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Research and Statistics : Number Needed to Treat and Intention to Treat Analysis

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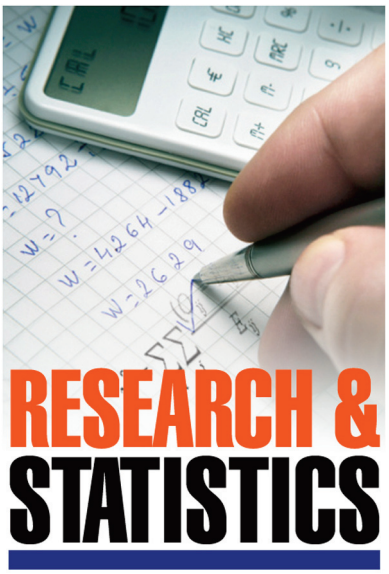

Author Disclosure

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Number Needed to Treat and Intention to Treat Analysis

Megan M. Tschudy, MD,* Peter C. Rowe, MD†

Case Presentation

An 8-month-old boy who has no history of wheezing or atopy presents to the emergency department with bronchiolitis. While discussing the case, a colleague mentions that a recent randomized, controlled trial in the New England Journal of Medicine *(NEJM) showed that the combination of nebulized epinephrine and oral dexamethasone may reduce hospital admissions in children who have bronchiolitis. (1) You have been seeing many patients this season who have bronchiolitis and wonder if you should change your clinical practice.*

Number Needed to Treat Analysis

Randomized, controlled trials (RCTs) are considered the gold standard for establishing the beneficial and harmful effects of a treatment. Investigators report the results of treatment using absolute difference in risk (absolute risk reduction), relative risk, or relative risk reduction. (2) Absolute risk reduction is the difference in risk of an event occurring in exposed individuals compared with nonexposed individuals. Relative risk is the ratio of the risk of the event occurring in the exposed population compared with the risk in the nonexposed group. Relative risk reduction is the percent reduction in events occurring in exposed compared with unexposed individuals. These estimates of risk are not easily extrapolated or relevant to clinical practice.

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Number needed to treat (NNT) analysis is an important measure to help clinicians determine the benefit-risk ratio for an individual patient. (3) NNT is the number of patients that the clinician would need to treat to prevent one additional adverse event. NNT is calculated by taking the inverse of the absolute risk reduction: (4)

$$\text{NNT} = 1 \div \text{Absolute Risk Reduction}$$

$$= 1 \div (\text{Rate in untreated group} - \text{Rate in treated group})$$

You decide to read the NEJM article by Plint and associates entitled "Epinephrine and Dexamethasone in Children with Bronchiolitis" to see if they present enough evidence for you to change your clinical practice in treating bronchiolitis. After examining the article, you determine that the results are generalizable to your patient, and the primary outcome measured in the study (hospitalization) would be of clinical importance. (5) Calculating the NNT is important to you to judge the relative clinical benefits and costs of the treatment for your patients. The article mentions that you would need to treat 11 infants to prevent one hospital admission in the first 7 days after initial presentation to the emergency department. How did the authors come up with this number? How many patients need to be treated to prevent hospitalization later in the illness?

A straightforward calculation of NNT can be performed with reported rates and relative risk. To calculate the NNT with epinephrine and dexamethasone instead of pla-

cebo (no intervention) to prevent one hospitalization by 7 days requires the following calculation using the relative risk from Figure 2 in the article: (1)

NNT=1÷(Admission rate of placebo treated at 7 days−Admission rate of treated with epinephrine and dexamethasone at 7 days)
=1÷(26.4%−17.1%)
=1÷9.3%
=1÷0.093
=11 patients need to be treated to prevent one admission by day 7

When calculating NNT, any decimals are rounded to the highest whole number. (4) The same calculation can be made using data from the study to determine the NNT with epinephrine and dexamethasone to prevent one hospitalization by 22 days, which would be 12 children. Although more mathematically intense, this calculation also can be computed with odds ratios to determine NNT. (3)

Another measure to consider when determining the clinical efficacy of a new treatment is number needed to harm (NNH) analysis. Because one of the first tenets of medicine is "first do no harm," when considering the benefits of a treatment, clinicians also must examine the risks. The NNH is the number of patients receiving the intervention associated with each additional adverse outcome. (5) The calculation for the NNH is the inverse of the absolute risk difference of a harmful event occurring between the intervention and control groups. When determining whether to implement the treatment in clinical practice, it is important to compare NNT and NNH to determine the risk-benefit ratio of the treatment.

