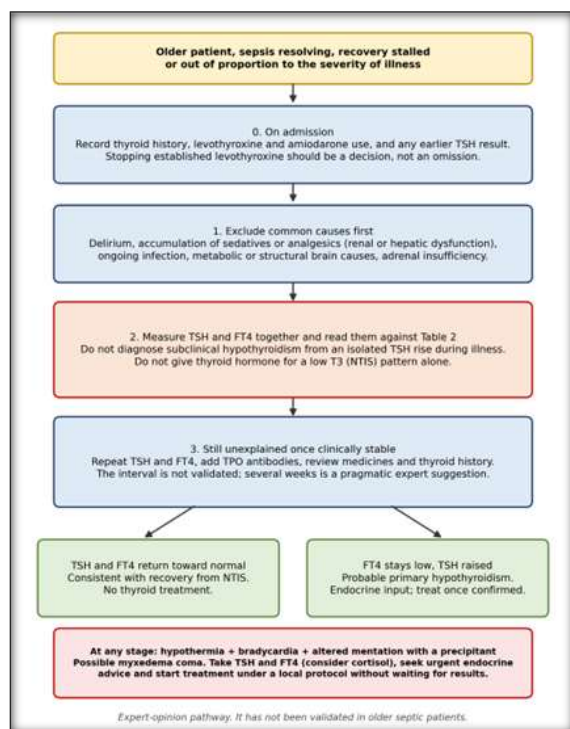


Figure 1: Suggested approach to an older patient whose recovery from sepsis has stalled. The pathway is expert opinion and has not been validated. FT4, free thyroxine; NTIS, non-thyroidal illness syndrome; TPO, thyroid peroxidase; TSH, thyroid-stimulating hormone.

The exception is a patient with hypothermia, bradycardia and altered mentation, particularly with a precipitant such as infection. Because each feature is also common in sepsis, the decision depends on pre-test probability: a history of thyroidectomy or thyroiditis, TPO positivity, amiodarone exposure or stopped levothyroxine.^[19] In such a patient we would take TSH and FT4 (and consider a cortisol level), call endocrine colleagues urgently, and begin treatment under a local protocol without waiting for the results, with close cardiac and haemodynamic monitoring. The French cohort and the systematic survey both support early diagnosis and prompt replacement in this setting.^[19,20] The regimen is outside the scope of this review and should follow institutional endocrine guidance.

Research priorities

The hypothesis can be tested. A prospective cohort of older adults admitted with sepsis should record pre-admission TSH from health records where available.

It should measure TSH, FT4, FT3 and TPO antibodies at admission, at ICU discharge and at a prespecified follow-up, and capture drug exposures, levothyroxine use, frailty and delirium. The primary outcome would be the proportion who meet the operational definition above. The study should report the assay platform and method-specific reference limits, because the cohorts in Table 1 show how much these vary. Sample size depends on a prevalence that is currently unknown, so a pilot phase is sensible. Linked ICU and outpatient laboratory datasets could give a first estimate more cheaply.

CONCLUSION

Whether primary hypothyroidism is hidden behind NTIS in older patients recovering from sepsis is an open question, and on current evidence the answer is probably “rarely”. The age-related rise in TSH is too small to be the explanation, and severe hypothyroidism in the ICU more often follows stopped levothyroxine, amiodarone or known thyroid disease than a silent first presentation. The sensible response is to take a thyroid history on admission, read TSH and FT4 together, avoid thyroid hormone for an NTIS pattern, repeat tests after recovery when the cause remains unclear, and treat promptly when myxedema coma is suspected. A serial-testing cohort would settle the matter.

Limitations: This is a narrative review. The authors selected papers against a hypothesis, which invites confirmation bias, and there was no dual screening or risk-of-bias appraisal. Only English-language papers were included. Numerical data were taken from PubMed abstracts and were not re-extracted from full texts. Much of the NTIS literature is retrospective, concerns prognosis rather than diagnosis, and comes from a small number of countries. Several foundational studies used assays that are no longer in use. The approach in Figure 1 and Table 2 is expert opinion. Finally, we used an AI-assisted search tool and a language model for drafting support, as declared below.

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