Committee placed on concern for early mortality predicted by these parameters.

These recommendations are problematic for several reasons:

1. No guidance is given regarding the indication for or timing of screening echocardiography to assess mortality risk.
2. There is no direct evidence that disease-modifying therapies have an effect on mortality for those with elevated TRV or NT-proBNP, or proven PH.
3. Although an elevated TRV may be found in 10 to 20% of children, the cited evidence suggests increased morbidity, not mortality, among children 8 years of age or older. Yet, the Guideline calls for initiating disease-modifying therapy without age limitation, even though mortality in children with elevated TRV has not been demonstrated. This seems inconsistent with the Committee's justification of intervention, despite potential harms, based on reduction in early mortality.
4. The majority of evidence reviewed by the Committee includes individuals with HbSS/Sβ^0 thalassemia; little information is provided or available for HbSC/Sβ^+ thalassemia. The term "SCD" is used throughout the paper without distinguishing among sickle genotypes. Approximately 40% of the ~90,000 individuals in the U.S. sickle cell population (2) have these milder forms of sickle cell disease with less sickling, anemia, and hemolysis, for which hydroxyurea therapy is not currently recommended, given a paucity of evidence demonstrating benefits. The authors note 10 to 25% of these individuals may have a TRV greater than 2.5 m/s, representing up to 9,000 individuals. Although listed as a "weak" recommendation, implementation of the Guideline calls for initiation of lifelong transfusion therapy for these patients. Chronic exchange transfusion will be required because baseline hemoglobin values are too high to permit simple transfusion, which results in a three- to fourfold increase in the amount of blood required (3) and attendant risks of alloimmunization and complications of indwelling lines typically required for indefinite transfusion therapy. There may also be significant adverse impact on school and/or work attendance. Importantly, the risk of early mortality in these individuals is not clear, calling into question the justification for and benefits of this costly intervention.
5. The Guideline recommends initiation of lifelong disease-modifying therapy solely for NT-proBNP greater than or equal to 160 pg/ml. Unlike the discussion providing context for TRV determination, no guidance is given about how or when to measure NT-proBNP. Transient acute elevation in TRV described in the paper could be associated with a similarly transient elevation in NT-proBNP, which is also affected by renal insufficiency. There are no data regarding impact on mortality risk of NT-proBNP values determined in these settings, but per the Guideline they could be used to justify initiation of hydroxyurea or chronic transfusion. Furthermore, the evidence cited is for patients with HbSS/Sβ thalassemia, not HbSC disease.

The concerns raised by the Guideline emphasize the need for research into causes of death associated with elevated TRV or NT-proBNP. Clinical trials are necessary to demonstrate benefits outweigh risks before recommending universal application of disease-modifying therapies based on these findings and for those with catheterization-proven PH. ■

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Reply

From the Authors:

Dr. Hassell and colleagues raise concerns about our recommendations to treat, with hydroxyurea or transfusions, patients with sickle cell disease (SCD) who are at high risk of death based on an elevated tricuspid regurgitant jet velocity (TRV), high levels of serum

N-terminal prohormone brain natriuretic peptide (NT-proBNP), or pulmonary hypertension (PH) identified by right heart catheterization (1). Although they point out important caveats concerning the age of screening and risks associated with blood transfusions, we disagree with their positions on hydroxyurea therapy in patients with SCD at the highest risk for death.

Although the use of hydroxyurea and chronic transfusions have not been specifically tested in placebo-controlled trials in patients with SCD with PH, and likely will never be tested based on lack of equipoise, the use of indirect evidence to inform judgments is acceptable and appropriate in guideline development, as long as it is transparently described and the quality of evidence adjusted accordingly. Hydroxyurea decreases the frequency of vasoocclusive events and the acute chest syndrome and improves survival for HbSS patients (2). It is safe and effective even in children with SCD and has been effective in small cohorts of patients with HbSC disease (3, 4). HbSS adults with an elevated TRV, NT-proBNP level, or PH diagnosed by right heart catheterization suffer an increased mortality risk ranging from 3- to 15-fold, established by more than eight independent prospective cohort studies (*see* full citations in Guidelines document, Reference 1). Furthermore, the risk of death with PH increases during vasoocclusive events and acute chest syndrome (5). Considering the extensive safety and efficacy data supporting hydroxyurea therapy, even in very young children with SCD (4), it is difficult to argue a position that would deny this therapy for the group of patients with SCD at highest risk of death.

Other concerns raised by Dr. Hassell and colleagues about the age of screening, the potential risks associated with chronic transfusion therapy, and potential limitations of single determinations of the levels of NT-proBNP are all important caveats to recognize and consider in judgments regarding intervention in patients with SCD at high risk of death. The literature supporting the use of chronic transfusions in SCD is not nearly as strong as that for hydroxyurea, and this reflects the weak recommendation for consideration of transfusions for only those hydroxyurea-intolerant patients at highest mortality risk. Although hydroxyurea therapy has not been as well studied in other SCD genotypes, including HbSC disease, the mortality risk of an elevated TRV or PH documented by right heart catheterization in these patients is similar to that observed in HbSS disease (6).

As the Guidelines point out, increased mortality risk in SCD is observed only in adults 18 years of age or older with an elevated TRV or NT-proBNP level, so these are the patients who should be considered for intensification of SCD-specific therapies, such as hydroxyurea or chronic transfusions. The optimal frequency of mortality risk assessment in the asymptomatic adults is unknown, but those on our committee advocated performing this every 1 to 3 years in those 18 years of age and older.

Although we have learned much about PH in SCD over the last decade, many questions remain, and their answers will better inform the future versions of these guidelines. The current version reflects the consensus of many individuals from the fields of adult and pediatric pulmonary, cardiology, and hematology, with integration of the available literature with our own clinical experiences. We would welcome working with the authors of the letter to move this field forward and address the major morbidity and mortality risks facing our patients with an elevated TRV, NT-pro-BNP level, and/or PH. ■

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