One limitation of using NNT calculations is that they do not take into account quality of life measures or relevant outcomes other than those explicitly considered in the study. The average NNT or NNH also may not be applicable to an individual patient if that patient has a different baseline risk or relative risk of events from the group that was studied. When generalizing from research to clinical practice, it is important to consider if the patient's baseline risk of the event and risk of harm from the treatment are similar to those of the study population. (3)

Intention to Treat Analysis

Intention to treat (ITT) analysis retains patients throughout every step of analysis in the groups to which they initially were randomly assigned. It is tempting for researchers to place patients who did not complete the full treatment protocol as designed into different groups or drop them from the analyses. It is possible that a patient did not start the intervention, was not compliant with the intervention, or had missing data responses. However, there are many reasons to keep such patients in the analysis using ITT analyses.

First, ITT analysis maintains the treatment groups as they were originally randomized. The process of randomization takes into account factors that we know are important and factors that we do not know are important. If individuals are not maintained in the groups to which they were originally assigned, the benefits of the randomization process may be lost.

Second, ITT analysis should be included when examining a new practice's effectiveness. (6) If a clinician is considering changing his or her practice based on the results of a randomized trial, ITT analysis takes into account many deviations from protocol that may occur in clinical practice. Leaving out patients who are not compliant with the original assigned treatment often leaves those in the analysis who are likely to have better outcomes.

The article by Plint and associates explicitly states in the methods section that "all analyses followed intention to treat principles." (1) In the results section, they further detail that although patients in two groups who received dexamethasone received only 80% of the allotted dose, they still were included in their original randomized groups throughout all analyses. This inclusion makes sense because the authors used ITT analysis. Although the researchers deviated from the protocol, patients were included in the analyses according to their initial random group assignments.

If large numbers of patients are lost to follow-up or cross over to a different study group, the validity of the study is questionable. (6) The greater the number of patients who are lost from their original assigned treatment, the more bias is introduced into a study, and clinical effectiveness of the intervention is overestimated (increases type II error). ITT analysis should be used to avoid bias and overestimation of effect in RCTs. If an RCT does not use ITT analysis, it is important to know of any deviations from the initial assigned protocol or randomization process as well as any missing response data. (7)

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In Brief

Abnormal Head Growth

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Author Disclosure

Dr Sniderman has disclosed no financial relationships relevant to this In Brief. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

Acquired Microcephaly: Causes, Patterns, Motor and IQ Effects, and Associated Growth Changes. Baxter PS, Rigby AS, Rotsaert M, Wright I. *Pediatrics*. 2009;124:590–595
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Measurement of the head circumference is a routine yet critical part of newborn, infant, and toddler health supervision care. Abnormal head growth may indicate a medical or developmental problem and often leads practitioners to further evaluation.

Normal head circumferences in term infants range from 32 to 38 cm. Microcephaly is defined as a head circumference 2 standard deviations (SDs) below the mean for age and sex or roughly less than the 2nd percentile. Conversely, macrocephaly is defined as a head circumference greater than 2 SDs above the mean or greater than the 98th percentile. *Bright Futures* recommendations state that head circumference measurements should be obtained at each health supervision visit from birth to 24 months of age, but the Centers for Disease Control and Prevention growth charts extend to 36 months.

Microcephaly can present as primary or acquired. Causes of primary microcephaly include autosomal dominant and autosomal recessive genetic disorders; trisomy 13, 18, and 21; various syndromes, including Cornelia de Lange syndrome, Smith-Lemli-Opitz syndrome, and Rett syndrome; inborn errors of metabolism; and hypothyroidism. Acquired microcephaly is distinguished by a normal head circumference at birth, followed by development of microcephaly in subsequent months or years, usually due to lack of brain development or growth. Causes of acquired microcephaly include sequelae from stroke, meningitis, or encephalitis; other infections, such as toxoplasmosis, rubella, cytomegalovirus, and herpes; in utero teratogen exposure; and hypoxic-ischemic encephalopathy. One study from England (Baxter PS, et al, 2009) noted three different patterns of head growth in infants who had acquired microcephaly, although the pattern of growth was not clearly linked with the cause. All patterns began with a normal head circumference. Some children demonstrated a deceleration in growth to below the 2nd percentile, followed by growth that remained parallel to, but below, the 2nd percentile. A second pattern was remarkable for falling below the 2nd percentile, followed by a slight recovery but always remaining below the 2nd percentile. The third pattern involved a progressive and continued decline below the 2nd percentile.

The evaluation for microcephaly should be dictated by the clinical presentation because there are no clear guidelines for a standardized assessment. The history should include perinatal events, developmental assessment, and

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