BENDING THE VALUE CURVE

Taking Chances With Strep Throat

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A previously healthy 22-month-old male child presented in the summer to his pediatrician's office with an acute febrile illness. Results of the physical examination were normal except for rhinorrhea, but because of the fever, the pediatrician performed a rapid antigen strep test. The test result was positive, and 10 days of amoxicillin/clavulanic acid were prescribed. After 7 days on the antibiotic, the patient developed a diffuse, erythematous rash on his trunk and extremities; he was taken to the emergency department, where he was prescribed oral steroids for the rash. The following morning, his pediatrician diagnosed the rash as a drug reaction and discontinued the amoxicillin/clavulanic acid and started azithromycin to complete the treatment course for group A streptococcus (GAS) pharyngitis or "strep throat." The following day, the patient's rash became more widespread and pruritic. A third visit with the pediatrician was scheduled, and erythema multiforme was diagnosed. The patient was nontoxic appearing, but the pediatrician decided to admit him to complete the treatment course for strep throat along with possible intravenous steroids as therapy for the erythema multiforme. On admission, the patient was noted to have an impressive rash without oral or ocular involvement and was otherwise well-appearing. Ultimately, a tactful discussion with the admitting pediatrician revealed that the preferred course for all parties would be discontinuation of antibiotics and steroids, and the patient was then discharged from the hospital.

In the practice of medicine, we should attempt to weigh the risks and benefits of each patient management decision. This particular case brings up various opportunities in which decisions might have been made differently if both the potential risks and benefits of the treatment were considered more explicitly. First, what were the chances that this child had strep throat? A positive rapid strep test result may indicate true infection or the carrier state (eg, colonization without infection) or laboratory error (eg, false-positive, mix-up with someone else's test sample). GAS pharyngitis is most commonly observed in children aged 5 to 15 years in the winter and spring months. Our patient was aged <2 years, did not have pharyngitis, and presented in the summer. The 2012 Infectious Diseases Society of America guidelines for the management of GAS pharyngitis do not recommend testing in those with clinical and epidemiologic factors strongly suggestive of viral etiology or in children <3 years of age because the potential sequela (acute rheumatic fever [ARF]) is rare in children aged <3 years.[1] These recommendations are offered because development of ARF is believed to be secondary to repeated exposures to GAS that will effectively prime the immune system over time to create the autoimmune response leading to ARF; testing, therefore, at a young age is not of high value.

Many pediatricians understand that the primary impetus to detect and treat strep throat is to prevent the harmful sequela of ARF that may lead to rheumatic heart disease (RHD), which had previously been a leading cause of death in the pediatric population.[2] Therefore, we should next consider the chances that this patient could develop

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ARF or RHD in the future. Rates of ARF and RHD in the United States have dropped drastically since they were diagnosed as rheumatism during the US Civil War. The link between hemolytic streptococcal infections and ARF was discovered in 1943 by studying a scarlet fever epidemic at the Fort Francis E. Warren Air Force Base in Wyoming.[3] Subsequent studies conducted from 1944 to 1945 on 3 different Army bases in California documented evidence of cardiac involvement in 1470 cases of ARF. This involvement included: carditis, as determined by abnormal electrocardiogram findings; the presence of cardiac murmurs indicating valvular disease; and cardiac insufficiency. It was reported that 50% of patients had carditis, 5% to 12% had murmurs, and <1% developed cardiac insufficiency.[4] There were a total of 3 deaths reported from subsequent heart failure over all study sites. These studies showed that during 1 of the largest recorded outbreaks in the United States, almost one-half of those with ARF would develop RHD. Of those, 3 died; thus, the risk of death due to RHD was 0.4% for all patients diagnosed with ARF. In 1985, Gordis[5] published a comprehensive report of multiple studies demonstrating the overall decline of rheumatic fever in the United States; only 5 cases of ARF were seen from 1977 to 1981, all of which were clinically mild. In the summary of notifiable diseases released by the Centers for Disease Control and Prevention in 1997 covering the years 1988 to 1994, a further downward trend in the incidence of ARF was observed, with a rate of 0.09 case per 100 000 population in the final year of the report (1994).[6] Because of the rarity of ARF, mandated reporting was discontinued in 1995.

