BUSTA 4

Quesito 1. I second tier test per lo screening neonatale su dried blood spot

Quesito 2. Protocolli di screening neonatale per Sindrome adrenogenitale

Inglese: Lettura e traduzione dell'abstract di lavoro scientifico allegato

Informatica: inserire un grafico a dispersione utilizzando i dati di un file Excel

BUSTA 2

Quesito 1. Il cut-off fisso e il cut-off variabile nei test per lo screening neonatale su dried blood spot

Quesito 2. Protocolli di screening neonatale per Galattosemia

Inglese: Lettura e traduzione dell'abstract di lavoro scientifico allegato

Informatica: collocare, in ordine decrescente, una serie di valori numerici in colonna in una tabella Excel

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SPECIAL ARTICLE

Guidelines for the Treatment of Hypothyroidism

Prepared by the American Thyroid Association Task Force on Thyroid Hormone Replacement

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Background: A number of recent advances in our understanding of thyroid physiology may shed light on why some patients feel unwell while taking levothyroxine monotherapy. The purpose of this task force was to review the goals of levothyroxine therapy, the optimal prescription of conventional levothyroxine therapy, the sources of dissatisfaction with levothyroxine therapy, the evidence on treatment alternatives, and the relevant knowledge gaps. We wished to determine whether there are sufficient new data generated by well-designed studies to provide reason to pursue such therapies and change the current standard of care. This document is intended to inform clinical decision-making on thyroid hormone replacement therapy; it is not a replacement for individualized clinical judgment.

Methods: Task force members identified 24 questions relevant to the treatment of hypothyroidism. The clinical literature relating to each question was then reviewed. Clinical reviews were supplemented, when relevant, with related mechanistic and bench research literature reviews, performed by our team of translational scientists. Ethics reviews were provided, when relevant, by a bioethicist. The responses to questions were formatted, when possible, in the form of a formal clinical recommendation statement. When responses were not suitable for a formal clinical recommendation, a summary response statement without a formal clinical recommendation was developed. For clinical recommendations, the supporting evidence was appraised, and the strength of each clinical recommendation was assessed, using the American College of Physicians system. The final document was organized so that each topic is introduced with a question, followed by a formal clinical recommendation. Stakeholder input was received at a national meeting, with some subsequent refinement of the clinical questions addressed in the document. Consensus was achieved for all recommendations by the task force.

Results: We reviewed the following therapeutic categories: (i) levothyroxine therapy, (ii) non–levothyroxine-based thyroid hormone therapies, and (iii) use of thyroid hormone analogs. The second category included thyroid extracts, synthetic combination therapy, triiodothyronine therapy, and compounded thyroid hormones.

Conclusions: We concluded that levothyroxine should remain the standard of care for treating hypothyroidism. We found no consistently strong evidence for the superiority of alternative preparations (e.g., levothyroxine–liothyronine combination therapy, or thyroid extract therapy, or others) over monotherapy with levothyroxine, in improving health outcomes. Some examples of future research needs include the development of superior biomarkers of euthyroidism to supplement thyrotropin measurements, mechanistic research on serum triiodothyronine

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levels (including effects of age and disease status, relationship with tissue concentrations, as well as potential therapeutic targeting), and long-term outcome clinical trials testing combination therapy or thyroid extracts (including subgroup effects). Additional research is also needed to develop thyroid hormone analogs with a favorable benefit to risk profile.

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INTRODUCTION

Background, Objectives, and Rationale

LEVOTHYROXINE (LT_4) HAS BEEN CONSIDERED the standard of care for treatment of hypothyroidism for many years. This treatment is efficacious when administered orally, has a long serum half-life that permits daily administration, and results in resolution of the signs and symptoms of hypothyroidism in the majority of patients. However, a small proportion of patients being treated for hypothyroidism feel that LT_4 therapy is not efficacious in restoring optimum health.

Several recent advances in our understanding of thyroid physiology may shed light on why some patients feel unwell while taking LT_4 monotherapy. For example, much has been learned about the sources and regulation of triiodothyronine (T_3) in the plasma and within specific tissues, as well as about the regulation of thyrotropin (TSH). In addition, new data have emerged on dissatisfaction with LT_4 therapy being associated with genetic variation in deiodinases, and fatigue and depression in treated hypothyroid patients being linked with genetic variations in thyroid hormone transporters. The mandate of this task force was to review the goals of LT_4 therapy, examine sources of dissatisfaction with LT_4 therapy, examine the evidence concerning treatment alternatives, discuss gaps in our current knowledge of these therapies, and determine whether new data provide reason to pursue such therapies.

