Systematic neonatal screening for severe combined immunodeficiency and severe T-cell lymphopenia: Analysis of cost-effectiveness based on French real field data

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Background: The inclusion of severe combined immunodeficiency (SCID) in a Europe-wide screening program is currently debated.

Objective: In making a case for inclusion in the French newborn screening program, we explored the costs incurred and potentially saved by early management of SCID.

Methods: For test costs, a microcosting study documented the resources used in a laboratory piloting a newborn screening test on Guthrie cards using the T-cell receptor excision circle quantification method. For treatment costs, patients with SCID admitted to the national reference center for primary immunodeficiency in France between 2006 and 2010 were included. Costs of admission were estimated from actual national production costs. We estimated the costs for patients who underwent early versus delayed hematopoietic stem cell transplantation (HSCT; age, ≤3 vs >3 months, respectively).

Results: The unit cost of the test varied between €4.69 and €6.79 for 33,800 samples per year, depending on equipment use and saturation. Of the 30 patients included, 27 underwent HSCT after age 3 months. At 1 year after HSCT, 10 of these had died, and all 3 patients undergoing early transplantation survived. The medical costs for HSCT after 3 months were €195,776 (interquartile range, €165,884-€257,160) versus €86,179 (range, €59,014-€272,577) when performed before 3 months of age. In patients undergoing late transplantation, active infection contributed to high cost and poor outcome.

Conclusion: Early detection of SCID could reduce the cost of treatment by €50,000-100,000 per case. Assuming a €5 unit cost per test, the incidence required to break even is 1:20,000; however, if the survival advantage of HSCT before 3 months is confirmed, universal screening is likely to be cost-effective. (J Allergy Clin Immunol 2015;135:1589-93.)

Key words: *Primary immunodeficiency, severe combined immunodeficiency, severe T-cell lymphopenia, newborn screening, health economics, cost-effectiveness, health policy*

The policy relevance of systematic newborn screening (NBS) for severe combined immunodeficiency (SCID) is still debated. SCID is a rare but devastating primary immunodeficiency (PID) ultimately leading to death in all cases by the age of 2 years without appropriate diagnosis and care. SCID is the most severe PID and constitutes a pediatric emergency.[1,2] Affected children are born with severely impaired cellular and humoral immunity and are therefore highly susceptible to bacterial, viral, fungal, and opportunistic infections. Hematopoietic stem cell transplantation (HSCT) is extremely effective and the only curative treatment for SCID, allowing the majority of affected children to live normal and fully functional lives. However, the success of HSCT is greatly influenced by age at diagnosis and presentation (whether the affected child has already experienced recurrent or opportunistic infections).[3,4] Although survival of patients receiving transplants has increased over recent decades, overall survival in the last decade is around 70%.[5] Recently, there have been reports of increased survival, better and earlier immune reconstitution, and better quality of life in patients given a diagnosis and undergoing transplantation before age 3.5 months,[6-10] paving the way for the implementation of NBS for SCID.

Accurate epidemiologic indicators of SCID frequency based on large-scale population studies are lacking. SCID incidence is conservatively estimated at around 1:50,000 to 1:100,000 live births (which would mean 10-20 children born with the condition per year in each of the largest European Union countries, such as

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Abbreviations used
CEREDIH: French National Center for Primary Immunodeficiencies
HSCT: Hematopoietic stem cell transplantation
NBS: Newborn screening
PID: Primary immunodeficiency
SCID: Severe combined immunodeficiency
TCL: T-cell lymphopenia
TREC: T-cell receptor excision circle

France, the United Kingdom, Germany, or Italy, which report between 500,000 and 830,000 live births per year),[11,12] but recently published data from SCID screening programs in the United States suggest the incidence of typical SCID, leaky SCID, and Omenn syndrome to be 1:58,000 (95% CI, 1:46,000-1:80,000) live births.[13,14] SCID incidence is even higher in populations with a high rate of consanguinity.[15,16]

Currently, 23 US states (including Wisconsin, Massachusetts, California, and New York) have implemented statewide universal NBS programs using the T-cell receptor excision circle (TREC) quantification method for SCID/severe T-cell lymphopenia (TCL).[17-19] However, Louisiana and Puerto Rico are examples of ending a program because of lack of funding (http://www.scid.net/, accessed July 2014).

European countries have not yet implemented SCID/severe TCL screening in their regular universal NBS programs, despite the fact that the revised Wilson and Jungner criteria for screening are obviously met by SCID.[20,21] France, the United Kingdom, Germany, and Sweden, among others, are moving toward implementation of universal SCID/severe TCL screening.

