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Increasing Prevalence of Nasal and Rectal Colonization with Methicillin-Resistant *Staphylococcus aureus* in Children with Cancer

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Abstract

Background—Infections with methicillin-resistant *Staphylococcus aureus* (MRSA), in community-settings, especially with strains carrying the Panton-Valentine Leukocidin (PVL) genes, have increased markedly in recent years. Colonization with *S.aureus* is a risk factor for infection. However, there are few studies that examine colonization and infection with PVL-positive strains of MRSA in cancer patients.

Procedure—The epidemiology of colonization and infection with MRSA was studied in children with cancer during two time periods: 2000/2001 and 2006/2007. PVL genes were screened and *spa* typing performed on the isolates.

Results—The prevalence of colonization with MRSA increased from 0.6% in 2000/2001 to 2.9% in 2006/2007 ($p=0.0003$). MRSA colonization at admission was associated with infection ($p<0.0001$; RR 38.32; 95% CI: 23.36 - 62.84). The prevalence of infection increased from 0.99% in 2000/2001 to 3.78% in 2006-2007 ($p=0.0002$). Of the 32 colonized patients, 18 (56%) had infection. None of the 14 colonized but non-infected patients had dual colonization of nares and rectum, while 8 of the 18 infected patients had colonization of both of these sites ($p=0.004$). Ten patients (31%) were colonized with PVL-positive strains. Patients colonized with PVL-positive strains were more likely to be colonized both in the nares and rectum ($p=0.005$), and more likely to have infection ($p=0.001$). Recurrent MRSA infections were seen in 22% of patients.

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Conclusion—An increasing prevalence of colonization with MRSA was observed in children with cancer at our institution. Colonization with MRSA especially with PVL-positive strains was associated with infection.

Keywords

Colonization; Methicillin-resistant *Staphylococcus aureus*; Children; Cancer; Panton-Valentine Leukocidin

Introduction

New strains of *Staphylococcus aureus* have been recognized to cause serious infections in otherwise healthy children and adults [1]. These strains also known as community-associated MRSA (CA-MRSA), typically bear the type IV *Staphylococcus* cassette chromosome (SCC) *mec* element [2] which encodes the gene for methicillin resistance. Further, they frequently carry the genes for the Panton-Valentine Leukocidin (PVL) leukotoxin [3], belong to the USA300 genotype [4] and are usually susceptible to clindamycin [5]. Skin and soft-tissue infections [6], necrotizing pneumonia [7], and sepsis [8] have been associated with these strains. Colonization by MRSA in healthy children has increased significantly since 2001[9]. Colonization with *S. aureus* is a risk factor for subsequent infection [10-11], and increased colonization may be an important factor in the emergence and spread of PVL-positive MRSA as a pathogen in healthy children.

We have shown an increasing prevalence of PVL-positive MRSA infection in patients with cancer [12]. However, the prevalence of nasal and rectal colonization with MRSA and in particular with PVL-positive strains in this population is not known. This study describes the prevalence of MRSA nasal and rectal colonization in children with cancer in 2000-2001 and 2006-2007. The frequency of PVL-positive strains and association between colonization and infection with MRSA are also reported.

Patients and Methods

This retrospective cohort study included patients with cancer at St. Jude Children's Research Hospital (SJCRH), a tertiary care hospital in Memphis, TN, which treats approximately 3,000 patients with cancer each year. Swab samples from the nares and rectum were collected according to the screening protocol from all patients within 48 hours of admission. Following approval by the SJCRH Institutional Review Board (IRB), patients with MRSA colonization in 2000-2001 and 2006-2007 with or without a concurrent or subsequent infection were retrospectively identified through a review of clinical microbiology culture results. The medical records were examined in patients colonized with MRSA for 2 years following initial detection of colonization, to determine the persistence of colonization. The independent variables obtained from the medical record review included age and race on all patients with cancer and age, race, gender, underlying malignancy, remission, transplant status and absolute neutrophil count in patients with MRSA isolated from the nares or rectum. Recurrent infections were defined for the purpose of epidemiological analysis as positive isolates obtained from the same case, 30 days or more after the last positive culture. Only the first infection was included in the analysis.

Microbiologic Analysis

Specimens to detect colonization were obtained with a Dacron-tipped applicator (Transporter Sterile Transport Swab, Healthlink, Italy), which was inserted into both the nares and the rectum, rotated, withdrawn, placed in Stuart's transport medium and sent immediately to the microbiology laboratory. The specimen was inoculated and streaked on

Trypticase Soy Agar (BD BBL; Becton Dickinson and Company, Sparks, MD) with 5% sheep blood and incubated in 5-7% CO₂ for 48 hrs at 35°C. Recovered *S. aureus* isolates were inoculated to oxacillin and vancomycin screening agars (BD BBL; Becton Dickinson and Company, Sparks, MD). Bacterial isolates were subsequently preserved at -80°C prior to subsequent analysis. In patients who had colonization of both the nares and the rectum, the isolate obtained from the nares specimen was used for subsequent analysis.

