Correlation of Discharge Diagnostic Codes with Laboratory-Confirmed Methicillin-Resistant Staphylococcus aureus Bloodstream Infections at a Large Pediatric Hospital

Andrew J. Kreppel
Wright State University - Main Campus, andrew.kreppel@wright.edu

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Correlation of Discharge Diagnostic Codes with Laboratory-Confirmed Methicillin-Resistant

*Staphylococcus aureus* Bloodstream Infections at a Large Pediatric Hospital

Andrew J. Kreppel, MD

Wright State University
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Abstract

**Background:** Methicillin-resistant *Staphylococcus aureus* (MRSA)-specific hospital discharge codes were introduced in October 2008. The purpose of this project is to study the correlation of these codes with laboratory-proven pediatric MRSA bloodstream infections.

**Methods:** Laboratory and discharge databases were used to identify patients <20 years old hospitalized at Cincinnati Children’s Hospital Medical Center from October 2008 through December 2010 with MRSA bloodstream infections. The laboratory database identified patients with a positive blood culture for MRSA, and the discharge database identified patients with an MRSA bloodstream discharge code (038.12 for MRSA sepsis or 041.12 for MRSA infection with either 790.7 for bacteremia or 771.81 for newborn sepsis or 771.83 for newborn bacteremia). The sensitivity and positive predictive value (PPV) of the codes were determined, using laboratory-confirmed infection as the gold standard.

**Results:** During the 27 month study period, 65 patients with MRSA bloodstream infection were identified from laboratory data and 58 patients were identified from administrative data; 36 were concordant. The overall sensitivity was 55.4%, and the overall PPV was 62.1%, and neither showed a significant trend over time. The sensitivity varied with the clinical manifestation of the bloodstream infection. Of the 22 patients coded for MRSA bloodstream infection without a positive blood culture, almost half (45.4%) had only a localized MRSA infection. Of the 29 patients with positive MRSA blood culture but insufficient discharge coding, the majority (55.2%) were coded only for MRSA infection without bloodstream involvement.

**Conclusions:** Discharge coding for MRSA bloodstream infection was found to be insensitive and to have a low PPV. Using these codes alone will lead to an underestimation of pediatric MRSA bloodstream infections.
Correlation of Discharge Diagnostic Codes with Laboratory-Confirmed Methicillin-Resistant \textit{Staphylococcus aureus} Bloodstream Infections at a Large Pediatric Hospital

Infection with methicillin-resistant \textit{Staphylococcus aureus} (MRSA) has become an increasingly common pediatric condition over the past 10-15 years. Unfortunately, the overall current epidemiology of MRSA invasive disease among pediatric patients has not been well-studied to date, except for small studies in various geographic locations. As has been done with other conditions, the national epidemiology of invasive pediatric MRSA infections potentially could be monitored using readily available, large-scale administrative databases containing International Classification of Diseases 9\textsuperscript{th} Revision (ICD-9) hospital discharge codes. Such administrative databases can be attractive for use because of their relative ease of availability and because of the large volume of data that is included. For example, the National Hospital Ambulatory Medical Care Survey (NHAMCS), the National Hospital Discharge Survey (NHDS), the Kids’ Inpatient Database (KID), and the Pediatric Health Information System (PHIS) are large datasets that include ICD-9 codes and have been used to monitor the burden of various other medical conditions. However, the extent to which these data reflect the true underlying clinical condition could vary significantly. Therefore, if administrative data will continue to be used more frequently, specifically for further research regarding pediatric MRSA infection, then a better understanding of the correlation between discharge diagnosis codes and clinical MRSA disease must be elucidated.

For this culminating experience project, the hypothesis is that ICD-9 hospital discharge codes will only moderately correlate with laboratory-proven MRSA bloodstream infections for children hospitalized at Cincinnati Children’s Hospital Medical Center (CCHMC). Per US Department of Health and Human Services Centers for Medicare and Medicaid Services,
hospital discharge codes specific to MRSA only came into effect in October 2008. Prior to this time, MRSA infections required at least 2 separate codes to adequately document the infection. Some adult studies done at that time already showed a relatively low sensitivity and positive predictive value for code combinations in capturing MRSA hospitalizations. Therefore, for this culminating experience, the project will only focus on hospitalizations after October 2008. The discharge code information will be obtained from the CCHMC Finance and Health Information Management Department (discharge database), and the MRSA blood culture information will be obtained from the CCHMC Infection Control Program (lab database). These two databases will be compared in order to determine the sensitivity and positive predictive value of the ICD-9 codes for pediatric MRSA bloodstream infections.

This project was approved by the Institutional Review Board at CCHMC, as part of a larger project assessing the overall burden of *Staphylococcus aureus* disease.
Statement of Purpose

The purpose of this project is to better understand the applicability of administrative hospital discharge data for monitoring the epidemiology of pediatric MRSA bloodstream infections. The research hypothesis is that ICD-9 hospital discharge codes specific to MRSA bloodstream infection (038.12 for MRSA sepsis or 041.12 for MRSA infection with either 790.7 for bacteremia or 771.81 for newborn sepsis or 771.83 for newborn bacteremia) will only moderately correlate with laboratory-confirmed MRSA bloodstream infections among patients less than 20 years old hospitalized at CCHMC during Oct. 2008 – Dec. 2010. The extent of this correlation will be based upon measurement of the sensitivity and positive predictive value of the codes. Further, any discordance between the administrative data and laboratory data will be assessed through chart review in order to identify reasons for incomplete correlation. This information is important in order to estimate the burden of and monitor trends for pediatric MRSA bloodstream infections in the future.
Review of Literature

*Staphylococcus aureus* (*S. aureus*) is a bacterium that commonly colonizes the nasal mucosa and skin of humans, but it can cause serious invasive disease when it breaches these outermost defenses. When *S. aureus* bypasses the skin or mucosal barriers and gains access to the deeper tissues and bloodstream, it can cause a wide spectrum of disease. Most commonly, *S. aureus* infection manifests as skin and soft tissue infection, but it can also cause pneumonia, bone and joint infection, bloodstream and cardiac infection, and disseminated disease, among others (Gorwitz, 2008). The factors that determine whether *S. aureus* causes localized disease or more systemic illness are not well-defined but are thought to involve the interplay between the host’s defense mechanisms and a myriad of bacterial factors. For example, it is known that individuals with indwelling medical devices, type I diabetes, intravenous drug users, hemodialysis or surgical patients, and those with the acquired immunodeficiency syndrome are at higher risk for staphylococcal infection (Lowy, 1998). On the other hand, *S. aureus* itself can produce different virulence factors and can have different antibiotic resistance patterns, resulting in various isolates that may be associated with different clinical disease states (David & Daum, 2010). Most prominent among these various isolates is methicillin-resistant *S. aureus* (MRSA), as opposed to methicillin-sensitive *S. aureus* (MSSA). MRSA is simply a type of *S. aureus* that is resistant to many of the antibiotics that could be used to treat MSSA. It was first described in 1961 as a pathogen linked to hospital outbreaks of infection, and over the next 20-30 years, it became a well-recognized, commonly isolated healthcare-associated bacterium. The first report of MRSA outside of the healthcare setting occurred in 1982. These first community-associated cases were isolated only from patients who were IV drug users, but subsequently, MRSA has
become a prevalent problem in the community at large (David & Daum, 2010; Lowell & Daum, 2008).

