Newborn Screening for Congenital Hypothyroidism: Recommended Guidelines

During the past decade newborn screening for congenital hypothyroidism has become an important health activity in most developed countries. These screening programs have not only benefited patients and their families but also have produced new information about the epidemiology, pathophysiology, diagnosis, and treatment of thyroid disease in infancy and childhood. During this period of implementation and growth of the screening programs, a variety of issues and questions arose. Some of these have been resolved, and some have not. The point has now been reached where collaboration of the combined experiences of the North American programs can address these issues. The reader should understand that what follows reflects current opinion and may require changes when the results of the next decade of screening are reviewed.

SCREENING METHOD

Thyroxine (T₄) and Thyroid-Stimulating Hormone (TSH)

Most North American programs use a two-tiered laboratory approach. An initial T₄ measurement is followed by measurement of TSH in specimens with low T₄ values. In addition to detecting infants with primary hypothyroidism (low or low normal T₄ level with elevated TSH value; prevalence 1:3,500 to 4,500 newborns), this approach can also identify infants with thyroxine-binding globulin deficiency and some with hypothalamic-pituitary hypothyroidism (low or low normal T₄ level with normal TSH value; prevalence 1:5,000 to 10,000 and 1:50,000 to 150,000 newborns, respectively). Programs that quantify T₄ values also have the option of identifying newborns with hyperthyroxinemia (1:20,000 to 40,000 newborns).

On the other hand, this approach will miss infants who have normal T₄ values but elevated TSH values. Such infants are relatively commonplace in European programs where initial screening is done by measurement of TSH. To identify such infants, the T₄ concentration cutoff (for TSH testing) must be increased well into the normal range.

TSH

A majority of European and Japanese programs favor screening by means of primary TSH measurements, supplemented by T₄ determinations on those infants with elevated TSH values. With this approach, infants with thyroxine-binding globulin deficiency, hypo- or hyperthyroxinemia, or hypothalamic-pituitary hypothyroidism will be missed.

Until further advances are made in the state of the art of screening, the choice of the method should be based on the experience of the program, needs of the population, and availability of resources. Until T₄ and TSH determinations can be done practically on all infants, physicians should be aware of potential limitations in each method of screening for congenital hypothyroidism. Even in the absence of technical or human errors, statistical information suggests that 6% to 12% of patients with infantile hypothyroidism will have normal screening hormonal concentrations regardless of the type of approach used and can be missed by the screening programs. (Combinations of values leading to misses could be normal T₄, high TSH; normal T₄, normal TSH; low T₄, normal TSH).

Quality Assurance

The proliferation of new screening programs and the expansion of older ones has underscored the need for clear guidelines for quality assurance. With this in mind, directors of newborn screening programs and physicians are advised to become familiar with the monograph, Legal Liability and Quality Control.
at room temperature, and not subjected to excessive
heat. The blood should completely saturate the
filter paper and be applied to one side only. Filter
paper spots should not be handled, placed on wet
surfaces, or contaminated by coffee, milk, or other
substances. All of the foregoing have the potential
to invalidate the results regardless of the method
used.

THE SPECIMEN

Every newborn infant should be tested before
discharge from the nursery. Results from specimens
obtained within the first 24 to 48 hours of life
occasionally are falsely positive for primary hypo-
thyroidism (using TSH as the primary screen) be-
cause of the elevated levels of TSH that occur
shortly after birth. However, screening before dis-
charge is preferable to missing the diagnosis of
hypothyroidism because of the lack of a clearly
defined policy of responsibility for blood collection
from infants discharged early. Because newborn
blood specimens are used for a variety of tests and
shared among different laboratories, every effort
should be made to collect adequate and sufficient
blood in the recommended manner (see Blood Col-
lection on Filter Paper for Neonatal Screening Pro-
grams: Tentative Standard, NCCLS publication
LA4-T, Villanova, PA, National Committee for
Clinical Laboratory Standards, 1985). The recall of
an infant because of an unsatisfactory specimen
causes needless delay in diagnosis and treatment of
a newborn with hypothyroidism. Although the test-
ing of an unsatisfactory specimen (because of in-
sufficient blood) can result in a false-negative TSH
value, false-negative values can also result from
human error in the processing of satisfactory spec-
imens or in erroneously reporting the results.

