The Continuing Saga of MRSA

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(See the article by Gorwitz et al., on pages 1226–34; the article by David et al., on pages 1235–43; and the article by Emonts et al., on pages 1244–53.)

In this issue of the Journal, there are 3 papers that expand our understanding of an old enemy, Staphylococcus aureus. They report changes in the prevalence of nasal colonization with S. aureus in the United States, explore the associations among host and bacterial genotypes and nasal carriage or skin infection, and question what defines a community-associated strain of methicillin-resistant S. aureus (MRSA), respectively [1–3].

Both scientific and public interest in MRSA have been heightened by a recent report estimating that MRSA infections were associated with death in 18,650 people in the United States in 2005. Since 2001, the incidence of invasive MRSA infection has increased 1.7-fold in Atlanta and 2.9-fold in Baltimore [4]. These findings resulted in a spate of articles in the lay press that described MRSA as a “superbug” that had killed more people in the United States than did AIDS in 2005.

The frequency of methicillin resistance in S. aureus has increased in isolates recovered from individuals infected and/or colonized with hospital-associated and community-associated strains. Currently, in many hospitals over half of infections caused by hospital-associated S. aureus strains involve methicillin-resistant organisms and, in some communities, nearly half of the community-associated strains recovered from skin and soft tissue infections (SSTIs) are methicillin resistant. [5, 6].

Gorwitz et al. [1] inform us that, although the overall prevalence of nasal carriage of S. aureus in the US population has declined significantly when the period from 2001–2002 is compared 2003–2004, the proportion of methicillin-resistant isolates recovered increased from 2.5% to 5.2%, and the proportion of MRSA isolates that are of the pulsed-field gel electrophoresis (PFGE) types typical of community-associated MRSA (CA-MRSA) strains rose from 8% to nearly 20%. Colonization with MRSA, in turn, is associated with increased risk of infection with MRSA. The study is population-based and so is probably a fairly accurate reflection of the situation in the United States in 2004. These trends are likely to continue.

Emonts et al. [2] demonstrate that differences in several host inflammatory response genes probably contribute significantly to the propensity for both colonization and infection with S. aureus in an elderly study population. Polymorphisms in each of the genes the authors studied had previously been shown to interact with S. aureus in various ways, either in vitro or in vivo, to increase the severity of infection with S. aureus (interleukin [IL]-4 deficiency), to interact with staphylococcal protein A (C-reactive protein [CRP]; and tumor necrosis factor [TNF]-α, concentrations of which are controlled by the TNFA promoter region), or respond to activation by CRP (complement factor H [CFH]). The investigators postulated that variants of some of these genes were likely to be overrepresented or underrepresented among individuals who were colonized or infected with S. aureus, and they were correct. A very large sample size (3851 participants), 678 (18%) of whom had persistent carriage of S. aureus and 1270 of whom had boils, as well as longitudinal design, conferred great statistical power on the study. Careful statistical analysis, which incorporated multivariate regression and controlling for confounding, further strengthened their findings of association.

The ILA – 524 C/C host genotype, as opposed to the ILA – 524 T allele, was associated with an increased probability of nasal carriage of S. aureus, irrespective of the strain’s genotype. In addition, persistent nasal carriage was associated with both the ILA – 524 C/C genotype and certain S. aureus AFLP strain markers, suggesting the complexity of the interaction between host and microbe. The authors postulate that the C allele, which results in lower levels of ILA4 serum concentration and mucin production, allows the increased frequency of nasal carriage because of decreased mucociliary clearance of the organism. Conversely, haplotype 2, the CRP (1184–2042–2911) G–C–C haplotype, was found more often in individuals
without carriage, and CRP C-C-G haplo-
type 3 was associated with a decreased oc-
currence of boils. Homozygosity for the
CFH 402Tyr variant was overrepresented
among individuals who reported a history of
boils. TNFA polymorphism was not as-
associated with nasal carriage of S. au-
reus.

The findings of Emonts et al. [2] fur-
ther illuminate the complex interaction
between this pathogen and its reluctant
human host. A picture emerges of a dy-
namic balance between host and patho-
gen, influenced by multiple features of
each. Subtle differences in either the
pathogen or the host lead to a greater or
less risk of colonization or disease. We
are just beginning to understand and cat-
aogue these differences, and the final
model of human–S. aureus interaction is
likely to be exceedingly complex.

David et al. [3] ask what traits actually
identify CA-MRSA, if any. The label
“hospital-associated” heretofore implied
resistance to multiple antibiotics and car-
rriage of staphylococcal cassette chromo-
some mec (SCC mec) type I, II, or III, and
the label “community-associated” im-
plied carriage of SCCmec IV and Panton-
Valentine leukocidin (PVL) genes; the
production of phenol-soluble modulin
peptides (discussed further below); and
comparatively limited antimicrobial re-
 sistance, a pattern that includes suscepti-
bility to clindamycin and doxycycline.
David et al. [3] ask whether the boundaries
between these 2 categories have become
so blurred that the terms “community-
associated MRSA” and “hospital-associated
MRSA” are no longer epidemiologically or
clinically useful. They conclude that “asso-
ciation with the healthcare environment
now has little predictive value for distin-
guishing patients with infection due to mul-
tiple resistant MRSA isolates from those in-
fected by CA-MRSA isolates,

First, some attempt at clarifying the
definitions of commonly used terms
involving MRSA is in order. There are
a bewildering array of terms applied to the
classification and description of MRSA
strains. With regard to the spectrum of
 antimicrobial susceptibility, MRSA can be
resistant to methicillin alone (MRSA), to
one or more additional antimicrobials
(or classes of antimicrobials) used to
treat staphylococcal infections (e.g., cli-
damycin, tetracyclines, quinolones, rifam-
 pin, trimethoprim-sulfamethoxazole, and/or
aminocyclitols), or to multiple antimicro-
classical (multidrug-resistant MRSA
[MDR-MRSA]). Most hospital-associated
strains are resistant to several classes of
 antimicrobial agents and most community-
associated strains are susceptible to clinda-
 mycin, as well as to tetracyclines and other
classes of antimicrobials.