Over the past several decades, the increased prevalence of MRSA in the community has led to more healthcare encounters for illnesses consistent with *S. aureus* infection. In Emergency Departments across the country, it was reported that the number of visits for skin and soft tissue infections (many of which are commonly caused by *S. aureus*) almost tripled between 1993 and 2005 (Pallin et al., 2008). This report was based upon data from the National Hospital Ambulatory Medical Care Survey (NHAMCS), which is a national survey of hospital emergency and outpatient departments that collects administrative data and applies weights based on the sampling method in order to allow for national generalizability (Centers for Disease Control and Prevention, 2009). This administrative database does not include any true microbiologic information, so the bacterial cause of the skin and soft tissue infections could not be verified as *S. aureus*. However, with the increase in skin and soft tissue infections being disproportionate to the overall increase in ED visits during the study (increased from 1.35% of 89 million visits in 1993 to 2.98% of 114 million visits in 2005), this denotes a likely true increase in the rate of skin and soft tissue infections and a probable increase in the rate of *S. aureus* infections (Pallin et al., 2008).

For patients requiring hospitalization related to *S. aureus*, the National Hospital Discharge Survey (NHDS) was used to assess the number of hospitalizations in 1999-2000 with *S. aureus* discharge codes, and then US Census data was combined with this to estimate the prevalence of *S. aureus* hospitalizations nationwide (Kuehnert et al., 2005). While this study was based upon administrative data, the process of combining national hospital discharge data specific to *S. aureus* with US Census data provided a framework for estimating the burden of *S. aureus* infections.
*aureus* hospitalizations across the country. Therefore, this same process was used by later researchers to observe further trends in the rates of *S. aureus* hospitalizations. In 2007, Klein, Smith, and Laxminarayan (2007) reported that the prevalence of *S. aureus* attributable hospitalizations increased by 62%, from 294,570 to 477,927 hospitalizations from 1999 to 2005. Because discharge data did not include reliable differentiation between MRSA and MSSA until new codes were introduced in 2008, these studies could not directly assess the proportion of MRSA present. To get around this difficulty, the prevalence of MRSA hospitalization was estimated from the numbers of resistant isolates in a national lab surveillance network and then extrapolated to the numbers in the discharge databases. By this process, the prevalence of MRSA hospitalizations increased by 119% between 1999 and 2005, from 127,036 hospitalizations to 278,203 hospitalizations (Klein, Smith, & Laxminarayan, 2007).

These national studies described amounts of *S. aureus* disease based upon estimates from administrative databases, but they also substantiated several smaller studies based upon laboratory defined *S. aureus* disease. In 2001 – 2002, Fridkin et al. (2005) performed prospective laboratory-based surveillance of culture-proven MRSA disease from clinical labs in Baltimore, MD, Atlanta, GE, and Minnesota, with a focus upon community-associated infections. The clinical data submitted with the laboratory samples, such as age, sex, and body site of sample collection, allowed the authors to define some of the basic clinical and demographic characteristics of patients with MRSA infection. Only seventeen percent of the 12,553 MRSA lab cultures in their study were deemed to represent community-associated infections and received further analysis (2107 positive cultures). Of these, they found that the annual incidence rate for community-associated MRSA infection was highest among children <2 years old. Also, 77% of these community-associated infections manifested as skin and soft
tissue infections, and only 6% occurred as invasive infections including bloodstream infection, osteomyelitis, or septic arthritis (Fridkin et al., 2005). Then, in 2004 – 2005, Klevens et al. (2007) used the Centers for Disease Control’s Active Bacterial Core (ABC) surveillance program to monitor invasive MRSA disease, defined as isolation of MRSA from a normally sterile body site. The ABC program is a laboratory-based system that, in 2005, included 9 US geographic areas and represented about 5.6% of the total US population (now includes 10 areas representing 13.6% of the population) (Centers for Disease Control and Prevention, 2011; U.S. Census Bureau, 2011). In this study, national MRSA incidence rates were calculated by multiplying site-specific rates with overall U.S. Census data. In contrast to Fridkin’s study, the incidence of invasive MRSA disease was highest among people >65 years old. Also, by comparing two of the sites used in Fridkin’s study (Atlanta, GA, and Baltimore, MD), Klevens showed large increases in the laboratory-proven incidence rates of invasive MRSA disease between 2000 and 2005 (Atlanta: 19.3 → 33.0 per 100,000; Baltimore: 40.4 → 116.7 per 100,000) (Klevens et al., 2007).

While some subsets of pediatric patients were included in the national epidemiologic studies of *S. aureus*, relatively few studies have focused specifically upon pediatric populations for this disease. Kaplan et al. (2005) performed a prospective laboratory-based, single-center surveillance study in 2001-2004 that looked only at community-associated infections, excluding all patients with chronic medical conditions, indwelling vascular access lines, or hospitalizations within the preceding year. During the three year study period, they did see an annual increase in the overall number of *S. aureus* isolates for this population (771 in the first year compared to 1562 in the third year), with a greater overall increase in MRSA (2.2-fold) compared to MSSA (1.7-fold). The vast majority of both MRSA and MSSA infections were manifest as skin and
soft tissue infections (95.6% and 91.8%, respectively) (Kaplan et al., 2005). Gerber, Coffin, Smathers, and Zaoutis (2009) used a national administrative database, the Pediatric Health Information System, to assess the incidence and characteristics of *S. aureus* infections requiring hospitalization at any one of thirty-three different free-standing U.S. children’s hospitals between 2002 and 2007. All of this data was based upon discharge diagnostic codes, and the distinction between MRSA and MSSA was based solely upon the presence or absence of a code denoting infection with resistant organisms. Despite this limitation, during the 6 years of the study, there was an overall increase in the incidence of *S. aureus* infection (20.8 ➔ 35.8 cases per 1000 admissions) as well as in increase in the incidence of MRSA infection (6.7 ➔ 21.2 cases per 1000 admissions). Though not all patients had the site of infection noted, of those who did, 61% involved the skin and soft tissues. As noted by the researchers, one of the major limitations of this study was that “the accuracy of ICD-9 codes for diagnosis of either *S. aureus* or MRSA infection has not been validated for this large population” (Gerber, Coffin, Smathers, & Zaoutis, 2009).