Considering the rarity of ARF and RHD today, what are the chances our particular patient would have benefited from antibiotic treatment to prevent either outcome or death? The number needed to treat (NNT) is debatable due to lack of accurate data on the incidence of pharyngitis, strep pharyngitis, and ARF in the pediatric population; however, Table 1 provides a sample of calculations based on our best estimates. Based on data from 2003, ~11 million people present with sore throat in the United States annually, and ~20% of those will have GAS as the etiologic agent. The value of 20% is an estimate from the reported rate of strep throat of 37% in children and 5% to 15% in adults.[7] This approach provides an estimate of just over 2 million cases of strep throat per year. As discussed earlier, the most recent available rate of ARF from 1994 was 0.09 per 100 000, or ~300 cases considering the population in 2003. Treating strep throat has been shown in several studies to reduce the risk for ARF to about one-quarter of that in the placebo group.[8] This assessment makes the absolute risk of ARF in the treated population 0.0034%, and the absolute risk reduction for treating strep throat ~0.01%; thus, the NNT is ~10 000 to prevent 1 case of ARF. Based on limited data (mainly from the army base outbreaks discussed earlier), one-half of those with ARF will develop RHD, making the NNT 20 000 to prevent 1 case of RHD, and 5 million to prevent 1 death if 0.4% of those with ARF die of RHD. A meta-analysis published in 2005 reported a much smaller NNT of 53 to prevent ARF.[9] These data included 10 studies; 8 of those were conducted in young adult male subjects living on military bases in the United States from 1950 to 1961 when there were much higher rates of ARF nationwide. Similar to our NNT calculation, Newman[10] demonstrates the same point by highlighting a 1940s military study population in whom ARF had an incidence of 438 per 100 000, which is 5000 times the incidence of ARF seen today. Newman then calculated that 200 patients would need to be treated at that time to prevent 1 case of ARF; currently, therefore, the NNT would be 1 million (5000 × 200). The author then assumed a mortality rate of 50% for ARF; 2 million patients would thus need to be treated to prevent 1 death based on those conclusions.

The pediatrician in the present case chose to treat the patient and prescribed amoxicillin/clavulanic acid. The first-line treatment of GAS is 10 days of penicillin. There has been no documentation of penicillin-resistant GAS to date.[1] Amoxicillin/clavulanic acid has a broader spectrum than required in this case as well as a higher likelihood of gastrointestinal adverse effects and higher cost. After 7 days, treatment with amoxicillin/clavulanic acid was discontinued due to the evolving rash, but what was the chance that GAS pharyngitis persisted at this time? Specific information regarding duration of treatment with amoxicillin/clavulanic acid for strep throat is lacking because it is not a recommended therapy. However, a randomized, multicenter trial found no statistically significant difference in treatment efficacy between 6 days of amoxicillin and 10 days of penicillin for the treatment of GAS tonsillopharyngitis.[11] In the present case, there was a high likelihood that GAS was eliminated by the time the rash appeared and the first antibiotic was discontinued. If the physician did have concern for a shorter course not being curative, a throat culture might have prevented the prescription of another expensive broad-spectrum drug (azithromycin) and possibly the hospital admission.

Our patient experienced an uncomfortable, pruritic dermatologic adverse event that brought him to the emergency department and ultimately got him admitted to the hospital, but what was the chance of his experiencing this adverse event or a more serious event such as anaphylaxis? Overall, adverse reactions to antibiotics occur in 5% to 25% of patients.[10] The rate of anaphylactic reactions is 1 in 400 prescriptions,[9] and

TABLE 1 NNT in Strep Throat Cases to Prevent 1 Death From RHD

AR Without Treatment of ARF	AR With Treatment of ARF	ARR for Treating Strep Throat	NNT to Prevent ARF	NNT to Prevent RHD	NNT to Prevent 1 Death
(300/2 200 000) 0.00014	(75/2 200 000) 0.000034	(0.00014–0.000034) 0.0001	(1/0.0001) 10 000	(10 000/0.5) 20 000	(20 000/0.004) 5 000 000

AR, absolute risk; ARR, absolute risk reduction.

there is a 0.3% chance of death from anaphylaxis.[12] Thus, what are the expected harms if we treat 5 million children with antibiotics for their strep throat to prevent 1 death from RHD? Adverse effects will occur in ~1 million children, 12 500 will experience anaphylaxis, and 37 can be expected to die of their anaphylactic reaction.

Strep throat is a fairly common illness with easily recognizable symptoms, potential serious sequelae, a rapid office-based test, and an inexpensive highly effective treatment. The busy pediatrician may be tempted to indiscriminately test children with a febrile illness and to treat those who test positive, believing he or she is preventing serious complications and also avoiding lengthy discussions of symptomatic care for viral illness. The immense decline in the incidence of ARF means that treating strep throat provides a vanishingly small reduction in the absolute risk of ARF, although other benefits such as shortened symptom duration and the possible prevention of suppurative complications and contagious spread still exist. However, because no test or treatment is without potential harm, several questions must be asked. What are the chances this child has strep throat or will suffer complications such as ARF if left untreated? What are the chances the treatment will cause harm, and what are the chances that the potential harms from the treatment outweigh the potential harms of the illness? Physicians have traditionally given less weight to the potential harms of testing and treatment than to the potential harms of missing a diagnosis or not treating an illness. If we are to deliver high-value care we must overcome our psychological biases and consider the potential harms and costs of treatment. We must find a way to discuss the risks and benefits of both treating and not treating in a way that families understand so they can participate in shared decision-making. The value of a course of penicillin for strep throat in 2015 is different from that in 1945. This case illustrates how the value of testing and treatment changes with the evolving epidemiology of infectious disease and how our treatment decisions must evolve with it.

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