In the past 10–15 years, the causes of col-
onization and/or infection with MRSA have
also increasingly been divided into strains
presumed to be healthcare-associated in or-
igin or healthcare-acquired in terms of
exposure (HA-MRSA) or strains that are
community-associated in origin or
community-acquired in terms of exposure
(CA-MRSA). This distinction has been
most useful for monitoring the rise of
community-associated strains over the
past decade, during which an increasing
proportion of MRSA isolates appear to be
of community origin and transmitted in
the community [3].

The term “acquired” implies that there
is strong epidemiologic evidence and evi-
dence from a patient’s clinical history in-
dicating that colonization and/or infec-
tion occurred after acquisition of the
organism from exposure to the healthcare
environment, or conversely, from an ex-
posure that occurred in the community.
The term “associated” is more commonly
used to denote distinct strain types that,
historically, were first seen in large num-
bers in hospitals or, more recently, to de-
scribe distinctive strains of MRSA recov-
ered from the community. Thus, we
suggest that “associated” refers to S. au-
reus strains, whereas “acquired” refers to
the location of the exposure that led to
colonization and/or infection.

Community-associated strains have
historically had the following traits: they
are predominantly of PFGE type USA300,
carry their mutant penicillin-binding
protein 2a (PBP2a) on mobile genes clas-
sified as SCCmec type IV, are resistant to
a few limited classes of antibacterial agents,
and harbor genes encoding for PVL, a pu-
tative virulence factor for pneumonia but
perhaps not for SSTI [7, 8]. Recently,
Wang et al. [9] have described a new class
of secreted, short staphylococcal peptides
that are associated with the virulence of
SSTI caused by community-associated
strains of MRSA, which are called phenol-
soluble modulin peptides. These peptides
recruit, activate, and lyse neutrophils, the
main human defensive response against
S. aureus. On the other hand, hospital-
associated strains were generally found to
be resistant to a broader spectrum of an-
timicrobial agents; to be more heteroge-
neous with respect to PFGE type; to carry
SCCmec types II and III; and often to lack
PVL genes and, probably, phenol-soluble
modulin peptides as well.

However, confusion arises because, more
recently, the onset of colonization and/or
infection with a community-associated or
hospital-associated strain of MRSA can re-
sult from either a healthcare-related ex-
posure or a community exposure. Thus, a
“hospital-associated” strain, originally ac-
cquired by one person as a result of contact
with the healthcare environment, could be
transmitted by to another person in the
community who has had no formal contact
with the healthcare environment. The or-
ganism would be accurately labeled a
hospital-associated strain, but it was ac-
cquired as a result of community exposure
and, epidemiologically, would be labeled
community acquired. Conversely, a person
who has had a history of exposure to the
healthcare environment could acquire a
strain that has laboratory characteristics
similar to those historically associated
with CA-MRSA, as David et al. point out in their
article [3].

Although David et al. [3] provide a
great deal of useful data on the character-
istics of MRSA in Chicago, where the sit-
Thus, the CDC criterion performed reasonably well at identifying isolates as community-associated that met both the risk factor criterion and possessed laboratory characteristics consistent with CA-MRSA, and the CDC criterion accurately identified most of the isolates that might have been healthcare-associated. These patients and isolates remain useful for epidemiologic studies of risk factors for infection and/or colonization with community-associated MRSA, as well as studies to collect other related data. The real value of the David et al. article [3], we believe, lies in the finding that, submerged within the group of isolates identified as possibly healthcare associated by the risk factor criterion, there are a number of isolates with laboratory characteristics that suggest CA-MRSA. These isolates were recovered from people who had incidental healthcare exposure but probably were acquired in the community setting, further underscoring the increasing overall importance of CA-MRSA strains.

As clinicians working in the emergency department or outpatient setting, we would be comfortable using clindamycin or doxycycline to treat uncomplicated SSTI in patients who lacked healthcare-associated risk factors, even in a geographic area with a known high prevalence of MRSA among outpatients with SSTI. On the other hand, in the David et al. study [3], clindamycin susceptibility was only 40% among strains recovered from patients with healthcare-associated risk factors, an unacceptably low figure if the infection is a serious or aggressive (complicated) SSTI or is located somewhere other than skin or soft tissue. These patients are generally admitted to the hospital anyway, until the infection has been controlled, or they are treated as outpatients and started on parenteral (vancomycin or daptomycin) or oral antimicrobial therapy using agents that are active against hospital-associated MRSA (e.g., linezolid) until the infecting organism’s antibiotic susceptibilities are known.

From a clinical standpoint, the CDC criteria remain useful for identifying 2 groups of patients: those with apparent staphylococcal disease who should respond to clindamycin as outpatients and patients for whom initial therapy would need to target HA-MRSA, which is more likely to be MDR. As S. aureus continues to evolve, its epidemiology is better understood, as host-microbe interactions continue to be better defined, and as we apply antimicrobial therapy more wisely, we can hope that the result is an ever-improving balance between host and microbe—in our favor.

References