With regard to more invasive disease, the first reports of fatal MRSA infection in pediatric patients came from the Minnesota-North Dakota area in 1999. The report described four patients between the ages of 12 months and 13 years who were from various socioeconomic and geographic backgrounds and who all succumbed to invasive MRSA infection ("Four pediatric deaths from community-acquired methicillin-resistant Staphylococcus aureus - Minnesota and North Dakota, 1997-1999," 1999). Other reports of invasive MRSA disease in pediatric patients were described in the Houston, TX and Chicago, IL areas in the early 2000’s (Gonzalez et al., 2005; Mongkolrattanothai, Boyle, Kahana, & Daum, 2003). Gonzalez et al. (2005) in TX noted an increase in pediatric patients presenting with severe MRSA sepsis from 1
case in 1999-2002 to 14 cases in 2002-2004. Mongkolrattanothai, Boyle, Kahana, and Daum (2003) tested several invasive strains of MRSA isolated from pediatric patients in IL and found the strains to be genetically similar to MSSA strains that were already prominent in the community. This suggested that the community MRSA isolates may have evolved within the previous background of MSSA disease already present (Mongkolrattanothai et al., 2003).

Looking specifically at bloodstream infections due to MRSA, Carrillo-Marquez, Hulten, Mason, and Kaplan (2010) retrospectively analyzed laboratory-based, single-center pediatric data surveilling for central vascular catheter associated S. aureus infections in 2001-2007. They found 124 episodes of S. aureus isolates causing bacteremia in 112 children. Of these, MRSA isolates comprised only 25.9% of all of the S. aureus infections (Carrillo-Marquez, Hulten, Mason, & Kaplan, 2010).

Given this relative lack of national epidemiologic information regarding pediatric S. aureus disease along with the overall increased incidence of MRSA infection in general, further studies assessing pediatric S. aureus epidemiology are warranted. However, since laboratory and clinical-based epidemiologic studies can be very complex and only representative of the local population, the use of larger administrative databases including discharge diagnosis data could provide a simpler assessment of the disease burden. This method has been used in several of the previously mentioned studies, but the technique requires validation in pediatric S. aureus disease. Similar validity tests have already been examined for other types of pediatric infections. In 2000-2001, Hsu et al. (2005) tested the validity of rotavirus discharge codes compared to laboratory testing in an active surveillance program at one pediatric institution. This study showed that the rotavirus discharge code only had a sensitivity of about 47%, thereby missing over half of all laboratory-proven cases (Hsu et al., 2005). In 2001-2004, Keren et al. (2006)
tested the validity of influenza discharge codes compared to all hospitalized patients with laboratory confirmed influenza. Here, the influenza discharge code had a sensitivity of about 65%, missing 35% of the laboratory-proven cases (Keren et al., 2006). Clearly, in these other infectious processes, the administrative data alone seems to be underrepresentative of the total disease burden, to variable extents.

For *S. aureus*, and specifically MRSA, no studies have assessed the validity of discharge coding to represent clinical disease in pediatric patients. For adult patients, this has been evaluated somewhat, particularly because certain states have passed legislation mandating the use of discharge diagnosis codes for reporting healthcare-associated infections including MRSA (Schaefer et al., 2010). At a single adult medical center during 2005-2007, Schaefer et al. (2010) correlated MRSA specific discharge diagnostic codes with confirmed MRSA cases. In this study, discharge codes only had a sensitivity of about 59% compared to cases confirmed by lab results and chart review, but the codes had a positive predictive value of 93%. Unfortunately, this study was completed prior to the introduction of the new MRSA-specific discharge codes in 2008, so the applicability of the results to the new codes is unknown (Schaefer et al., 2010).

Given the ongoing importance of MRSA infection among pediatric populations and the need for better epidemiology of the disease in this age group, more studies will likely make use of administrative datasets in order to better understand the burden of disease. Therefore, the purpose of this project is to assess the sensitivity and positive predictive value of discharge diagnosis codes for MRSA bloodstream infections, so as to better understand the limitations of using administrative data to track this disease.
Methods

Sampling

The population of study in this project is all patients less than 20 years old hospitalized at Cincinnati Children’s Hospital Medical Center (CCHMC) from October 2008 through December 2010 with MRSA bloodstream infections. Bloodstream infections were chosen because this type of infection was felt to be the “most clean.” In other words, from a clinical standpoint, blood cultures that grow S. aureus are almost always treated as true infections. This may not be the case for other cultures that grow S. aureus, in which the positive result may be more likely interpreted as colonization or contamination. Therefore, it was thought that bloodstream infections would likely have the strongest correlation between administrative and lab data, compared to other types of MRSA infection.

The sampling frames for this population include the database generated by CCHMC Infection Control Program (a.k.a. lab database) and the database generated by CCHMC Finance and Health Information Management Department (a.k.a. discharge database). The lab database contains all positive blood cultures from the Clinical Laboratory, and the discharge database contains all discharge codes for any given hospitalization. From the lab database, subjects were selected if they had a positive blood culture for MRSA; from the discharge database, subjects were selected if they had a discharge code indicating MRSA bloodstream infection (038.12 for MRSA sepsis or 041.12 for MRSA infection with either 790.7 for bacteremia or 771.81 for newborn sepsis or 771.83 for newborn bacteremia). From these frames, no direct sampling method was used, but rather all hospitalizations which met the selection criteria were included. Once the hospitalization was identified by either positive blood culture or positive discharge code, the corresponding medical record was reviewed. Through chart review, if the medical
providers prescribed treatment (most commonly the use of antimicrobials against MRSA) then the hospitalization was counted as having true MRSA infection. Also through chart review, additional clinical information was obtained, including the presence or absence of underlying chronic medical disease and the clinical manifestations of the bloodstream infection. Categories were established for both underlying disease and clinical manifestations associated with the bloodstream infection. The estimated incidence of MRSA bloodstream infection at CCHMC is approximately 25 hospitalizations per year, resulting in 50 – 75 subjects for this study.

Measurement

The primary constructs utilized in this project are MRSA bloodstream infection and MRSA discharge diagnostic coding. To measure MRSA bloodstream infection, the construct was operationalized by selecting all positive blood cultures for MRSA from the lab database, determining the associated hospitalization, and then reviewing the corresponding medical record to assure true MRSA disease. In this way, the combination of positive blood culture result together with clinical information abstracted from the chart review served as the “gold standard” for defining MRSA bloodstream infection. To measure MRSA discharge diagnostic coding, this construct was operationalized by selecting all medical records from the discharge database that contained certain ICD-9 codes. In order to determine which ICD-9 codes to use, the goal was to include only those codes that would represent MRSA bloodstream infection, excluding other MRSA infections that did not involve the bloodstream. Per the Centers for Medicare & Medicaid Services, there are only three codes which indicate MRSA infection in ICD-9. Those are 038.12 for MRSA sepsis, 041.12 for MRSA infection elsewhere, and 482.12 for MRSA pneumonia. Prior to October 2008, MRSA infection had to be coded by using a S. aureus code in combination with an antibiotic resistance code, but this need has now been obviated by the
introduction of the MRSA-specific codes (Centers for Medicare & Medicaid Services, 2011). For this study, in order to capture all potential cases of MRSA bloodstream infection, 038.12 was selected along with the combinations of 041.12 with 790.7 for bacteremia or 041.12 with 771.81 for newborn sepsis or 041.12 with 771.83 for newborn bacteremia. The only other MRSA specific code, 482.42 for MRSA pneumonia, would still require an additional MRSA sepsis or MRSA infection with bacteremia code if the patient’s pneumonia was accompanied by bloodstream involvement (personal communication with CCHMC Health Information Management coding specialist, July 13, 2011). Thus, the aforementioned codes should capture all instances of MRSA bloodstream infection.