The decision analytic models that have explored the cost-effectiveness of SCID screening have produced 2 sets of important results, namely the actual incremental cost-effectiveness of a population-based program and the main sources of uncertainty. Among the sources of uncertainty are the actual incidence of the disease, the cost of the test, and the benefits (survival and cost) of early versus delayed treatment rank highest.[22,23]

In preparing to make the case for inclusion of SCID in national and Europe-wide screening programs, we explored the costs incurred and potentially saved by early diagnosis and treatment of SCID. These costs include (1) the costs of screening, (2) the cost of early HSCT, and (3) the cost of delayed HSCT.

METHODS

We estimated the costs from the viewpoint of the health care and social care systems, collecting actual resource data for the diagnosis of patients with SCID who underwent HSCT in France over a 1-year period using records from the Necker Children's Hospital (a university teaching hospital) and the French National Registry of PIDs under the auspices of the French National Reference Center for Primary Immune Deficiencies (CEREDIH).[11]

This article does not contain any studies with human or animal subjects. We used epidemiologic and billing information recorded. Authorization to access and use this information was granted. Ethics board approval was obtained for research on patients cared for by the French National Reference Center for Primary Immune Deficiencies (CEREDIH; CCTIRS: nb 06.327 obtained on September 7, 2006). National hospital claims database use with record linkage was approved by the French national data protection agency (CNIL 1165361 obtained on September 28, 2013).

Screening costs

A microcosting study was performed to prospectively document the resources used in a laboratory piloting an SCID screening test based on quantification of TRECs using dried blood spot samples routinely collected as part of the national French NBS program for other conditions.[24] TRECs are small pieces of DNA that are formed by the rearrangement of T-cell receptor genes and are markers for the number of naive T cells that have recently emigrated from the thymus. SCID/TCL is characterized by undetectable or very low levels of circulating TRECs. We collected data on laboratory machine use (acquisition and depreciation over a 5-year period and maintenance), labor time measured as part of a time-motion study, and the costs of specific reagents. Other laboratory resources and overhead costs were retrieved from the accounting department and allocated in proportion to testing time. The TREC screening procedure included spot sample punching, manual DNA extraction, DNA amplification by using real-time quantitative PCR with a calibration curve and a control gene, data interpretation, and report of results. All phases were observed and valued. We used purchase prices for equipment and supplies and actual gross salaries for staff. We varied assumptions on the number of yearly tests performed. Labor costs were €0.57/min for a laboratory technician and €0.81/min for a biologist. We assumed a repeat analysis for problems in interpreting results, with a repeat PCR rate of 17% and a repeat total procedure rate of 2%. Computations were made for one 65-well plate used to screen 65 patients. We assumed the current use of the equipment with 33,800 samples per year and tested 2 other hypotheses: partially saturated equipment use (allowing other analyses than TREC to be run) and dedicated equipment use.

Treatment costs

Necker Hospital, a university teaching hospital, is the largest center for SCID treatment in France and manages the French National registry of PIDs. All patients given a diagnosis of SCID who underwent HSCT at Necker Hospital from January 1, 2006, to December 31, 2010, were included. We excluded patients with Omenn syndrome and patients with variant/leaky SCID to limit potential biases in terms of comorbidities and higher incidence before and after HSCT complications (ie, additional infections under immunosuppressive drugs indicated for the treatment of Omenn syndrome features). Identification of patients was based on the diagnosis of SCID and the initiation of curative HSCT; other treatments (eg, gene therapy or enzyme therapy) were not considered. We used record linkage in the national claims database and worked backward to retrieve all hospital admissions from the time of birth to the diagnosis of SCID and forward to retrieve all posttransplantation admissions, including outpatient admissions from up to 1 year after HSCT. The hospital information system records resource use at the patient level. These include length of stay in each type of unit, procedures, imaging, tests, drugs, devices, housekeeping, and overhead. The hospital cost is constructed from activity-based costs collected at the patient level and then aggregated to the diagnosis-related group level. We used this information to calculate patient-specific costs for neonatal and pediatric intensive care units and pediatric hematology wards based on actual length of stay and resource use. Out-of-hospital costs were not documented under the assumption that posttransplantation follow-up would be managed by university hospital–based teams in most countries.

We separately estimated the costs for patients treated with early versus delayed HSCT ($\leq$3 vs >3 months, respectively). We also attempted to document welfare benefits and social care costs associated with SCID by using hospital benefit claims records. These costs included support payments to families during treatment, disability benefits for children, support from charities, and extra regulatory payments by Statutory Health Insurance. Records were abstracted to identify the type and duration of each payment.

Descriptive statistics (medians and interquartile ranges) for length of stay and costs were used. Nonparametric tests for comparisons were used when relevant and feasible. The Kruskal-Wallis test was chosen to compare costs because of their nonnormal distribution and the small sample size in each group. One-year survival was estimated from hospital charts and plotted as a Kaplan-Meier curve for descriptive purposes only. The study was performed in accordance with the Declaration of Helsinki, Good Epidemiological

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