It is highly desirable that the blood be collected
between three and six days, but there will be situ-
ations when this is virtually impossible. In in-
stances such as home births, discharge before 24
hours, or a critically ill or premature neonate, blood
should be obtained by seven days after birth. When
an infant is transferred to another hospital, the
first hospital must indicate whether the specimen
has been collected. The second hospital should ob-
tain a specimen if there is no proof that blood was
collected before the transfer.

Mothers who have undergone treatment for thy-
roid disorders or who have a history of a previous
child with goitrous or nongoitrous congenital hy-
pothyroidism should be identified during pregnancy
to expedite the screening of the offspring.

Accurate screening results depend on good qual-
ity blood spots. Specimens that are technically un-
satisfactory or contain insufficient amounts of
blood should not be assayed. Blood samples
should be collected on approved filter paper forms, dried
at room temperature, and not subjected to excessive

TEST RESULTS

Normal T₄ Values

The normal range of T₄ values and the cutoff
level for TSH testing usually are established by the
individual program. Generally, the cutoff value var-
ies from 1.5 to 2 SD below the mean of the normal
range. However, many programs have opted to use
a tenth percentile cutoff.

Long-term follow-up for late-onset cases has not
been reported. Programs in which second speci-
mens are obtained (4 to 6 weeks) have indicated
that 10% of hypothyroid infants with T₄ values in
the normal range and elevated TSH values or with
initially low TSH values were missed during initial
screening. Clearly, infantile hypothyroidism can
still develop even when the screening T₄ value is
reported to be normal. Repeat testing should be
done on serum during infancy whenever there is a
clinical suspicion of hypothyroidism or when there
is a family history of thyroid disease in pregnancy
or familial thyroid dysshormonogenesis.

Low T₄, Elevated TSH Values

Any infant with a low T₄ and TSH value greater
than 40 μU/mL of serum is considered to have
primary hypothyroidism until proved otherwise.
Such infants should be examined immediately and
have confirmatory serum tests done to verify the
diagnosis. Treatment with replacement l-thyroxine
should be initiated before the results of the con-
firmatory tests are available. (Clinical management
of infants with hypothyroidism is described below.)
A small number of infants with abnormal screening
values will have transient hypothyroidism as dem-
onstrated by normal T₄ and TSH values on the con-
firmatory (follow-up to screening) laboratory
tests. Transient hypothyroidism frequently results
from intrauterine exposure to antithyroid drugs
(including iodine), maternal antithyroid antibodies,
or endemic iodine deficiency. Cases also have been
reported in association with pseudohypoparathy-
roidism and prenatal or postnatal exposure to ex-
cess iodides (povidone iodine, iodinated contrast
materials). The practice of using liberal quantities
of iodine-containing solutions as disinfectants in
newborn nurseries should be balanced against the
potential for producing transient hypothyroidism.
Idiopathic transient hypothyroidism and cases associated with postnatal iodine exposure are 30 times more common among premature neonates. Other features that suggest a transient condition are relatively modest elevations of TSH values (20 to 100 μU/mL), male sex, and a eutopic gland on radioisotope scanning. Because transient hypothyroidism will not be recognized in some infants, initial treatment will be similar to that in any infant with permanent infantile hypothyroidism. For this reason, it is important to determine at some later time whether or not the hypothyroidism is permanent and whether the infant in fact requires lifelong treatment (see “Assessment of Permanence of Hypothyroidism”). The one recognized exception to this is the infant with transient hypothyroidism born of a mother receiving an antithyroid drug. In virtually all such cases, the T₄ and TSH values return to normal within 1 to 3 weeks after birth without treatment.