The secondary constructs for this project include chronic underlying disease and clinical manifestations of MRSA bloodstream infection. To measure these, the constructs were operationalized by denoting specific categories for each on medical record review. Chronic underlying disease was categorized as the presence or absence of any of the following conditions: cancer, chronic otitis media, chronic skin disease, diabetes mellitus, genetic / metabolic disorder, immune deficiency, lung disease, neurologic disease, prematurity ≤ 36 weeks gestation, prior transplant, renal disease, liver disease, cardiac disease, hematologic disease, GI disease, or “other chronic illness.” Based upon medical record review, each hospitalization was categorized as either having no chronic medical disease or having chronic disease in one of these categories. Similarly, the clinical manifestations of MRSA bloodstream infection were divided into the following categories: disseminated disease, primary bacteremia, osteomyelitis, joint / bursa infection, pulmonary infection, ear-nose-throat infection, intraabdominal infection, deep tissue infection, central nervous system infection, urinary tract infection, or skin / soft tissue infection. Bloodstream infection may occur in the setting of any of these manifestations, and
each hospitalization was categorized into one of these groups based upon medical record review. For purposes of this project, the groups were established to be mutually exclusive. So, a hospitalization was only assigned to one clinical manifestation group, based upon the primary presentation.

Data Collection and Analysis

The initial list of positive MRSA blood cultures was generated from the lab database and then reviewed to find all associated hospitalizations. All medical records for these hospitalizations were then obtained and reviewed. Clinical information from the medical record, including verification of MRSA infection, presence or absence of chronic disease, and the associated clinical manifestation, was recorded on a case report form and entered into an electronic management database. If on chart review, the positive blood culture was found not to indicate true infection (e.g.: colonization or contamination), the hospitalization was not included in further analysis.

The list of positive MRSA bloodstream infection discharge codes was generated from the discharge database and then reviewed for overlap with the lab database. For any hospitalizations not previously identified, medical records were obtained and reviewed. In this way, all hospitalizations could be categorized as either MRSA bloodstream infection with MRSA bloodstream discharge code, or MRSA bloodstream infection without MRSA bloodstream discharge code, or MRSA bloodstream discharge code without MRSA bloodstream infection. Subsequently, two-by-two tables could be constructed (Table 1) in order to determine the sensitivity and the positive predictive value of the MRSA ICD-9 codes.
Once the two-by-two tables are created, the sensitivity of the ICD-9 code is calculated as $a/(a+c)$, and the positive predictive value as $a/(a+b)$. 95% confidence intervals (95% CI) can also be calculated for each of these ratios based upon the sample sizes, using the “plus-4 method” for sample sizes ≥10 or the Fischer exact test for sample sizes <10 (Gerstman, 2008b). Unfortunately, because there is no way to determine the value of box d, this data will not allow for determination of specificity or negative predictive value. In addition to determining the overall sensitivity and positive predictive value for all MRSA bloodstream infections, these measures are also calculated for each year, for presence or absence of chronic disease, and for each different clinical manifestation. Categorical differences between these groups are then assessed using chi-square measurements, with results considered significant at an $\alpha$ level of 0.05 (Gerstman, 2008a).

Aside from the quantitative outcomes noted above, a qualitative assessment will be made to understand the reasons why some hospitalizations were not congruent in both the lab and discharge databases. This will be done by reviewing the data to see if themes arise that may account for why a hospitalization with MRSA bloodstream infection did not have the appropriate discharge code or why a hospitalization with MRSA bloodstream discharge codes did not have a positive MRSA blood culture in the lab. If consistent themes become evident for these
scenarios, then these may serve as potential starting points for improving the sensitivity and positive predictive value of the discharge codes over time.

**Research Ethics**

This project was approved by the CCHMC Institutional Review Board (see Appendix) as part of the larger approved study, “Determining the Burden of *Staphylococcus aureus* Disease in the Cincinnati Metropolitan Area.” The IRB approval number is 2010-1450 and expires on 4/26/2013.
Results

The total number of hospitalizations at CCHMC identified through the lab database for positive MRSA blood culture during October 2008 – December 2010 was 65; the total number of hospitalizations identified through the discharge database for positive discharge code indicating MRSA bloodstream infection was 58. Thirty-six were concordant and 51 were discordant, resulting in a total of 87 hospitalizations for chart review and analysis. Among the 65 hospitalizations identified from the lab database, all positive MRSA blood cultures were deemed true infections based upon chart review because the medical providers prescribed treatment in every case.

Two-by-two tables were constructed for total and yearly lab and discharge data (Figure 1). The lab data are denoted as positive or negative based upon whether or not there was a positive blood culture for MRSA. The discharge data are denoted as positive or negative based upon whether or not one of the four possible ICD-9 discharge codes or code combinations for MRSA bloodstream infection was present. The overall sensitivity was 55.4%, with 95% CI = 43.3% - 66.8%, and the overall positive predictive value was 62.1%, with 95% CI = 49.2% - 73.4%. Of note, there were far fewer cases in 2008 compared to 2009 or 2010 because of the limited number of months in 2008 (only October – December due to the timing of introduction of MRSA-specific codes). Of the 36 hospitalizations appropriately coded for MRSA bloodstream infection, only one-third (12 cases) were coded using the single MRSA sepsis code of 038.12. The other two-thirds used code combinations, including an MRSA infection code, 041.12, together with a code indicating bloodstream infection, either 790.7 or 771.81 or 771.83.
### Correlation of ICD-9 Codes with MRSA Bloodstream Infection

#### Figure 1

<table>
<thead>
<tr>
<th>TOTAL</th>
<th>Blood culture for MRSA</th>
</tr>
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<tr>
<td></td>
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<tr>
<td>+</td>
<td>35</td>
</tr>
<tr>
<td>-</td>
<td>29</td>
</tr>
</tbody>
</table>

Sensitivity = 55.4% (95% CI = 43.3, 66.8)  
PPV = 62.1% (95% CI = 49.2, 73.4)

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<th>Blood culture for MRSA</th>
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<td>+</td>
<td>4</td>
</tr>
<tr>
<td>-</td>
<td>4</td>
</tr>
</tbody>
</table>

Sensitivity = 50.0% (95% CI = 15.7, 84.3)  
PPV = 44.4% (95% CI = 13.7, 76.8)

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<td>+</td>
<td>13</td>
</tr>
<tr>
<td>-</td>
<td>13</td>
</tr>
</tbody>
</table>

Sensitivity = 50.0% (95% CI = 32.1, 67.9)  
PPV = 59.1% (95% CI = 38.7, 76.7)

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<th>Blood culture for MRSA</th>
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<td>+</td>
<td>19</td>
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Sensitivity = 51.3% (95% CI = 43.8, 76.2)  
PPV = 70.4% (95% CI = 51.3, 84.2)

*Figure 1. Total and yearly MRSA sensitivities and positive predictive values*
Chi-square analysis for trend was performed in order to assess how the yearly sensitivities and positive predictive values changed over time. While the positive predictive value did increase each year, from 44.4% in 2008 to 70.4% in 2010, neither the positive predictive value nor the sensitivity demonstrated a statistically significant trend over the study period (Figure 2).

