Methicillin-resistant *Staphylococcus aureus* (MRSA) has emerged over the past 4 decades as a major cause of nosocomial infection and, more recently, as an important cause of community-acquired staphylococcal infection—especially skin and soft-tissue infections [1]. The worldwide emergence of community-associated MRSA clones [2] has created an even greater reservoir for transmission and infection in both community and health care environments, making infection control strategies even more challenging [3]. In addition, it has now been demonstrated that MRSA clones of community origin have been introduced into health care facilities and now can account for a significant proportion of health care–associated MRSA infections [4]. There has been much discussion and debate about what strategies are effective in controlling MRSA in health care facilities, given that MRSA has become endemic in many institutions [5–8]. Unlike the community, where skin and soft-tissue infections are most prevalent, a significant proportion of MRSA infections in the hospital are bloodstream infections, which have often been attributed to the presence of risk factors found in hospitalized patients, including a stay in an intensive care unit, the presence of a central venous catheter or other vascular access device (VAD), MRSA colonization, and previous antibiotic use [9, 10].

In this issue of *Clinical Infectious Diseases*, Edgeworth et al. [11] describe a 2-year outbreak of MRSA caused by a particular strain they designate as TW, which they report is associated with an increased risk of VAD-related blood stream infection. Transmission of TW apparently occurred primarily within the hospital, with few cases of colonization of the nares, axilla, or groin detected in newly admitted patients. A limitation of their study is that TW was initially defined by a particular antibiogram pattern, which is a phenotypic method of identification. An optimal typing method should show high typeability, reproducibility, and discriminatory power [12]. Phenotypic methods, including phage typing and antibiotic susceptibility pattern analysis (both of which were employed in this report), can lack typeability or discriminatory power. Shortcomings of phenotypic methods have led to the development of genotypic typing methods, which have proven to be powerful tools in investigating outbreaks and chains of transmission. Commonly employed molecular typing methods for MRSA include PCR-based techniques (e.g., random amplified polymorphic DNA or repetitive-element sequence-based PCR), PFGE, and sequence-based typing methods, such as staphylococcal protein A (*spa*) typing and multilocus sequence typing (MLST) [12, 13]. The most definitive evidence in their report that TW represented a single MRSA clone was that 15 of 16 TW isolates that were studied using DNA microarray technology [14, 15] carried the same composition of mobile genetic elements.

In the report by Edgeworth et al. [11], only 1 TW isolate was genotyped using MLST [16] and was identified as member of the sequence type (ST)–239 lineage. MLST relies on the sequence analysis of 7 housekeeping genes, as opposed to a restriction enzyme–based method like PFGE [13, 17, 18]. In addition to yielding unambiguous, comparable results by way of analyzing known elements of the bacterial genome, MLST allows for the assessment of evolutionary relationships—in this case, placing TW in the “core clone 8” [19].
group, which corresponds to the “Brazilian/Hungarian MRSA” group of strains [13]. The discriminatory power of MLST may be inferior, compared with PFGE, partly because of the lower rate of evolutionary changes in these housekeeping genes (a “slower clockspeed”), which explains the genetic diversity of ST-239 isolates that is noted in the report. Non-TW isolates in the report by Edgeworth et al. [11] were identified to most commonly belong to the types that were endemic in their institution, epidemic MRSA (EMRSA)—15 and EMRSA-16. These were identified using phage typing, which is based on the lysis patterns on MRSA culture plates caused by a defined set of bacteriophages [20] and experiences the limitation of phenotypic methods described above. EMRSA-15 and EMRSA-16 correspond to the MLST ST-22 and ST-36 lineages, respectively (the latter corresponding to the PFGE type USA200 [13]). The nomenclature that has been used to identify MRSA strains using different typing methods (phenotypic and genotypic) is confusing and somewhat arbitrary [19]. This can lead to imprecise designations when trying to describe strains identified by different methods, such as the designation of EMRSA-7 as an ST-239 strain; it actually belongs to ST-8, which is one of ST-239’s parent lineages [13, 19, 21].

The provocative nature of this report is the assertion that the TW clone has an enhanced ability to cause bloodstream infections, compared with the endemic strains of MRSA found at Guy’s and St. Thomas’ Hospital in London, England. This conclusion is somewhat tempered by a few limitations in this study, including the fact that MRSA strain designations were performed using phenotypic methods and non-TW strains of MRSA were not studied using molecular typing methods. In addition, in their epidemiologic analyses, Edgeworth and colleagues used a novel exposure variable, CAA-MRSA days, that has the complicated definition of “total duration of insertion of all arterial and central venous VADs, while known to be colonized with MRSA but without receiving treatment with gentamicin or vancomycin (if active against the acquired MRSA strain)” [11, p. 495–6]. It would have been of interest to see the analysis performed using total days with a VAD or a central venous catheter as a potential risk factor for bloodstream infection (as has been used in other studies), regardless of the colonization status, rather than restricting the variable used to known days colonized with MRSA. Their findings of a seemingly paradoxical protective effect of VAD exposure (using the CAA-MRSA variable) against MRSA blood stream infection complicates the interpretation and implications of their findings. It also would have been of interest to control for prior antibiotic receipt, which has been associated with MRSA infection in a number of previous reports [22].