Isolates causing infection were initially identified as *S. aureus* by Staphaurex plus® antigen testing (Remel Europe Ltd, Dartford, Kent, UK) and subsequently preserved at -80°C prior to subsequent analysis. Isolates were screened for methicillin resistance using 30 µg cefoxitin disks (BD BB1 Sensi-Disc, Becton Dickinson and Company, Sparks, MD). A zone <23 mm was interpreted as confirming methicillin resistance. Mupirocin resistance on these isolates was confirmed by using a 5 µg mupirocin disk (kindly provided by GlaxoSmithKline, Collegeville, PA). Isolates that had a zone diameter of <13 mm were considered resistant to mupirocin.

Antimicrobial susceptibility testing for penicillin, cefoxitin, vancomycin, clindamycin, trimethoprim-sulfamethoxazole (TMP-SMZ), erythromycin, gentamicin, and ciprofloxacin was performed on using the Vitek Legacy system (Vitek 32 system, BioMerieux, Inc., Durham, NC). One colonizing isolate was unavailable for testing. Results were determined after 24 hr of incubation at 35°C according to the Clinical and Laboratory Standards Institute (CLSI) breakpoints. The CLSI methodology was followed in all testing methods [13]. For all isolates that were erythromycin-resistant and clindamycin-susceptible, detection of the inducible macrolide-lincosamide-streptogramin B resistance phenotype was performed by double-disk diffusion with clindamycin and erythromycin disks set 15–20 mm apart (D test) [13]. Reported results of clindamycin resistance included the inducible resistance phenotype.

Molecular Characterization of *S. aureus* Colonizing and Infecting Isolates

The presence of the lukF and lukS genes of PVL was determined by PCR as previously described [14]. DNA sequence-based typing of *S. aureus* protein A (*spa*) gene was performed as previously described using template DNA extracted from overnight cultures [15-16]. *S. aureus* MLST sequence and types and assignment to community- or hospital acquired sources were inferred from correlation of our observed *spa* type with type descriptions from the Ridom StaphType database. USA pulsed-field types were inferred from the observed *spa*-type and our pulsed-field gel electrophoresis (PFGE) determinations [17].

Statistical Analysis

Descriptive statistics, including frequencies, percentages or means, were obtained for the demographic and treatment variables of the patients with cancer and MRSA colonization. Chi-square test or exact chi-square test was applied to compare incidence of MRSA colonization, infection and PVL-positivity in the colonizing isolates between the periods 2000-2001 and 2006-2007. It was also used to study the association between infection and colonization of both the nares and rectum, between PVL-positivity and colonization of both the nares and rectum, and between infection and PVL-positivity. Exact chi-square test, t-test or Wilcoxon rank sum test was used to study the association of the independent variables with MRSA colonization, infection and PVL-positivity separately. All analyses were performed in statistical software package SAS 9.1.3 (SAS Institute Inc, Cary, North Carolina).

Results

Prevalence of MRSA Colonization in Children with Cancer

Five patients out of 810 tested (0.6%) were colonized with MRSA in 2000 and 2001, compared to 27 patients out of 925 (2.9%) in 2006 and 2007. This five-fold increase in the prevalence of MRSA colonization was statistically significant ($p=0.0003$).

Nine of the 32 (28%) MRSA-positive patients in the two periods were colonized in the rectum alone and would have been missed if swabs from only the nares had been obtained for testing. The mean age of patients colonized with MRSA was 8 years and 4 months. There were 17 males; 23 were Caucasians, 7 African-Americans and 2 from other races. Sixteen patients had an underlying diagnosis of leukemia / lymphoma and 16 had a diagnosis of a solid tumor malignancy. Seven patients had undergone hematopoietic stem cell transplantation. There was no significant difference in the age and race between screened cancer patients colonized and those not colonized with MRSA ($p=0.80$ for age and 0.86 for race). There was no significant difference in the number of surveillance cultures obtained per person in the two time periods.

Prevalence of MRSA Infection in Children with Cancer

Colonization with MRSA increased the relative risk of infection ($p<0.0001$; RR 38.32; 95% CI: 23.36 - 62.84; Table I). The prevalence of infection increased from 0.99% in 2000-2001 to 3.78% in 2006-2007 ($p=0.0002$; Table I). Of the 32 colonized patients, 18 (56%) had infection with MRSA. Thirteen patients (72%) had cutaneous infections (pustules, nodules and abscesses) and 5 (28%) had central venous catheter-related blood-stream infections. There were no significant differences in the distribution of age, race, sex, underlying malignancy, transplant status or absolute neutrophil count between patients colonized with MRSA with or without infection.

