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Screening for Hemoglobinopathies in Newborns: Reaffirmation Update for the U.S. Preventive Services Task Force

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The information in this report is intended to help clinicians, employers, policymakers, and others make informed decisions about the provision of health care services. This report is intended as a reference and not as a substitute for clinical judgment.

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Introduction

Inherited variants in a recessive gene that encodes the synthesis of a portion of adult hemoglobin (hemoglobin A) produce a spectrum of hemoglobin disorders known as hemoglobinopathies. Individuals who inherit two copies of the variant hemoglobin S develop sickle cell anemia, a chronic disease characterized by an increased risk for invasive infections, recurrent painful crises, and cardiovascular and pulmonary complications. Sickle cell anemia affects 1 out of every 375 African American infants born in the U.S.[1]

In 1996, the United States Preventive Services Task Force (USPSTF) recommended "screening newborn infants for hemoglobinopathies with hemoglobin electrophoresis or other tests of comparable accuracy on umbilical cord or heelstick blood specimens (A recommendation)" in order to "identify infants who may benefit from antibiotic prophylaxis to prevent sepsis."[1] The USPSTF also recommended prompt followup for infants identified with sickle cell disease; genetic counseling regarding testing of family members and risks to future offspring; education; and referrals. All 50 states have since instituted universal newborn screening programs for hemoglobinopathies.

In 2007, the USPSTF decided to update its recommendation statement on screening for hemoglobinopathies in newborns. Noting that the 1996 recommendation was made on a strong evidence base and that it would take large, high-quality studies or evidence of substantial harms to overturn the current recommendation, the USPSTF chose to perform a reaffirmation update for this topic. The USPSTF performs reaffirmation updates for older recommendation statements that remain USPSTF priorities, are within the scope of the USPSTF, and for which there is compelling reason for the USPSTF to have a current recommendation statement.

To assist the USPSTF in updating its 1996 recommendation on screening for hemoglobinopathies in newborns, staff at the Agency for Healthcare Research and Quality (AHRQ) performed a literature search and consulted with subject area experts.

The goal of this targeted review was to find new, high-quality evidence regarding the benefits and potential harms of screening for hemoglobinopathies in newborns. Sixty-nine studies were initially identified. The literature search methodology is described in Appendix I. One systematic review of benefits of screening, one systematic review of benefits of penicillin prophylaxis, and three articles about potential harms met inclusion criteria and are discussed in the following review.

Evidence of the Benefits of Screening for Hemoglobinopathies in Newborns

Thus far, national policies on universal newborn screening for hemoglobinopathies have been based on evidence of the benefits of treatment, in the absence of direct evidence of the value of screening. A national policy was first recommended by a 1987 National Institutes of Health Consensus Conference panel[2] following the publication of a randomized controlled trial that demonstrated a 84 percent reduction in the incidence of infections in children with hemoglobin SS disease who received prophylactic oral penicillin starting at 4 months of age, compared to children taking placebo.[3] The 1996 USPSTF recommendation on screening for hemoglobinopathies in newborns was similarly based on an extrapolation of evidence of benefit from early penicillin prophylaxis, rather than evidence of benefit in trials of screening versus no screening.

Our initial literature search identified no new randomized controlled trials of screening for hemoglobinopathies in newborns. A 2000 systematic review of randomized trials comparing diagnosis of sickle cell disease by neonatal screening to clinical diagnosis also found no eligible studies.[4]

A supplemental literature search limited to the Cochrane Database of Systematic Reviews identified a 2002 systematic review of randomized trials comparing prophylactic antibiotics to placebo to prevent pneumococcal infections in children with sickle cell disease. This review included three studies, all of which were published prior to 1996. The review concluded that infants with hemoglobin SS disease who receive prophylactic

penicillin have a significantly lower risk for pneumococcal infection (odds ratio = 0.37, 95% CI 0.16 – 0.86) and minimal adverse reactions.[5]

Evidence of the Harms of Screening for Hemoglobinopathies in Newborns

In 1996, the USPSTF observed that false-positive and false-negative screening results are rare in U.S. screening programs.[1] Since that time, however, screening technology has become capable of identifying several hundred hemoglobin variants, most of negligible clinical significance. Identifying newborns with sickle cell trait – individuals who inherit one copy of hemoglobin S and one copy of hemoglobin A, and are also known as sickle cell carriers – is of uncertain benefit and has the potential to cause psychological harms. Three recent articles have addressed potential harms of disclosing sickle cell carrier status to parents of affected newborns.

Laird and colleagues discussed theoretical concerns raised by notifying parents of their newborn's carrier status, including exposure of non-paternity, stigma and discrimination, negative impact on self-esteem, and anxiety about future health problems. Since, in the United States, withholding carrier status from parents is generally considered to be unethical, access to genetic counseling services is critically important to minimize the risk of these harms.[6]

A 2004 systematic review limited to controlled trials addressing the impact of disclosing newborn carrier status identified by newborn blood spot screening found no eligible studies.[7] A more comprehensive 2004 systematic review of psychosocial aspects of genetic screening identified two articles, both published prior to 1996, that examined the acceptability of genetic counseling for parents of infants with sickle cell trait. However, neither study described nor attempted to quantify harms resulting from notification of carrier status.[8] No new studies of health outcomes or psychological harms related to false positive results or communication of carrier status were identified.