**Low T₄, Normal TSH Values**

Infants with low T₄ (approximately 2 SD below the mean of the normal range) but normal TSH values seldom have thyroid insufficiency. The low T₄, normal TSH profile, seen in 3% to 5% of neonates, is associated with protein-binding disturbances such as thyroxine-binding globulin deficiency (1:5,000 to 10,000 newborns), a benign state of hypothalamic immaturity, hypothalamic-pituitary hypothyroidism (1:50,000 to 150,000 newborns), or with primary hypothyroidism in an infant with a delayed TSH response (1:100,000 newborns). Neonates who are premature or ill are found with disproportionate frequency among those with this set of laboratory values. Because there is no clear consensus with respect to follow-up, programs have elected (1) to take no further action, (2) to follow the infant until the T₄ level becomes normal, (3) to request a repeat blood sample for measurement of thyroxine-binding globulin and free T₄ concentrations, or (4) to perform a thyrotropin-releasing hormone test for the diagnosis of hypothalamic pituitary hypothyroidism. In the final analysis, the responsibility for deciding which course of action to follow rests with the judgment of the attending physician. Treatment of these infants (with the exception of those with secondary hypothyroidism) with l-thyroxine is seldom justified and may do more harm than good.

**Low T₄, Delayed TSH Level Increase**

There is now ample proof that infants with congenital hypothyroidism can be born with low T₄ concentrations and normal range TSH values. Serum TSH values in these infants increase during the first few weeks of life to values characteristic of primary hypothyroidism. It is important, therefore, that screening be repeated on any infant in whom clinical signs of hypothyroidism appear. Based on experience, the prevalence of such cases is one in 50,000 to one in 100,000 newborns.

The possibility that such infants, plus those with elevated TSH values but normal T₄ concentrations, would be missed on initial screening has prompted a few programs to rescreen all newborns at 2 to 4 weeks of age. Despite significant detection rates on a second screen at 2 to 6 weeks, most programs have not established a routine second screen because of: (1) the increased cost of such screening, (2) a relatively low yield of cases, (3) diversion and dilution of key personnel, (4) inability to implement new programs, (5) the prognosis of this cohort is uncertain.

**CLINICAL MANAGEMENT OF NEWBORN INFANTS WITH LOW T₄ AND ELEVATED TSH VALUES**

Infants with low T₄ and elevated TSH levels have congenital hypothyroidism until proven otherwise. Management should include:

1. Seeing the infant without delay, and if possible, evaluation by a pediatric endocrinologist.
2. Complete history, including parental thyroid status (drugs and medications) and physical examination.
3. Serum for confirmatory measurements of TSH and T₄ concentrations. Serum thyroglobulin or triiodothyronine determinations may differentiate athyreotic hypothyroidism from the other types.
4. (optional). ¹²³I-radiiodine uptake and/or scan (technetium second choice) to identify functional thyroid tissue.

There is some controversy regarding the risk to benefit ratio of early thyroid scanning of suspect infants. For those physicians who opt for imaging, the benefits can be summarized as follows: (a) If an ectopic gland is demonstrated, the permanence of thyroid disease is established. (b) The absence of thyroid gland uptake, most often associated with thyroid atrophy or hypoplasia, almost always indicates permanent hypothyroidism. However, occasionally no gland is visualized in normal infants scanned with technetium. (c) Normal scan findings (or a goiter) suggest an enzyme defect and alert the physician to the possible hereditary nature of the disorder. The presence of any enzyme defect is especially important for those families planning additional children; the scan enables the physician to arrange for genetic counseling. (d) Some infants with normal scan findings at birth may have tran-
sient disease due to blocking antibodies or drugs, and for that reason they should have a careful follow-up evaluation at 3 to 4 years of age under the conditions described in “Assessment of Permanence of Hypothyroidism.”

If a scan with \(^{123}\!\!\text{I}\) is not performed within the first few days after starting treatment, any residual thyroid function might be compromised as a consequence of TSH inhibition by the exogenous thyroid medication. However, treatment should never be delayed to obtain a satisfactory scan. If need be, the scan can be postponed until the child is of an age when treatment can be briefly interrupted without danger to the developing CNS.

Despite the arguments in favor of thyroid scanning or imaging, there remains the possibility of a slight but undefinable risk of radiation exposure. For this reason the procedure should be performed by experienced personnel with optimum equipment using the minimally recommended tracer dose. The preferable isotope for optimal scanning is \(^{123}\!\!\text{I}\), which is not available in all laboratories.