**Table 1**

<table>
<thead>
<tr>
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<th>Pos culture, Neg coding</th>
<th>Expected</th>
<th>Pos culture, Pos coding</th>
<th>Pos culture, Neg coding</th>
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</table>

Chi-square p-value: 0.66

**Table 2**

<table>
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<tr>
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<th>Observed</th>
<th>Pos coding, Pos culture</th>
<th>Pos coding, Neg culture</th>
<th>Expected</th>
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</tbody>
</table>

Chi-square p-value: 0.36

*Figure 2.* Chi-square trend analyses for yearly (a) sensitivities and (b) positive predictive values.

For further analysis of the calculated sensitivity, hospitalizations were subdivided among those involving patients with or without chronic medical conditions, and among those involving each various clinical manifestation of MRSA bloodstream infection. The sensitivity of the ICD-9 codes in each group is shown in Table 2, along with the number of subjects and the 95% confidence intervals. Cases of Primary Bacteremia were also further divided out depending upon
the presence of absence of a central venous catheter (CVC). As can be seen in Table 2, central venous catheters were associated with 73.7% (14 out of 19) of the total cases of MRSA primary bacteremia.

Table 2. *Sensitivity, by chronic disease and by primary clinical manifestation of MRSA bloodstream infection*

<table>
<thead>
<tr>
<th>Condition</th>
<th>Number</th>
<th>Sensitivity</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Chronic Disease Present</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>YES</td>
<td>34</td>
<td>61.8%</td>
<td>45.0, 76.1</td>
</tr>
<tr>
<td>NO</td>
<td>31</td>
<td>48.4%</td>
<td>32.0, 65.1</td>
</tr>
<tr>
<td><strong>Clinical Manifestation</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary Bacteremia</td>
<td>19</td>
<td>78.9%</td>
<td>56.0, 91.9</td>
</tr>
<tr>
<td>CVC-associated</td>
<td>14</td>
<td>78.6%</td>
<td>51.5, 92.9</td>
</tr>
<tr>
<td>Not CVC-associated</td>
<td>5</td>
<td>80.0%</td>
<td>28.4, 99.5</td>
</tr>
<tr>
<td>Osteomyelitis</td>
<td>17</td>
<td>35.3%</td>
<td>17.3, 58.9</td>
</tr>
<tr>
<td>Disseminated</td>
<td>10</td>
<td>60.0%</td>
<td>31.2, 83.1</td>
</tr>
<tr>
<td>Skin / Soft Tissue</td>
<td>6</td>
<td>33.3%</td>
<td>4.3, 77.7</td>
</tr>
<tr>
<td>Joint / Bursa</td>
<td>5</td>
<td>40.0%</td>
<td>5.3, 85.3</td>
</tr>
<tr>
<td>Pulmonary</td>
<td>5</td>
<td>60.0%</td>
<td>14.7, 94.7</td>
</tr>
<tr>
<td>ENT</td>
<td>1</td>
<td>100.0%</td>
<td>2.5, 100.0</td>
</tr>
<tr>
<td>Deep Tissue</td>
<td>1</td>
<td>100.0%</td>
<td>2.5, 100.0</td>
</tr>
<tr>
<td>CNS</td>
<td>1</td>
<td>0.0%</td>
<td>0.0, 97.5</td>
</tr>
<tr>
<td>Intraabdominal</td>
<td>0</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Urinary Tract</td>
<td>0</td>
<td>N/A</td>
<td>N/A</td>
</tr>
</tbody>
</table>

Groups with the largest sample sizes were then selected for further comparison. Specifically, chi-square comparisons were made between those with chronic disease vs. those without chronic disease and also between those with primary bacteremia vs. those with osteomyelitis (Figure 3). Because of the small number of hospitalizations in all other groups, no
other between-group comparisons were made. There was not a statistically significant difference
between the sensitivity of the group with chronic disease vs. the group without chronic disease.
However, there was a significant difference, with \( p < 0.01 \), between the sensitivity of the primary
bacteremia group vs. the osteomyelitis group.

\[ \begin{array}{|c|c|c|c|c|c|}
\hline
\text{Observed} & \text{Pos culture,} & \text{Pos culture,} & \text{Expected} & \text{Pos culture,} & \text{Pos culture,} \\
 & \text{Pos coding} & \text{Neg coding} & & \text{Pos coding} & \text{Neg coding} \\
\hline
\text{Chronic Disease} & 21 & 13 & \text{Chronic Disease} & 18.631 & 15.169 \\
\hline
\text{No Chronic Disease} & 15 & 16 & \text{No Chronic Disease} & 17.169 & 13.831 \\
\hline
\end{array} \]

\( \chi^2 \text{-value: 0.28} \)

\[ \begin{array}{|c|c|c|c|c|c|}
\hline
\text{Observed} & \text{Pos culture,} & \text{Pos culture,} & \text{Expected} & \text{Pos culture,} & \text{Pos culture,} \\
 & \text{Pos coding} & \text{Neg coding} & & \text{Pos coding} & \text{Neg coding} \\
\hline
\text{Primary Bacteremia} & 15 & 4 & \text{Primary Bacteremia} & 11.083 & 7.917 \\
\hline
\text{Osteomyelitis} & 6 & 11 & \text{Osteomyelitis} & 9.917 & 7.083 \\
\hline
\end{array} \]

\( \chi^2 \text{-value: <0.01} \)

Figure 3. Chi-square analyses of sensitivity between groups, (a) chronic disease vs. no chronic
disease and (b) primary bacteremia vs. osteomyelitis

Next, the discordant hospitalizations (those in either the lab database or the discharge
database, but not both) were qualitatively assessed to determine any underlying themes for why
they were found in one or the other, but not both databases. For the hospitalizations from only
the lab database, there were several reasons why they did not meet ICD-9 discharge coding
criteria for MRSA bloodstream infection (Table 3). Most common among these was that an
MRSA infection code was present, but not a code denoting any bloodstream involvement of the
infection. Of note, five hospitalizations with MRSA bloodstream infection were coded as having MSSA bloodstream infection instead.