Recent Recommendations from Other Groups:

In May 2006, an expert group on newborn screening convened by the Maternal and Child Health Bureau (MCHB) and the American College of Medical Genetics (ACMG) included hemoglobin SS, hemoglobin S/β-thalassemia, and hemoglobin SC disease in its 29-condition uniform newborn screening core panel. The group noted that current screening programs can detect over 700 variant hemoglobins, of which only 25 are considered clinically significant.[9]

In September 2006, the American Academy of Pediatrics revised and updated its Newborn Screening Fact Sheets. The fact sheet on sickle cell disease recommends universal newborn screening and confirmatory testing on a second blood sample, no later than 2 months of age, for infants with initial positive screens.[10]

The United Kingdom's National Health Service (NHS) has established a linked antenatal and newborn screening program for sickle cell disease and thalassemia, and published standards for universal newborn screening in November 2006.[11]

In 2002, the National Heart, Lung and Blood Institute (NHLBI) guideline on management of sickle cell disease affirmed the conclusion of the 1987 NIH Consensus Conference to recommend universal newborn screening. It also noted that "no national consensus has yet been produced to guide neonatal screening programs and clinicians in the followup of infants with unidentified hemoglobin variants."[12]

Emerging Issues and Research Gaps

There is a paucity of research on the psychosocial effects of communicating newborn carrier status information to parents or on which counseling practices are most likely to minimize harmful effects. A descriptive study of current communication practices in the U.K. is underway, with results expected in 2008.[13]

While screening for hemoglobinopathies in newborns is mandated in all 50 states and the District of Columbia, the methods used for initial screening differ. Most states use thin-layer isoelectric focusing (IEF) or high-performance liquid chromatography (HPLC) as their primary screening method, but a few continue to use electrophoresis or DNA testing. Consensus is lacking as to the optimal screening technique. Also, laboratories differ in which hemoglobin variants they commonly report. There is ongoing research into using newer techniques such as mass spectrometry-mass spectrometry (MSMS) to detect only clinically significant hemoglobinopathies, and thereby avoid the problem of what to tell parents of newborns with unidentified hemoglobin variants found incidentally on screening.[14]

The availability of pneumococcal vaccine has altered the calculation of benefits and harms. Starting in 2000, universal childhood vaccination with a 7-valent pneumococcal conjugate vaccine beginning at 2 months of age has resulted in a sharp decline in invasive pneumococcal disease in all children, including those with sickle cell anemia.[15] Although the vaccine is not completely protective and thus does not obviate the need to give prophylactic penicillin to infants with sickle cell anemia, it has had the effect of making universal newborn screening significantly less cost-effective in comparison to selective newborn screening than in years past.[16]

Although the ACMG core panel[9] and the NHLBI guideline[12] recommend prophylactic penicillin for children younger than 5 years of age with hemoglobin SC disease, it is uncertain if these patients require prophylaxis because they were not included in the RCT that established benefit. Compared to hemoglobin SS disease, hemoglobin SC disease is characterized by a mild anemia and preserved splenic function. Citing reports that children with hemoglobin SC have a higher incidence of bacteremia, the NHLBI guideline asserts that "protection of SCD-SC patients with prophylactic penicillin and antipneumococcal vaccine is probably wise even without experimental data."[12] This opinion, however, is not universal among sickle cell experts.[17]

Conclusion

In summary, we found no substantial new evidence since 1996 on the benefits or harms of screening for hemoglobinopathies in newborns. Future research is needed to identify counseling practices that minimize negative psychosocial effects of communicating newborn carrier status information and to develop alternative screening methods that are capable of identifying only clinically significant hemoglobinopathies.

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Appendix: Literature Search Process for the Reaffirmation Update

AHRQ staff performed a targeted literature search for the benefits of screening for hemoglobinopathies and the potential harms of screening. A baseline search strategy was not available from the 1996 USPSTF recommendation. For this reaffirmation update, searches were limited to the period 1/1/95 to 12/31/06.

Consistent with USPSTF reaffirmation update protocols, initial searches were limited to PubMed core journals. When the initial searches revealed a paucity of eligible articles, the searches were expanded to include non-core journals. Results from PubMed searches were supplemented with recommendations from subject matter experts and reference list reviews.

Since the 1996 USPSTF recommendation was based on strong evidence of benefit from early penicillin prophylaxis, rather than evidence of benefit in a RCT of screening versus no screening, a supplemental search limited to the Cochrane Database of Systematic Reviews was performed to identify new evidence regarding the benefit of prophylactic medication in patients with sickle cell anemia.

All articles were reviewed for predetermined inclusion/exclusion criteria by two team members at each stage of review (title/abstract, full article). A consensus process was used to resolve any reviews which resulted in differences of opinion.