5. In addition to the other recommendations, ancillary studies such as bone maturation by standard means or by bone surface measurements may be of prognostic value in evaluation of the infant. As mentioned earlier, athyreotic infants frequently have low thyroglobulin and/or triiodothyronine concentrations.

**MEDICATION**

Replacement therapy should be done with T\(_4\), not triiodothyronine. The average dose of l-thyroxine at the start of treatment is 10 to 15 \(\mu\text{g/kg of weight (37.5 to 50 \(\mu\text{g/d for a term infant). The serum concentration of T}_4\) (corrected for variation in thyroxine-binding globulin level) should be maintained at all times in the upper half of the normal range during the first year of life. There is evidence that those infants whose serum T\(_4\) decreases to less than 8.0 \(\mu\text{g/dL, accompanied by a TSH value >15 \(\mu\text{U/mL within 6 to 9 weeks after initiation of l-thyroxine should serve to alert the physician that the child may not be receiving adequate l-thyroxine regularly. At this point, careful inquiry should be made regarding compliance, dose of medication, and method of administration. When attempting to achieve the optimal level of circulating T\(_4\), physicians should always bear in mind the danger of excessive medication (eg, premature craniosynostosis) and thus be prepared to monitor blood levels of T\(_4\) at close intervals.**

**FOLLOW-UP**

Two to four weeks after the start of treatment, clinical examination should be performed and serum obtained for TSH and T\(_4\) determinations. Physical examination and measurement of T\(_4\) and TSH should be performed 4 weeks after any change in l-thyroxine dosage. Routine clinical examination (including growth curves) should be performed, and serum submitted for measurement of T\(_4\) and TSH concentrations at 3, 6, 9, 12, 18, and 24 months of age and at each succeeding birth date and each change of dosage. Because most screening procedures are not designed to detect high levels of T\(_4\), filter paper blood specimens should not be used to monitor the absolute concentration of circulating T\(_4\) in the infant. A failure of the serum T\(_4\) concentration to increase into the upper half of the normal range by 2 to 4 weeks and/or TSH concentration to decrease to less than 20 \(\mu\text{U/mL within 6 to 9 weeks after initiation of l-thyroxine should serve to alert the physician that the child may not be receiving adequate l-thyroxine regularly. At this point, careful inquiry should be made regarding compliance, dose of medication, and method of administration. When attempting to achieve the optimal level of circulating T\(_4\), physicians should always bear in mind the danger of excessive medication (eg, premature craniosynostosis) and thus be prepared to monitor blood levels of T\(_4\) at close intervals.**

**ASSESSMENT OF PERMANENCE OF HYPOTHYROIDISM**

Permanent thyroid disease can be assumed if the thyroid uptake and/or scan has revealed absent thyroid tissue, an ectopic gland, or goiter (with the previously mentioned exceptions) or if the serum TSH is seen to increase above 15 \(\mu\text{U/mL after the first year, presumably because of inadequate T}_4\) replacement.

When permanence of thyroid disease is not established, l-thyroxine administration should be discontinued sometime after the child is 3 or 4 years of age and the child not treated for 30 days. At that time, serum should be obtained for measurement of T\(_4\) and TSH levels. If the T\(_4\) and TSH concentrations remain in the normal range, euthyroidism is assumed and a diagnosis of transient hypothyroidism recorded. In this instance, however, the physician should monitor the child carefully and repeat the hormonal analysis at the slightest suspicion of relapse. If the T\(_4\) is low and the TSH elevated, permanent hypothyroidism is confirmed, and therapy is reinstituted. If the results are inconclusive, careful follow-up and repeat testing will be necessary.

**ADMONITION**

Finally, physicians cannot and must not relinquish their clinical judgment and experience in the face of normal newborn thyroid test results. Failure of normal development can result from hypothyroidism in infants who have had normal T\(_4\) and
TSH screening results. The disorder can become manifest or acquired after the screening tests have been carried out, or rarely, the test results can be in error.
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