Table 3. *Reasons for discordance between discharge and lab databases in patients with a positive MRSA blood culture*

<table>
<thead>
<tr>
<th>Reason (total number = 29)</th>
<th>Number</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>MRSA infection code present, but no bloodstream code</td>
<td>16</td>
<td>55.2%</td>
</tr>
<tr>
<td>MSSA sepsis code <em>or</em> MSSA infection code with bloodstream code present, but nothing denoting MRSA infection</td>
<td>5</td>
<td>17.2%</td>
</tr>
<tr>
<td>Neither MRSA infection code nor bloodstream code present</td>
<td>5</td>
<td>17.2%</td>
</tr>
<tr>
<td>Bloodstream code present, but no MRSA infection code</td>
<td>3</td>
<td>10.4%</td>
</tr>
</tbody>
</table>

For the hospitalizations from only the discharge database, there were also several reasons why they did not have any lab blood cultures positive for MRSA (Table 4). Most common among these was that the patient had a localized MRSA infection without bloodstream involvement, but a bloodstream infection code was generated for another reason, such as a blood culture with a different organism. Of note, eight hospitalizations involving bloodstream infections due to MSSA received hospital discharge codes indicating MRSA bloodstream infection instead.

Table 4. *Reasons for discordance between discharge and lab databases in patients without a positive MRSA blood culture*

<table>
<thead>
<tr>
<th>Reason (total number = 22)</th>
<th>Number</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Localized MRSA infection without evidence of bloodstream involvement</td>
<td>10</td>
<td>45.4%</td>
</tr>
<tr>
<td>MSSA bloodstream infection, rather than MRSA</td>
<td>8</td>
<td>36.4%</td>
</tr>
<tr>
<td>MRSA colonization only (no treatment provided)</td>
<td>2</td>
<td>9.1%</td>
</tr>
<tr>
<td>Prior hospitalization with MRSA bloodstream infection, but no new infection during the current admission</td>
<td>2</td>
<td>9.1%</td>
</tr>
</tbody>
</table>
Discussion

The results of this study support the research hypothesis that ICD-9 hospital discharge codes specific to MRSA bloodstream infection would only moderately correlate with laboratory-confirmed MRSA bloodstream infection. In fact, the overall sensitivity and positive predictive value of the codes was quite low, at 55.4% and 62.1%, respectively. This finding implies that if administrative data, such as the ICD-9 codes used in this study, were employed to monitor MRSA bloodstream infection in pediatric hospitalizations, almost 45% of the total actual MRSA bloodstream infections would be missed. Further, of the hospitalizations identified by the use of these codes, almost 40% of them would not even involve an MRSA bloodstream infection at all. Clearly, these findings demonstrate the inherent difficulties in using administrative data to define particular clinical scenarios.

Over the time period involved in this study, both the sensitivity and positive predictive value increased, but not with a statistically significant trend. The increase may represent some improved familiarity with the new diagnosis codes over time, but the fact that there was no significant trend shows the relatively static nature of the underlying reasons for inaccuracy. For example, a major difficulty with both the sensitivity and positive predictive value measurements was that two codes, both an etiology and a manifestation code, often had to be present in order to meet the ICD-9 coding criteria for this study. While requiring both codes certainly affected the study outcomes (65% of the discordant hospitalizations in Table 3 had one or the other but not both), there is no other way to indicate the presence of MRSA bloodstream infection as opposed to some other type of MRSA infection. The MRSA sepsis code, 038.12, can be used as a single code to indicate MRSA bloodstream infection, but even among the appropriately coded hospitalizations, only one-third utilized this code. Presumably, the remaining hospitalizations
could not use this code because the patients had bacteremia (bloodstream infection) rather than true sepsis (bloodstream infection with more severe clinical findings such as low blood pressure). Unfortunately, this study was not designed to tease out the clinical differences between bacteremia and sepsis, and so the sensitivity of the single code for sepsis vs. the combined codes for bacteremia could not be assessed. Regarding the positive predictive value, the combination of codes was also problematic in that many hospitalizations coded for MRSA bloodstream infection really only had localized MRSA disease without a bloodstream component (45% of the discordant hospitalizations in Table 4). This finding was due to the presence of a localized MRSA infection together with a completely separate bloodstream infection due to a different organism, and coding for both conditions. Because there is no mechanism to link etiology and manifestation codes, these hospitalizations were misidentified by the administrative data as having MRSA bloodstream infection when they really did not.

Of note, the current national discharge coding system, ICD-9, will be replaced on October 1, 2014 with a new system, ICD-10. Per the Center for Medicare & Medicaid Services website, the new ICD-10 data will include thousands more codes, thus allowing the diagnostic codes to more accurately reflect various different clinical scenarios. Hopefully, this new coding system would then allow for better quality assessments by “facilitat[ing] evaluation of medical processes and outcomes” (Centers for Medicare & Medicaid Services, 2010). Unfortunately though, in order to evaluate the medical processes and outcomes surrounding MRSA bloodstream infection, identification of this clinical entity may still be problematic. Though there will be many more codes within the ICD-10 system, combinations of codes will still be required in order to fully describe the etiology and manifestation of infections, including MRSA bloodstream infections. Like the current ICD-9, the only intrinsically combined MRSA codes
will be those for sepsis and pneumonia (Centers for Medicare & Medicaid Services, 2012). Therefore, it is concerning that the same difficulties with sensitivity and positive predictive value that were seen in this study will persist despite the adoption of ICD-10.

Interestingly, the sensitivity of the discharge codes seemed to vary with the clinical manifestation of bloodstream infection. In this study, the sensitivity of the codes for hospitalizations involving MRSA primary bacteremia was 78.9%, while the sensitivity of the codes for osteomyelitis-associated MRSA bloodstream infection was only 35.3%. This difference was statistically significant, with a p-value < 0.01. While the exact reasons are not clearly defined, it may be postulated that the relative clinical importance of the bloodstream component of infection may be different for these different clinical situations. For example, if a patient is hospitalized because of primary bacteremia, then treating the bloodstream infection is the main purpose of the hospitalization. On the other hand, if a patient is hospitalized because of osteomyelitis and the bacteremia is noted incidentally or in support of the osteomyelitis, then treating the bone infection remains the main purpose of the hospitalization. Therefore, the physician may be more likely to appropriately document the MRSA bloodstream infection in the first scenario compared to the second because it is not as clinically relevant. Because discharge codes are generated by hospital coders based directly upon physician documentation, a difference in physician documentation would certainly lead to differences in coding and subsequent measurements of code sensitivity. Unfortunately, in this study, the groups with other manifestations of MRSA bloodstream infection were too small to allow for reasonable analysis of other between-group differences.

When comparing the groups with chronic disease vs. those without chronic disease, this study was not able to detect a statistically significant difference in sensitivity between them.
Before starting this project, the author presumed that the sensitivity of the codes would be higher among patients without chronic disease because of the inherent surprise that is usually associated with a diagnosis of serious invasive infection in an otherwise healthy individual. On the contrary though, the point estimate for sensitivity among patients without chronic disease was actually lower than that for patients with chronic disease. Because of the limited number of subjects, this difference did not reach statistical significance. More hospitalizations would have to be reviewed in order to see if there really is a difference and if so, which group has the higher sensitivity. Further, any difference in sensitivity between these two groups could also be due to the underlying differences in sensitivity that were seen with the varied clinical manifestations, as discussed previously.