Colonization was detected concomitantly with infection in 12 patients and preceded infection in 6 patients by a median of 20 days. In 15 and 9 patients who were colonized with MRSA in the nares or rectum respectively, 8 (53%) and 2(22%) were concurrently or subsequently infected ($p=0.2$). However, in the 8 patients who were colonized in both the nares and rectum, all (100%) were concurrently or subsequently infected with MRSA ($p=0.004$; Table II).

Antibiotic Susceptibility Results

Antimicrobial susceptibility testing was performed on 31 of the 32 colonizing isolates. Ten isolates (32%) were resistant to clindamycin of which 5 were due to inducible resistance. One isolate had intermediate susceptibility to gentamicin and one was resistant to trimethoprim-sulfamethoxazole (3%), 25 isolates (81%) were resistant to erythromycin and 5 isolates (16%) were resistant and another 5 had intermediate susceptibility to levofloxacin.

Susceptibility testing was performed on isolates of 17 of the 18 patients who had both colonization and infection. There was concordance between the susceptibility patterns of the colonizing and infecting isolates except for 1 isolate causing infection that was susceptible to clindamycin, 1 that was susceptible to erythromycin and 1 that was resistant to gentamicin with the corresponding colonizing isolates being resistant to clindamycin and erythromycin and susceptible to gentamicin, respectively. In these 3 cases the *spa* types were identical for the colonizing and infecting isolates. Of the 17 infecting isolates tested, 16 (94%) were susceptible to mupirocin and 1 showed low-level resistance. All the colonizing and infecting isolates were susceptible to vancomycin. Of the 31 colonizing isolates tested, 12 isolates had

an MIC of <0.5 µg/mL and 19 isolates had an MIC of 1 µg/mL. Of the 17 infecting isolates tested, 11 isolates had an MIC of <0.5 µg/mL and 6 had an MIC of 2 µg/mL.

PVL Status in Patients Colonized with MRSA

Of the 32 patients colonized with MRSA, 10 (31%) of the colonizing strains were PVL-positive. Six of the 10 patients colonized with PVL-positive strains were colonized in both the nares and rectum while 2 of the 22 patients colonized with PVL-negative strains were colonized in both sites ($p=0.005$). There was no significant difference in colonization with PVL-positive strains in the two time periods ($p=1.0$). None of the variables including age, race, sex, underlying disease, transplant status and absolute neutrophil count was different between patients colonized with PVL-positive or PVL-negative strains.

Of the 22 patients colonized with PVL-negative strains, 8 (36%) were colonized and infected with MRSA. Of the 10 patients colonized with PVL-positive strains, 10 (100%) were colonized and infected with MRSA ($p=0.001$). Cutaneous infection by PVL-positive strains was seen in 7 patients and catheter-related blood-stream infection was seen in 3 patients. All the PVL-positive isolates were susceptible to clindamycin.

Molecular Epidemiology of the Colonizing and Infecting isolates

Spa typing was performed on 13 pairs of colonizing and infecting isolates. Colonizing isolates 1C-9C were concordant with infecting isolates 1I-9I, while colonizing isolates 10C-13C were discordant with infecting isolates 10I-13I (Table III). Seven of the concordant pairs were USA300 clones. Of the 4 discordant pairs, 2 infecting and no colonizing isolates were USA300 clones. The isolate 13I's *spa* type could not be assigned to a pulsed-field type.

Duration of Colonization and Incidence of Recurrent Infections

Colonization in all patients was intermittent and not detected on a subsequent admission. On an average each patient who was colonized had one set of nasal and rectal surveillance cultures performed for every 28 days of observation. Recurrent MRSA infections were seen in 4 patients (22%); cutaneous (3 patients) and catheter-related blood-stream infection (1 patient), both for the initial and recurrent infection. The recurrences occurred at 100, 110, 117 and 225 days after the initial infection during subsequent hospital admissions (mean interval 140 days). Three patients had initial infection with PVL-positive MRSA. Three patients were colonized only with the initial infection and 1 only with the recurrent infection. None of the patients received therapy with mupirocin in an attempt at decolonization.

Discussion

This study describes the changing trend of MRSA colonization in patients with cancer. There was a statistically significant increase in the prevalence of colonization from 0.6% to 2.9% between 2000/2001 and 2006/2007.

