37. Jone PN, Anderson MS, Mulvahill MJ, Heizer H, Glode MP, Dominguez SR. Infliximab plus intravenous immunoglobulin (IVIG) versus IVIG alone as initial therapy in children with Kawasaki disease presenting with coronary artery lesions: is dual therapy more effective? Pediatr Infect Dis J 2018;37:976-80.
38. Miyata K, Kaneko T, Morikawa Y, Sakakibara H, Matsushima T, Misawa M, et al. Efficacy and safety of intravenous immunoglobulin plus prednisolone therapy in patients with Kawasaki disease (Post RAISE): a multicentre, prospective cohort study. Lancet Child Adolesc Health 2018;2:855-62.
39. Nagatomo Y, Muneuchi J, Nakashima Y, Nanishi E, Shirozu H, Watanabe M, et al. Effective infliximab therapy for the early regression of coronary artery aneurysm in Kawasaki disease. Int J Cardiol 2018;271:317-21.
40. Hamada H, Suzuki H, Onouchi Y, Ebata R, Terai M, Fuse S, et al. Efficacy of primary treatment with immunoglobulin plus ciclosporin for prevention of coronary artery abnormalities in patients with Kawasaki disease predicted to be at increased risk of non-response to intravenous immunoglobulin (KAICA): a randomised controlled, open-label, blinded-endpoints, phase 3 trial. Lancet 2019;393:1128-37.
41. McCrindle BW, Rowley AH. Improving coronary artery outcomes for children with Kawasaki disease. Lancet 2019;393:1077-8.
42. Uehara R, Belay ED, Maddox RA, Holman RC, Nakamura Y, Yashiro M, et al. Analysis of potential risk factors associated with nonresponse to initial intravenous immunoglobulin treatment among Kawasaki disease patients in Japan. Pediatr Infect Dis J 2008;27:155-60.
43. de Zorzi A, Colan SD, Gauvreau K, Baker AL, Sundel RP, Newburger JW. Coronary artery dimensions may be misclassified as normal in Kawasaki disease. J Pediatr 1998;133:254-8.
44. Belay ED, Maddox RA, Holman RC, Curns AT, Ballah K, Schonberger LB. Kawasaki syndrome and risk factors for coronary artery abnormalities: United States, 1994-2003. Pediatr Infect Dis J 2006;25:245-9.
45. Tsuda E, Yashiro M, Nakamura Y. cardiac valvular lesions due to Kawasaki disease: a Japanese nationwide survey. J Pediatr 2020;218:78-84.

50 Years Ago in *The Journal of Pediatrics*

Erythromycin versus Penicillin for the Treatment of Streptococcal Skin Infections

Derrick CW, Dillon HC. Further studies on the treatment of streptococcal skin infections. J Pediatr 1970;27:696-700.

The study of Derrick and Dillon is a well-construed, complex allocation, prospective clinical trial of therapies for streptococcal skin infection in children across 2 July-through-November seasons in Birmingham, Alabama. In 1967, 335 patients with proven streptococcal impetigo were alternately assigned by odd-even medical record numbers to treatment with erythromycin orally 4 times per day for 7 days or a single dose of benzathine penicillin (Bicillin) intramuscularly. In 1968, 373 children were assigned in the same fashion to receive the same erythromycin orally 4 times per day but for 10 days or phenoxymethyl penicillin (Pen VK) orally 3 times per day for 10 days. Primary outcomes (as we would so specify today a priori) would seem to have been clinical cure of impetigo and skin eradication of *Streptococcus pyogenes* at 14 days. Secondary outcomes were the prevalence and impact of therapy on respiratory tract colonization, and "recurrent" streptococcal impetigo in the seeming 6+ weeks of follow-up. Although intuitively a noninferiority trial with benzathine penicillin as the comparator, neither sample size calculations nor statistical bounds of noninferiority were specified.

Cliff Notes on the findings were that (1) clinical cure exceeded 98% in all groups, (2) respiratory tract colonization at entry, which occurred in 12% of patients (likely secondary to impetigo), was "eradicated" at 14 days best by benzathine penicillin, (3) recurrences of impetigo at 3-4 weeks occurred in 3.6%-6.3% of patients across groups, the lowest rate being in the benzathine penicillin group (not statistically significant, although statistics not reported), (4) recurrences after benzathine penicillin tended to occur at 5-6 weeks, and (5) early recurrences tended to be due to the same serotype of *S pyogenes* (relapses), whereas later recurrences tended to be due to new serotypes (reinfections).

An additional caveat was that *S aureus* also was isolated from skin lesions in approximately one-half of cases of streptococcal impetigo, with one-half of *S aureus* isolates resistant to penicillin, but all susceptible to erythromycin. Despite this, all outcomes (ie, cure of impetigo, fate of streptococcal colonization, and recurrence of impetigo) were similar in the penicillin- and erythromycin-treated groups. Compared with earlier studies assessing topical treatment of streptococcal impetigo, which showed that persistence of infection and recurrences were common, any systemic therapy in the Derrick-Dillon trial was clearly superior.

This study figured importantly in what we currently consider to be optimal management of streptococcal impetigo. In the 1960s, the stakes were high as post-streptococcal acute glomerulonephritis was common. In fact, 91 of the 708 study participants in the Derrick-Dillon study were impetigo cases in siblings of patients with poststreptococcal acute glomerulonephritis. One wonders where nephritogenic strains of *S pyogenes* went and why. This was an excellent study and we are grateful for its lessons. Although penicillin effectiveness would still be >98%, expected macrolide performance of 1968 would have to be tempered by current *S pyogenes* resistance rates of 5%-10% in most areas of the US, with some rates as high as 20%.

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