This study exemplifies many issues encountered in the core areas of public health, including epidemiology, biostatistics, environmental health, health economics, health systems, and global health. In terms of epidemiology, the burden of MRSA disease certainly seems to have increased over the past 10 years, and better methods should be employed to track this illness, as noted in the introduction. Administrative data are an attractive source for monitoring, but significant differences exist between clinical data and their reflection in administrative data. These differences were demonstrated clearly in this project by the low sensitivity and positive predictive values observed for discharge coding of MRSA bloodstream infection. In terms of biostatistics, the sensitivity and positive predictive value measured in this study are commonly used tools for various diagnostic tests in medicine. However, the closeness of these measurements to the truth is based largely upon the sample size from which they are calculated. As a result, this study provided samples large enough to generate reasonable sensitivities and positive predictive values, but not large enough to allow for many comparisons between groups.
Further studies are needed in order to more precisely measure the sensitivity and positive predictive value in specific populations, and therefore more accurately generalize these results to those groups. In terms of environmental health, MRSA has become a ubiquitous pathogen, with large portions of the population simply colonized with this bacteria (Lowell & Daum, 2008). However, MRSA is still often considered a nosocomial pathogen in the hospital environment. Further, people who have more healthcare exposures overall are more likely to develop nosocomial infections (Lowy, 1998). In this project, such a predisposition to MRSA bloodstream infection was seen in that over three-fourths of the cases of MRSA primary bacteremia were associated with an indwelling central venous catheter. Unfortunately, because the total number of hospitalizations involving central venous catheters during the study period is unknown, the difference between these two groups cannot really be assessed statistically. However, the predominance of central vascular catheter associated infections seen here still highlights the vital importance of environmental measures affecting care and maintenance of medical devices to prevent infection. In terms of health economics, many researchers have attempted to examine the cost difference between infections with MRSA vs. MSSA. While it may seem that infection with MRSA is more expensive to the total healthcare system because of the cost of more potent antibiotics, this presumption has not always been born out in the literature. In fact, depending upon the statistical method used to compare the two types of infection, some differences have been seen in overall costs and length of hospitalization while others have not (Ben-David, Novikov, & Mermel, 2009; Cosgrove et al., 2005). This project did not focus specifically on the economic impact of MRSA bloodstream infection, but further analysis could be performed using this data in conjunction with data on MSSA bacteremia during the same time period to determine whether or not there were significant differences in lengths of
hospitalization and overall costs. Determining the proportion of the expenses specifically due to the MRSA or MSSA infection though, as opposed to other medical issues that arise during the hospitalization, may be much more difficult. In terms of health care systems, this project examined a fundamental part of the link between health care providers and health care payers, namely diagnostic codes. These diagnostic codes are fundamental because they provide a dominant portion of the determination of reimbursement for healthcare services. As medical care in this country still largely functions in a fee-for-service modality, the fees generated should be proportional to the services provided which, for hospitalizations, are often estimated based upon the discharge diagnoses present. So, in theory, the more accurately the discharge diagnoses reflect the underlying clinical situations, the more relevant the fees charged to the payers and the more appropriate the reimbursements paid to the hospital and providers. Lastly, in terms of global health, MRSA infection is a problem in patients worldwide, though the extent of the disease burden seems to vary geographically. Per 2008 monitoring data from the European Union, the percentage of blood isolates of *S. aureus* that were methicillin-resistant varied from <5% in some countries to >50% in others (Kock et al., 2010). Data for MRSA infection in developing countries is much sparser. Difficulties that have been cited for developing countries include the lack of diagnostic microbiologic laboratories necessary to identify MRSA. For this reason, “almost nothing is known about the emergence and transmission of MRSA in resource-poor regions of the world” (Nickerson, West, Day, & Peacock, 2009). However, some emerging data from China and India suggests that MRSA may account for a significant portion of *S. aureus* disease in these countries. Additionally, the ready availability of over-the-counter antibiotics in developing countries raises concern for the further emergence of community-
associated MRSA (Nickerson et al., 2009). Therefore, better surveillance methods for MRSA infection are needed, not only in the United States, but also globally as well.

This project has several important limitations. First, the fact that all of the data was collected from a single center limits the generalizability of the results. The concept of proximal similarity indicates that results from a study can be generalized to other populations depending upon how similar or dissimilar the two groups are. So, for this project, populations that would be more similar include those hospitalizations in a similar geographic area (as the epidemiology of MRSA infections may vary from one part of the country to another), those involving tertiary free-standing children’s hospitals, and those with a similar process of coders assigning discharge codes based upon physician documentation in the medical record (rather than physicians assigning the codes themselves). Additionally, because the incidence of MRSA infection seems to be evolving over time, proximal similarity would also indicate applicability of the data to the present and near future, but not necessarily to the more distant future. However, even if all of these criteria are met, there still may be some amount of inter-institutional variability in the coding sensitivity and positive predictive value. Therefore, in order to apply the outcomes of this study to national administrative datasets, this project would likely need to be repeated at other institutions that provide inpatient pediatric care. Second, the inclusion dates of the discharge database and the lab database were not exactly the same. Initially, hospitalizations were identified from the lab database if the admission date of the hospitalization occurred within 30 days of the date of the positive culture. Because this method could omit some prolonged hospitalizations in which the positive culture did not occur within the first 30 days of admission, the database was re-queried without this time limit. When this was completed, no additional hospitalizations were identified. For the discharge database, the initial query was for
hospitalizations that had both admission and discharge dates within the timeframe in question. However, this method could have omitted hospitalizations in which the patient was admitted before October 1, 2008 or discharged after December 31, 2010. So, the database was rerun with a broader time window, and only 1 additional hospitalization was identified. Therefore, the date ranges used for querying the two databases would need to be considered if repeating this project at another institution in order to make sure no hospitalizations were missed. Third, there is a possibility for confounding bias since some patients could be involved in more than one hospitalization. In fact, in this project, there were two patients who were admitted multiple times with different episodes of MRSA bloodstream infection. However, both of these patients had hospitalizations separated over considerable time periods, and therefore the patients likely had distinct episodes of MRSA bloodstream infection. Thus, two out of the total 65 hospitalizations identified from lab data did not represent the first time the patient had MRSA bacteremia. These hospitalizations did not likely affect the measured sensitivities or positive predictive values though, since the coding process should be independent of the patient’s history of prior similar infections.

