Persistent Macrolide Resistance among Group A Streptococci: The Lack of Accomplishment after 4 Decades

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(See the article by Richter et al. on pages 599–608)

After isolation of erythromycin from a culture of Streptomyces erythreus in 1952 and the soon-to-follow introduction of erythromycin to clinical practice, erythromycin resistance required <2 decades to become apparent among clinical isolates of group A streptococci (GAS; Streptococcus pyogenes). A 1968 report in 1968 by Sanders et al. [1] about an erythromycin-resistant GAS (M type 12) isolate recovered from a patient’s upper respiratory tract concluded with the admonition, “Therefore, determination of the in-vitro susceptibility of group A streptococci to these drugs appears advisable whenever their use is contemplated, and imperative when either the infection threatens life or there is an increased risk that late sequelae of such infections will develop.” Now, decades later, Richter et al. [2] similarly admonish physicians in their survey of macrolide resistance in the United States: “In vitro testing of S. pyogenes for macrolide susceptibility is warranted for patients who are allergic to β-lactams” (p. 606).

Unfortunately, during this 37-year interval, there has been little change in the need to caution practitioners about the potential for macrolide resistance.

There continue to be numerous reports that address clinical, epidemiological, and microbiological aspects of macrolide resistance for S. pyogenes. A review of PubMed citations revealed 240 studies related to macrolide resistance in GAS from the beginning of 2000 to April 2005. Recently published macrolide resistance rates range from ~3%–4% in most areas of continental North America (e.g., [3]; new data indicate a similar figure for the Hawaiian Islands [4]) to more than 10 times that prevalence for several European countries. Many studies include emphasis on the molecular mechanisms responsible for macrolide resistance in GAS and the relationship of these mechanisms to clonality, as does the report by Richter et al. [2]. This is undoubtedly an important area for scientific investigation, but there remain inadequately addressed questions about how resistance affects clinical effectiveness for both the individual patient and for the public health and about what action can be effective in controlling resistance. All too often, authors only state, as the Richter and colleagues do in their conclusion, that there are “several large clones with potential for expansion” [2, p. 606]. The paramount issue is not adequately addressed. The practitioner is left wondering whether there is a role for surveillance and, if so, why does the problem persist, and what can be done to rectify the current situation?

After reading their analysis of 1885 GAS isolates from 45 United States medical centers, one might question some of the conclusions drawn by Richter and colleagues [2], but the message should not be ignored by clinicians and public health authorities. Does examination of ~200 strains from each of the 9 geographic regions in the United States, each of which contains millions of inhabitants, indicate whether their report is an accurate assessment of geographic distribution of macrolide resistance? Furthermore, the authors have not made an effort to correlate the prevalence of macrolide-resistant strains with local/regional antibiotic use in the United States. Such information could have been important and practically useful in rectifying the situation.

The documented increase in the prevalence of macrolide resistance undoubtedly relates to macrolide use in clinical practice. In a review of the past history of macrolide use, Bass et al. [5] noted that, in the 1960s and 1970s, the prevalence of macrolide resistance among GAS in Japan was >50%. This was associated with widespread use of erythromycin.

A relationship between clinical use and
resistance has been extensively reported from Europe. The 1997 report from Finland by Seppela et al. [6] emphasized the temporal relationship between macrolide use and macrolide resistance among GAS. After there were nationwide reductions in the use of macrolide antibiotics for outpatient therapy (a reduction of 40% from 1991 to 1994), there was a significant decrease in the frequency of erythromycin resistance among GAS isolates (from 16.5% of isolates in 1992 to 8.6% in 1996) [6, 7]. In 1999, Hjaltested et al. [8] reported that the prevalence of macrolide resistance in Iceland increased during a single year (from 0% to 56%) concomitantly with the introduction and widespread use of a long-acting macrolide-related drug. Confirmatory reports can be cited from other countries [9, 10].

Similar information has been reported from southern Europe. From 1991 to 1996, the percentage of S. pyogenes isolates in Genoa, Italy, that were resistant to erythromycin increased from 0% to 50%, whereas it decreased in 1997 and the first half of 1998. Analysis of antibiotic use revealed an increase in the use of macrolides, from 0.44 defined daily doses (DDDs)/1000 inhabitants/day in 1994 to 1.14 DDDs/1000 inhabitants/day in 1996. In contrast, during 1997 and the first half of 1998, the rate of use decreased to 0.9 DDDs/1000 inhabitants/day and 0.8 DDDs/1000 inhabitants/day, respectively [11].

Cizman et al. [12, 13] confirmed that this trend was happening in Slovenia. The rate of macrolide use went from 1.89 DDDs/1000 inhabitants/day to 3.84 DDDs/1000 inhabitants/day during the same time that the rate of macrolide-resistant GAS increased from 0% to 7.4% (P = .014). From 1991 to 1996, there was a 3.5-fold increase in the number of macrolide prescriptions for outpatients that was temporally related to the significant increase in macrolide resistance observed in S. pyogenes in 1997.

What approaches can be taken to avoid continuing problems with the prevalence of macrolide-resistant GAS? The extent of this correlation (i.e., how much and how quickly consumption needs to increase to produce a given resistance level) is not completely understood, and relatively little is understood about the reversibility of this phenomenon and about the time interval necessary for variation in use to significantly affect resistance. Pertinent to the ultimate understanding of this issue is the report by Austin et al. [14], which elegantly described (using a theoretical model) how, after being exposed to selective pressure of an antibiotic, the reduction in the prevalence of resistance is much slower in returning toward normal than is the sharp rise in resistance upon exposure to large amounts of antibiotics.

Information is also limited about the relative likelihood of different macrolide compounds—and their pharmacokinetic and pharmacodynamic properties—in eliciting and maintaining resistance in S. pyogenes. A number of reports have indirectly implicated newer macrolides, but whether the antibiotics themselves or the promotion and use of them are responsible has not been definitely established. Information is also limited with regard to a possible correlation between specific antibiotic use patterns and different resistance genotypes.

There have been commendable efforts by advisory groups to reduce unnecessary use of macrolides. The "Get Smart" campaign by the Centers for Disease Control and Prevention is one of the most recognized efforts (http://www.cdc.gov/drugresistance/community/). Despite such programs, the problem remains, as evidenced by the continuing number of reports of macrolide resistance, including reports suggesting an increase in rates of resistance in locales where it had not been a clinically relevant problem [15]. Does this necessitate continuing or even intensified surveillance? We support this approach, but we believe that it must be recognized that isolated surveillance reports alone have not provided a solution to the problem. How much more similar evidence is needed? There are examples in which localized surveillance has led to educational programs and a reduction of unwarranted use of macrolides or to use of first-line antibiotics instead of macrolides. One cannot easily legislate control of the use of macrolides. A recent report from Taiwan suggests another approach—one that is not infrequently used in hospital settings. Hsuueh et al. [16] reported a decrease in macrolide use after placement of reimbursement restrictions. One would hope that this is not the solution to the problem. At the present time, there is little need for so many reports about the prevalence of macrolide resistance. What is needed is a practical and realistic collaboration between public health agencies, professional societies, and industry that effectively transmits findings and suggestions to clinicians.

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References