In this document the latest data regarding combination therapy, liothyronine (LT_3) monotherapy, compounded thyroid hormones, and nutraceuticals are presented. As a secondary objective, we also review the literature on thyroid hormone analogs. Pharmacology and regulatory aspects of the therapies that we reviewed are discussed. The potential for genetic variations to influence the ability to optimize thyroid hormone therapy is explored. The challenges of titrating thyroid hormone therapy in specific groups such as the pediatric, pregnant, and elderly populations are considered. However, the topic of subclinical hypothyroidism (SCH) is not addressed, other than in the pediatric population, because of prior extensive reviews of this topic in adults (1–4). Thyroid hormone therapy in patients with thyroid cancer is only mentioned if it is germane to the topic being discussed. Our goal is to promote discussion to improve our understanding of these issues, provide recommendations where possible, and to identify areas where further research is needed.

A recent comprehensive document, the "Clinical Practice Guidelines for Hypothyroidism in Adults Co-sponsored by the American Association of Clinical Endocrinologists (AACE) and the American Thyroid Association (ATA)," covers broader aspects of the management of hypothyroidism (3). In addition, two recent consensus documents published by the ATA and the Endocrine Society address the management of hypothyroidism during pregnancy (1,2). While this document was in preparation, guidelines from the European Thyroid Association (ETA) specifically addressing the issue of combined treatment with LT_4 and LT_3 were published (5). We acknowledge these guidelines, and our document was prepared with a goal of minimizing redundancy. We intended that the features that would distinguish this document from these guidelines would be (i) attention to the basic science and translational underpinning for the various thyroid hormone therapies, (ii) extensive consideration of ethical issues, (iii) focus on treatment itself, as opposed to other aspects of diagnosis and management, and most importantly (iv) focus on evaluation of treatment alternatives. We also wished to explore promising preclinical data for potential future therapies. For each topic, we evaluated the scientific validity of the studies cited.

The target audience for these guidelines includes clinicians providing care to patients with hypothyroidism. We outline what we believe is rational and optimal medical practice based on our evaluation of the evidence at the time of publication. However, areas of uncertainty and difference of opinion among experts remain, and it is not the intent of these guidelines to replace clinical judgment or individual decision-making. Rather, these recommendations are intended to inform the clinical decision-making process.

Approach Utilized in Conducting This Review

Our task force was commissioned and approved by officers of the ATA. We formed in the summer of 2011 and our composition included members with particular expertise in mechanistic and translational science (four members), members with particular expertise in clinical thyroidology (six members), a member with a background in pediatric endocrinology, a member with expertise in design and evaluation of health research, and a bioethicist. As of October 2011, we were redirected and specifically asked to develop clinical practice guidelines. Our task force met face to face in October 2011, June 2012, September 2012, June 2013, October 2013, and June 2014 with seven interim discussions using conference calls. A spring meeting of the ATA that was open to all potential stakeholders (e.g., health care providers, patients, public) was held on April 25 and 26, 2013, to highlight and promote broad discussion regarding relevant and topical issues (6). Information needs identified by stakeholders at this meeting were incorporated in task force group decisions in considering topics for review.

Task force members identified 24 questions relevant to the treatment of hypothyroidism, which were divided among the members. The clinical literature relating to each question was then reviewed by a primary reviewer, who summarized the findings, and compiled a response to the question in the form of a recommendation. The summary of the literature and response to each question were next revised by a secondary reviewer. Clinical reviews were supplemented, when relevant, with related mechanistic and bench research literature reviews, performed by a translational scientist and reviewed by a panel

BUSTA 1

Quesito 1. Il cut-off nei test per lo screening neonatale su dried blood spot: definizione e criteri di selezione

Quesito 2. Protocolli di screening neonatale per Ipotiroidismo Congenito

Inglese: Lettura e traduzione dell'abstract di lavoro scientifico allegato

Informatica: calcolare media e mediana di una serie di valori numerici in colonna in una tabella Excel

BUSTA 3

Quesito 1. Sensibilità e specificità dei test per lo screening neonatale su dried blood spot

Quesito 2. Protocolli di screening neonatale per Deficit di Biotinidasi

Inglese: Lettura e traduzione dell'abstract di lavoro scientifico allegato

Informatica: inserire un grafico a barre utilizzando i dati di un file Excel