In summary, this project showed the important finding of low sensitivity and positive predictive value of ICD-9 discharge codes for pediatric MRSA bloodstream infections. By qualitative review, a substantial reason for these low measures is the need for multiple codes to document etiology and manifestation of infection, and this may not be specifically addressed by the new ICD-10 coding system. In order to generalize these results and apply them to national administrative datasets, further validation studies in other pediatric institutions will be required.
References


Appendix A: IRB Approval

Institutional Review Board - Federalwide Assurance #00002988
Cincinnati Children's Hospital Med Ctr
Date: 4/27/2012 3:07 PM
From: IRB Committee
Principal Investigator: Mary Allen Staat
Infectious Disease
Study ID: 2010-1450
Study Title: Determining the Burden of Staphylococcus aureus Disease in the Cincinnati Metropolitan Area
Re: The above referenced protocol and all applicable additional documentation provided to the IRB were reviewed and RE-APPROVED using an EXPEDITED review procedure set forth in 45 CFR 46.110(b)(1), Category(ies)(see below) on 4/27/2012.

This study will be due for continuing review at least 30 days before 4/26/2013.

Study Documents:
Determining the Burden of Staphylococcus aureus Disease in the Cincinnati Metropolitan Area

Please note the following requirements:
AMENDMENTS: The principal investigator is responsible for notifying the IRB of any changes in the protocol, participating investigators, procedures, recruitment, consent forms, FDA status, or conflicts of interest. Approval is based on the information as submitted. New procedures cannot be initiated until IRB approval has been given. If you wish to change any aspect of this study, please submit an Amendment via ePAS to the IRB, providing a justification for each requested change.
CONTINUING REVIEW: The investigator is responsible for submitting a Continuing Review via ePAS to the IRB at least 30 days prior to the expiration date listed above. Please note that study procedures may only continue into the next cycle if the IRB has reviewed and granted re-approval prior to the expiration date.
UNANTICIPATED PROBLEMS: The investigator is responsible for reporting unanticipated problems promptly to the IRB via ePAS according to current reporting policies.
STUDY COMPLETION: The investigator is responsible for notifying the IRB by submitting a Request to Close via ePAS when the research, including data analysis, has completed.

Research Categories
5. Research involving materials (data, documents, records, or specimens) that have been collected, or will be collected solely for nonresearch purposes (such as medical treatment or diagnosis). (NOTE: Some research in this category may be exempt from the HHS regulations for the protection of human subjects. 45 CFR 46.101(b)(4). This listing refers only to research that is not exempt.)

Please note: This approval is through the IRB only. You may be responsible for reporting to other regulatory officials (e.g. VA Research and Development Office, UC Health - University Hospital). Please check with your institution and department to ensure you have met all reporting requirements.

Statement regarding International conference on Harmonization and Good Clinical Practices: The Institutional Review Board is duly constituted (fulfilling FDA requirements for diversity), has written procedures for initial and continuing review of clinical trials; prepares written minutes of convened meetings, and retains records pertaining to the review and approval process; all in compliance with requirements defined in 21 CFR Parts 50, 56 and 312 Code of Federal Regulations. This institution is in compliance with the ICH GCP as adopted by FDA/DHHS.

Thank you for your cooperation during the review process.
Appendix B: Tier 1 Core Public Health Competencies Used in CE

### Domain #1: Analytic/Assessment
- Identify the health status of populations and their related determinants of health and illness (e.g., factors contributing to health promotion and disease prevention, the quality, availability and use of health services)
- Describe the characteristics of a population-based health problem (e.g., equity, social determinants, environment)
- Use variables that measure public health conditions
- Use methods and instruments for collecting valid and reliable quantitative and qualitative data
- Identify sources of public health data and information
- Recognize the integrity and comparability of data
- Identify gaps in data sources
- Adhere to ethical principles in the collection, maintenance, use, and dissemination of data and information
- Describe the public health applications of quantitative and qualitative data
- Collect quantitative and qualitative community data (e.g., risks and benefits to the community, health and resource needs)
- Use information technology to collect, store, and retrieve data
- Describe how data are used to address scientific, political, ethical, and social public health issues

### Domain #2: Policy Development and Program Planning
- Gather information relevant to specific public health policy issues
- Gather information that will inform policy decisions (e.g., health, fiscal, administrative, legal, ethical, social, political)
- Describe the public health laws and regulations governing public health programs
- Identify mechanisms to monitor and evaluate programs for their effectiveness and quality
- Demonstrate the use of public health informatics practices and procedures (e.g., use of information systems infrastructure to improve health outcomes)

### Domain #3: Communication
- Communicate in writing and orally, in person, and through electronic means, with linguistic and cultural proficiency
- Solicit community-based input from individuals and organizations
- Convey public health information using a variety of approaches (e.g., social networks, media, blogs)
- Participate in the development of demographic, statistical, programmatic and scientific presentations

### Domain #4: Cultural Competency
- Recognize the role of cultural, social, and behavioral factors in the accessibility, availability, acceptability and delivery of public health services
<table>
<thead>
<tr>
<th>Domain #5: Community Dimensions of Practice</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recognize community linkages and relationships among multiple factors (or determinants) affecting health (e.g., The Socio-Ecological Model)</td>
</tr>
<tr>
<td>Identify stakeholders</td>
</tr>
<tr>
<td>Maintain partnerships with key stakeholders</td>
</tr>
<tr>
<td>Describe the role of governmental and non-governmental organizations in the delivery of community health services</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Domain #6: Public Health Sciences</th>
</tr>
</thead>
<tbody>
<tr>
<td>Relate public health science skills to the Core Public Health Functions and Ten Essential Services of Public Health</td>
</tr>
<tr>
<td>Identify the basic public health sciences (including, but not limited to biostatistics, epidemiology, environmental health sciences, health services administration, and social and behavioral health sciences)</td>
</tr>
<tr>
<td>Describe the scientific evidence related to a public health issue, concern, or, intervention</td>
</tr>
<tr>
<td>Retrieve scientific evidence from a variety of text and electronic sources</td>
</tr>
<tr>
<td>Discuss the limitations of research findings (e.g., limitations of data sources, importance of observations and interrelationships)</td>
</tr>
<tr>
<td>Describe the laws, regulations, policies and procedures for the ethical conduct of research (e.g., patient confidentiality, human subject processes)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Domain #7: Financial Planning and Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adhere to the organization’s policies and procedures</td>
</tr>
<tr>
<td>Report program performance</td>
</tr>
<tr>
<td>Apply basic human relations skills to internal collaborations, motivation of colleagues, and resolution of conflicts</td>
</tr>
<tr>
<td>Demonstrate public health informatics skills to improve program and business operations (e.g., performance management and improvement)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Domain #8: Leadership and Systems Thinking</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incorporate ethical standards of practice as the basis of all interactions with organizations, communities, and individuals</td>
</tr>
<tr>
<td>Identify internal and external problems that may affect the delivery of Essential Public Health Services</td>
</tr>
<tr>
<td>Use individual, team and organizational learning opportunities for personal and professional development</td>
</tr>
<tr>
<td>Participate in the measuring, reporting and continuous improvement of organizational performance</td>
</tr>
<tr>
<td>Describe the impact of changes in the public health system, and larger social, political, economic environment on organizational practices</td>
</tr>
</tbody>
</table>