Basic outline of PubMed search strategies:

Limited to: English
Human
Publication Date from 01/01/1995 to 12/31/2006

For benefits

MeSH terms: "hemoglobinopathies," "mass screening"

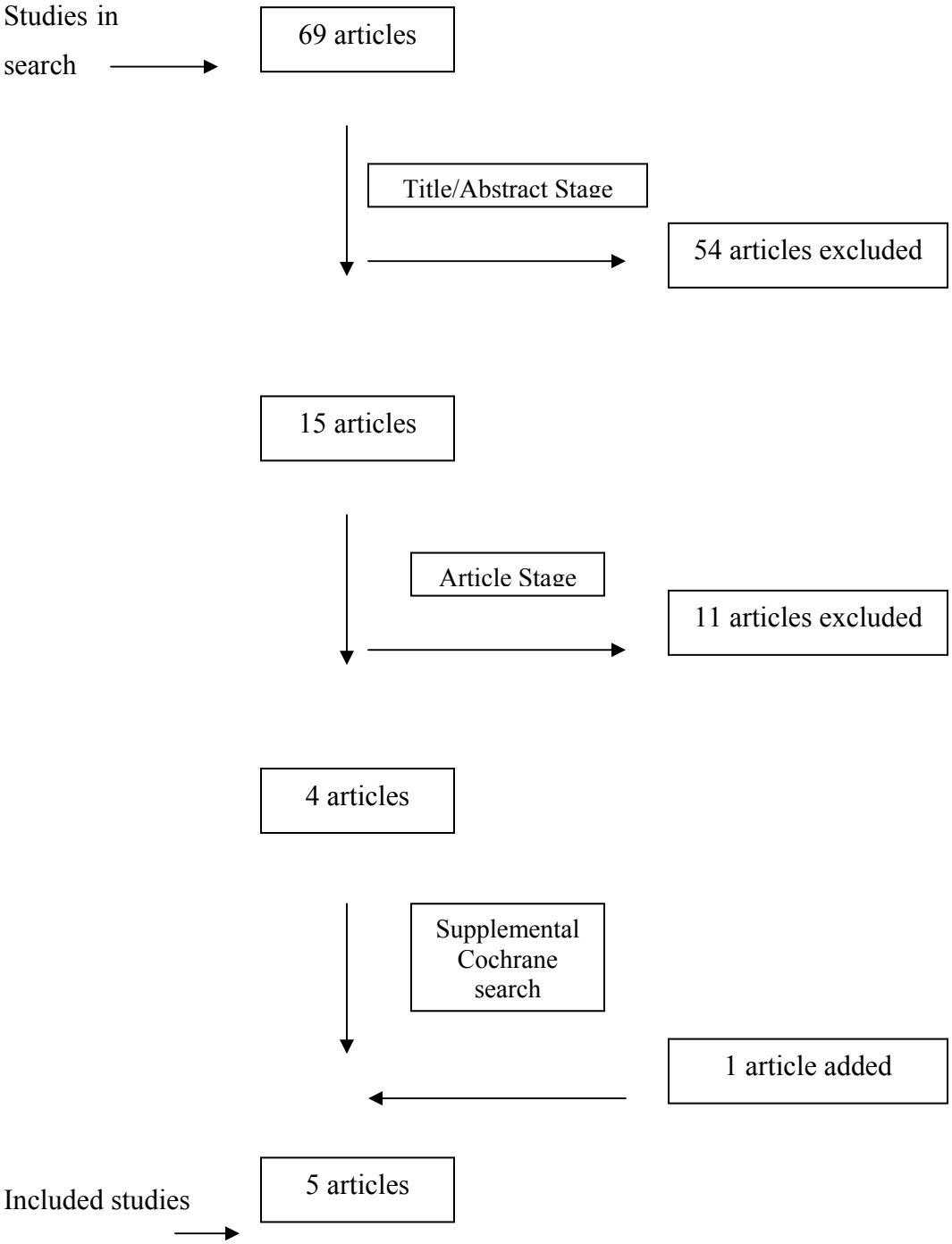
Limited to: randomized controlled trials, meta-analyses, systematic reviews

For harms

MeSH terms: "hemoglobinopathies," "mass screening"
Other terms: "false positive reactions," "harms", "anxiety"
Excluded: editorials, comments, news items and letters

A series of searches using combinations of MeSH terms and subsets and keyword searches were performed. More details of the search strategies may be obtained from the author.

Results of the Application of Inclusion/Exclusion Criteria



Reasons for Exclusion:

Reason	Description
Not Newborn (18)*	Study of screening a population other than newborns (eg, pregnant women)
Not Condition (10)	Study not on hemoglobinopathies
Study Design (1)	Study not meeting design inclusion criteria (eg, case report)
No Outcomes (30)	Study or narrative review without information on appropriate hemoglobinopathy-screening-specific harms or benefit outcomes
Not Screening (6)	Study not about screening (eg, treatment of complications)

*Number of excluded studies in parentheses