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**WHAT'S HOT IN... MEDICINE , July/August 2008**
**Cautious Use of Antibiotics Old and New in the Age of MRSA**
*by David W. Sharp*


Alexander Fleming, the man who discovered penicillin but failed to develop his finding, is quoted as having said of the staphylococcus that it is "a very clever organism. No matter what antibiotic we find, it will get resistant to it." He got that bit right at least. The earliest resistance problems were ascribed to penicillinase (beta-lactamase), so novel penicillin-like molecules with structures lacking a beta-lactam ring came on the market. One of these, introduced in 1960, was methicillin (the "h" is optional). This drug is no longer in clinical use but the name lives on in the well-known and widely feared term **MRSA**, which stands for methicillin-resistant *Staphylococcus aureus*.

The first case of resistance to this drug was recorded in 1959 in the U.K. (Anyone interested in the history of MRSA could start with the **recent volume** in the Wellcome Witnesses to Twentieth Century Medicine series). At first few alarm bells were rung (or heeded), but in the 21st century MRSA has become a cause of grave concern not just to patients but also to healthcare providers, administrators, and politicians.

For example, here in the U.K. the Department of Health was pressured into setting a target of halving the rate of MRSA bacteremia between 2004 and 2008, and earlier this year figures in league-table form for hospital deaths associated with MRSA attracted the usual "superbug" headlines.

As with *S. aureus* itself, MRSA can be carried by people who remain symptom-free. Although it causes most concern in hospital settings, there is another sort, community-acquired MRSA, and there are differences between the

**Medicine Top Ten Papers**

Rank	Papers	Cites Jan- Feb 08	Rank Nov- Dec 08
1	C.L. Ogden, <i>et al.</i> , " <b>Prevalence of overweight and obesity in the United States,1999-2004,</b> " <i>JAMA</i> , 295(13): 1549-55, 5 April 2006. [Ctrs. for Disease Control, Atlanta, GA] *028RG	156	1
2	S.E. Nissen, K. Wolski, " <b>Effect of rosiglitazone on the risk of myocardial infarction and death from cardiovascular causes,</b> " <i>New Engl. J. Med.</i> , 356(24): 2457-71, 14 June 2007. [Cleveland Clinic, OH] *178DR	73	2
3	T. Sjoblom, <i>et al.</i> , " <b>The consensus coding sequences of human breast and colorectal cancers,</b> " <i>Science</i> , 314(5797): 268-74, 13 October 2006. [11 U.S. institutions] *093TV	48	6
4	B. Escudier, <i>et al.</i> , " <b>Sorafenib in advanced clear-cell renal-cell carcinoma,</b> " <i>New Engl. J. Med.</i> , 356(2): 125-34, 11 January 2007. [15 institutions worldwide] *124NE	42	†
5	R.J. Motzer, <i>et al.</i> , " <b>Sunitinib versus interferon alfa in metastatic renal-cell carcinoma,</b> " <i>New Engl. J. Med.</i> , 356(2): 115-24, 11 January 2007. [10 institutions worldwide] *124NE	41	5

two epidemiologically, clinically, and biologically.

For example, community-acquired MRSA is less likely to be multiply drug resistant. Paper #8 looks at staphylococcal skin and soft-tissue infections in 422 patients coming to emergency departments in U.S. cities. Among the patients, 76% of had *S. aureus*. Of those isolates, 78% were methicillin resistant, and on further testing almost all of them were community associated.

Three-quarters of the patients were treated with antibiotics, usually accompanied by incision and drainage of the lesion, but in 100 (57%) of the 175 MRSA infections for which an antibiotic was given, that treatment was not concordant with tests for antibiotic susceptibility.

Fortunately, this does not appear to have affected the long-term outcome for these particular patients. A message from paper #8, supported by the accompanying editorial (M.L. Grayson, *New Engl. J. Med.*, 355[7]:724-7, 2008), is that when a staphylococcal infection is suspected an antibiotic may not always be necessary. Treatment options are, says Dr. Grayson, "weighted in favor of surgical drainage as the priority intervention—a concept better known to clinicians before the days of penicillin."

That MRSA is indeed linked to previous antibiotic exposure is confirmed by a very recent meta-analysis of 76 studies in 24,230 patients, which revealed a 1.8-fold increase in risk (E. Tacconelli, *et al.*, *J. Antimicrob. Chemother.*, 61[1]:26-38, 2008). That this microorganism is far from being vanquished is illustrated by data from a U.S. surveillance network of almost 300 laboratories and 380,000 isolates of *S. aureus*. Of these isolates, 58% were MRSA in 2007, the good news being that there was little change from two years earlier (G.S. Tillotson, *et al.*, *J. Antimicrob. Chemother.* E-pub April 8, 2008 [abstract accessed May 24, 2008]).

Several drugs are available for patients with MRSA and, though resistance is sometimes reported it is not (yet) on a huge scale. One such is daptomycin (the focus of a companion paper to #8, by V.G. Fowler, *et al.*, *New Engl. J. Med.*, 355[7]:653-65, 2006).

However, the battle will not be won by pharmaceuticals alone. Simple hygienic practices to prevent cross-contamination and cross-infection and susceptibility testing before any antibiotic is given have vital parts to play. ■

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Keywords: methicillin –resistant *Staphylococcus aureus*, MRSA, *S. aureus*, antibiotic-resistant bacteria, antibiotic resistance, bacterial infection.



6	S. Volinia, <i>et al.</i> , " <b>A microRNA expression signature of human solid tumors defines cancer gene targets</b> ," <i>PNAS</i> , 103(7): 2257-61, 14 February 2006. [5 institutions worldwide] *013LU	38	†
7	R.A. Morgan, <i>et al.</i> , " <b>Cancer regression in patients after transfer of genetically engineered lymphocytes</b> ," <i>Science</i> , 314(5796): 126-9, 6 October 2006. [Natl. Cancer Inst., NIH, Bethesda, MD] *091LU	37	†
8	G.J. Moran, <i>et al.</i> , " <b>Methicillin-resistant <i>S. Aureus</i> infections among patients in the emergency department</b> ," <i>New Engl. J. Med.</i> , 355(7): 666-74, 17 August 2006. [U., Calif., Los Angeles; Ctrs. Disease Control & Prevent., Atlanta, GA] *074AN	35	†
9	The Heart Outcomes Prevention Evaluation (HOPE) 2 Investigators (E. Lonn, <i>et al.</i> ), " <b>Homocysteine lowering with folic acid and B vitamins in vascular disease</b> ," <i>New Engl. J. Med.</i> , 354(15): 1567-77, 13 April 2006. [Writing Group: 9 institutions worldwide] *031WW	34	†
10	The DREAM Trial Investigators (H.C. Gerstein, <i>et al.</i> ), " <b>Effect of rosiglitazone on the frequency of diabetes in patients with impaired glucose tolerance or impaired fasting glucose: a randomised controlled trial</b> ," <i>Lancet</i> , 368(9541): 1096-1105, 23 September 2006. [Correspond. address: Population Health Res. Inst., Hamilton, Ont., Canada] *089IC	33	†

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