The Use of Mupirocin in Controlling Methicillin-Resistant *Staphylococcus aureus*

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Methicillin-resistant *Staphylococcus aureus* (MRSA) have become the bane.of the hospital epidemiologist and infection control practitioner (ICP) because they necessitate countless calls to the nursing service, housekeeping department and doctors involved in the case. Even in the face of increasing information about the genetic basis of methicillin-resistance, we seem to have more patients who are colonized with the problem organism and even more actual infections. Where will the problem end? What can we expect for the 1990s? I do not have the answers, but I will offer some comments on the study by Cederna and colleagues in this issue, as well as some predictions for the future.

Why do we seem to have more MRSA today than in the previous decade? Some of the increase is related to changes in laboratory methods used to identify MRSA. The inclusion of 2% NaCL in virtually all of the susceptibility test media is a partial explanation, as is an increased awareness of MRSA in microbiology laboratories. Increased use of cultures in larger teaching centers may also be a reason for the increase, because there is almost a knee-jerk reaction to start vancomycin therapy when a patient has a proven or suspected staphylococcal infection, and the need to justify the use of vancomycin, I suspect, results in many nasal and other cultures that would not otherwise be obtained. Another reason for the increase in MRSA may be real; that is, the extensive use of cephalosporins. Oral cephalosporins such as cephalexin are widely used in chronic care facilities and by narcotic addicts. Parenterally administered second and third-generation cephalosporins commend a major part of the hospital antibiotic armamentarium of most internists and surgeons.

Why are MRSA methicillin-resistant? The reason for MRSA is the production of a new penicillin-binding protein, PBP2a, that has a low affinity for all β-lactam antibiotics.[1] Certainly some MRSA are not really MRSA of the altered PBP2a type, but rather are strains in which production of β-lactamase has become constitutive at a high level so that otherwise β-lactamase stable compounds such as oxacillin (the agent used to test for MRSA) are now competitive substrates that are hydrolyzed at an appreciable enough rate to make organisms have minimum inhibitory concentrations (MICs) of 8 to 16-ug/ml. These organisms are the ones that are susceptible to ampicillin-sulbactam, amoxicillin-clavulanate and imipenem.[2] This is very important because these isolates are not really MRSA, and when so considered and so treated add to a hospital's cost in terms of the need for isolation of MRSA patients and the use of more expensive antibiotics to treat infections. Hopefully these high producers of β-lactamase will be more easily detected in the next few years to help reduce some of the costs of recognition of MRSA.

Does the use of third-generation cephalosporins truly cause proliferation of MRSA? We do not know. Unlike the more easily documented increase in enterococcal infections with the use of cephalosporins, the situation for the association of MRSA and cephalosporins is much less clear.[3] Indeed, when I began my training in the early 1960s, I remember the problems of MRSA that occurred with the availability of methicillin, oxacillin, cloxacillin and other β-lactamase stable semisynthetics.[4]

Did they cause MRSA? No, because the organisms disappeared in the early 1970s. I believe that MRSA are caused by changes in the healthcare system. Large numbers of elderly patients in chronic care facilities, the inability of tertiary care hospitals to

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place patients, as well as the extraordinary advances in respiratory medicine have kept patients alive who would have died approximately 15 years ago.[5,6] These patients are repeatedly treated with antibiotics with the ultimate selection of resistant bacteria. Hence we have MRSA, cephalosporin-resistant *Enterobacter cloacae, Pseudomonas aeruginosa* resistant to the latest fluoroquinolone, *Pseudomonas maltophilia* resistant to everything and enterococci with high level aminoglycoside resistance, β-lactamase production and vancomycin resistance.[7]

At the Columbia-Presbyterian Medical Center (CPMC) in New York, we have 15% of hospital isolates of *S aureus* as MRSA. At Stamford Hospital in Connecticut, there are less than 1% of *S aureus* that are MRSA. The patient populations differ in the institutions to a degree that one can predict those areas of CPMC in which MRSA are or will be a problem.

How can we prevent, control and avoid MRSA? Prevention and treatment of colonization is the message of the article by Cederna, et al. Mupirocin is a unique antimicrobial agent produced by *Pseudomonas fluorescens*.[8] It does not cross-react with any other agent and it has a unique effect on protein biosynthesis. Application of mupirocin to treat nasal mucosa has successfully eradicated nasal carriage in the United Kingdom,[9] and the use of mupirocin has been advocated by the British Society for Antimicrobial Chemotherapy to eradicate MRSA nasal colonization in hospital staff and in patients.[10] The study by Cederna, et al. substantiates the earlier studies, but the sample size was too small and the topical preparation used was that advocated for topical skin use, but not for nasal use. Could there be a difference in the two preparations? Yes, the polyethylene glycol has some effect to decrease the organisms on skin, and conversely it can irritate thereby leading to recolonization.

Several points should be made about the use of mupirocin. Resistance to mupirocin has developed in the United Kingdom and is well documented in several letters to journals.[11,12] Furthermore, it can be plasmid-mediated. How likely is this to occur in the United States? Very likely I fear, because there will undoubtedly be improper use of the medication. The mechanism is related to use of niupirocin in patients with indwelling foreign bodies. Patients who have indwelling nasal feeding tubes, tracheostomies, nasotracheal tubes, percutaneous gastrectomies and large decubitus ulcers will not have staphylococci eradicated, and the organisms will become resistant. Use of rifampin plus oxacillin, minocycline and recently ciprofloxacin to treat staphylococci around the foreign body or in the decubitus ulcers or chronic leg ulcers of diabetic patients has resulted in resistance.14 Mupirocin will not be different. Furthermore, if hospital staff become nasally colonized from such patients, they will harbor the organisms and transfer the bacteria to other patients from their nose and hands. Indeed in our laboratory we have a post-doctoral scientist who had nasal colonization with MRSA that was mupirocin- and rifampin-resistant approximately ten months after leaving the unit where mupirocin was used. Mupirocin-resistant MRSA persisted in his nose during this entire period.

The foregoing is not a condemnation of mupirocin, but rather a plea that ICPs use judgment when the Food and Drug Administration (FDA) eventually approves mupirocin for eradication of nasal colonization. It is also a major plea not to immediately duplicate the reported study with the unapproved medication and then rush in with letters to The New *England Journal of Medicine, Lancet, The Annals of Internal Medicine, JAMA* and other journals with observations that mupirocin use results in resistant bacteria. Improper use of mupirocin can readily result in selection of resistant bacteria. I can easily produce imipenem-resistant *P maltophilia,* cefotaxime- ceftazidime-resistant *E cloacae* and ciprofloxacin-resistant *P aeruginosa* or *S aureus.* A fool can do that by allowing improper use of a drug or performing ill-conceived clinical studies. Mupirocin can stop a hospital outbreak if used appropriately, but note that a different preparation was used.[13]

I hope that our readers will take to heart my comments and try to keep mupirocin a useful, helpful agent to control MRSA in hospital staff and patients. If we do that, we will have achieved something more than another paper saying resistance occurs.

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