In the literature, there are some reports of the introduction of a new strain or clone of MRSA into a setting where MRSA has been endemic that has led to an outbreak of disease [22], as is reported by Edgeworth et al. [11]. The mechanisms by which this occurs are not well understood. However, it is clear from a number of reports that those patients who were colonized with MRSA were at a substantially increased risk for developing MRSA infection [10], and cross transmission of TW occurred after initial introduction of this strain into this British hospital. Further studies are needed to define what genetic determinants are responsible for the evolutionary success of such epidemic strains.

Additional investigations are needed to validate the report by Edgeworth et al. [11] that certain MRSA strains, such as TW, have an increased affinity for VAD and, therefore, are more likely to cause bloodstream infection. It does seem plausible that there may be genetic factors linked to organisms within a species that cause different manifestations of disease. For example, MRSA strains of community origin, such as the USA300 clone, which is widely distributed in the United States and carries Panton-Valentine leukocidin, have a predilection to cause skin and soft-tissue infections [4], frequently with abscess formation. Elucidation of the genome of USA300-0014 has led to the finding of the presence of a gene cluster, arginine catabolic mobile element [23]. Arginine catabolic mobile element has not been found in other S. aureus isolates that have been sequenced to date, but is common among Staphylococcus epidermidis isolates [23]. It has been hypothesized that the products of arginine catabolic mobile element enable the USA300 clone to evade host immune responses and to survive and spread [23]. Similarly, Edgeworth et al. [11] suggest a role for organism-related factors determining the observed increased affinity of TW to VAD and its relative absence from the nares, axilla, and groin. Using microarray technology developed at their institution, the authors attempted to identify genes specific to TW as compared with related strains with no increased risk for bloodstream infection from a pool of 3623 genes, identified from 7 S. aureus strains with a predicted number of genes per strain ranging from 2587 to 3777 [14]. The detected mobile genetic element profile mainly determining resistance and virulence was different compared with strains of related MLST lineages, but did not reveal any genes exclusive to TW among this group. The authors hypothesize that a presumptive blood stream infection-associated (novel) gene was not carried by any of the 7 strains used for constructing the microarray chip. Additional information may be provided by the sequencing of the entire genome of TW, which the authors note is underway. On the basis of another group’s findings of a related strain that had an enhanced ability to produce biofilm on inert polystyrene surfaces and to adhere to and invade epithelial cells [24], Edgeworth et al. [11] further hypothesize that enhanced biofilm formation might be involved in the pathogenesis of TW; this sounds attractive, but clearly needs supportive evidence. There is also the possibility that a certain combination of known genetic elements is responsible for the ad-
adaptation of S. aureus to a specific ecologic niche.

What also makes the article by Edgeworth et al. [11] notable is the fact that they used DNA microarray technology in the setting of an outbreak investigation. There are limited data on the use of microarrays as a tool for epidemiologic typing of bacterial pathogens [15]. A DNA microarray, as used in the current study, is a collection of microscopic DNA spots attached to a solid surface, such as a glass, plastic, or silicon chip, forming an array for the purpose of simultaneously assessing the presence of thousands of genes in a bacterial isolate [14, 25, 26]. By comparing TW with other ST-239 strains using DNA microarray technology, the authors demonstrate that the mobile genetic element composition in S. aureus is more variable than what is detectable by MLST and, presumably, other current standard phenotyping or genotyping methods, a fact that also recently was nicely illustrated by a Swiss group of researchers [27]. The use of microarray technology has the promise of allowing for the definition of novel marker genes and chromosomal regions specific for given groups of isolates, thereby providing better discrimination and additional information compared with PFGE, MLST, and other common molecular typing methods [28]. This underlines the usefulness of tools for the characterization of bacterial characteristics that not only reliably differentiate between clones but would (eventually) predictably affect a patient’s clinical course and outcome, and maybe even suggest approaches for the prevention of acquisition of the organism or disease. The microarray method used in this outbreak and other similar approaches [28, 29] seem to be promising steps in this direction. Microarray analysis is currently not widely available as a molecular epidemiologic typing tool for MRSA in most health care settings, and such use would be cost prohibitive [15]. However, future applications could use selected regions of variability discovered in whole-genome array assays, which probably has a much better chance of becoming standard procedure in epidemiologic investigations rather than arrays that cover entire genomes of bacteria [15]. The prospects of the complete sequencing of an increasing number of S. aureus strains, including TW, have the potential to provide greater insight into determinants of adaptation to certain ecologic niches, transmissibility, virulence, and drug resistance. Hopefully, these efforts will lead to discoveries that will help infection control programs, as well as clinicians, to better protect patients from nosocomial infections.

Acknowledgments


References

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