A statistically significant increase in nasal colonization with MRSA in healthy children from 0.8% in 2001 to 9.2% in 2004 was shown by Creech et al. in a prospective study from Nashville, TN [9,18]. This was confirmed in a population-based prospective study in the U.S where nasal colonization with MRSA was shown to increase from 0.8% to 1.5% during the same period [19-20], and also in Taiwan where MRSA colonization was shown to increase from 0.7% to 2.8% between 2004- 2006 [21].

The increase in MRSA colonization in the above studies may be underestimated as rectal screening was not performed. More than a quarter (28%) of our MRSA carriers would have

been missed if rectal screening had not been performed simultaneously. This is corroborated by other studies. Eveillard et al. estimated that 27% of MRSA carriers may have been missed if nasal cultures had been used alone [22]. Carriage in the nares and rectum signifies a higher load and a greater risk of dispersion [23]. For all patients, MRSA carriage both in the nares and rectum was associated with a significantly higher risk of infection compared to colonization at either site alone.

In our previous study of MRSA infections in children with cancer [12] there were higher proportions of children 0-12 years of age and African-Americans with MRSA infection and cancer compared to older children and those of other races with MRSA infection and cancer. No association between age and race with MRSA colonization was found in the present study.

The association between *S. aureus* nasal carriage and staphylococcal wound infection was first reported in 1931 [10]. Subsequently, *S. aureus* carriage was identified as a risk factor for the development of bacteremia [11]. Colonization with MRSA was associated with a 38-fold increased risk of infection in our study. The increased prevalence of colonization between the two time periods was associated with an increased prevalence of infection. More than half of the carriers in this study (56%) had an infection, most often cutaneous, which resolved with appropriate therapy. There was strong concordance in the antibiotic susceptibilities between the colonizing and infecting isolates.

Five patients had catheter-related bacteremia, necessitating removal of the catheter in 4 patients due to persistent bacteremia for more than 72 hours, despite administration of vancomycin. In patients with catheter-related bacteremia, colonization was detected at a mean interval of 1 week before the infection. Three of these patients had colonization both in the nares and the rectum. In a previous study of *S. aureus* bacteremia in children with cancer [24], we identified 10 patients with MRSA bacteremia between 2000-2007, of whom 9 were colonized with MRSA. Catheters were removed for persistent bacteremia in 6 of these patients; there were no complications.

PVL is a bicomponent, pore-forming leukotoxin. While epidemiological studies suggest that emergence of CA-MRSA strains has been associated with increased incidence and severity of community-associated *S. aureus* infections, the role of PVL in this setting remains unclear [25-26]. PVL genes were detected in 56% of our colonizing MRSA strains compared to 22% of MRSA isolates in healthy children [18] and 66% of 45 recovered MRSA isolates from the nares of healthy adults in a study by Ellis et al [27].

Colonization with PVL positive strains in all patients was associated with infection. This included cutaneous infections in 7 patients and catheter-related bacteremia in 3 patients. This corroborates the findings of Ellis et al. who detected PVL genes in all of the 9 clinical isolates available for analysis [27]. Patients colonized with PVL-positive strains were more likely to be colonized both in the nares and the rectum, suggesting that a higher bacterial load may have increased the risk of infection. Alternatively, infection may have led to inoculation and colonization of non-nasal body sites.

Four infection isolates were discordant with the corresponding colonizing isolates. The infecting isolate 10I, isolated a month later, was closely related to the colonizing isolate with a sequence variation possibly representing rare *in-situ* mutation. The other 3 infecting isolates 11I-13I, isolated 5 days, concurrently and 1 wk apart, most likely came from a different source than the colonizing site.

A single recurrent MRSA infection was seen in 22% of our patients after a mean interval of 142 days. None of the patients were colonized for both the initial and recurrent infection.

Huang et al. noted recurrent MRSA infections in 60 (29%) of 209 adult patients studied retrospectively. Nineteen patients (9%) had more than one episode of subsequent infection which occurred at a mean of 102 days after the initial infection. Colonization was seen in 22% of patients with the initial MRSA infection, half of whom had persistent colonization with the recurrent infection [28].

CA-MRSA infection may occur in the absence of nasal colonization, and can be acquired from non-nasal body sites (skin-skin transmission) due to a higher prevalence of colonization in the inguinal area and rectum [29]. Decolonization strategies that rely on nasal decolonization alone may not be successful and preventative efforts may require decolonization of non-nasal sites.

Twenty-six percent of patients colonized with MRSA in a surgical ICU developed MRSA infection, compared with 1.3% of those who were not colonized [30]. Short term nasal application of mupirocin is effective in temporarily eliminating MRSA colonization with a success rate of 90% after 1 week and 60% over a longer follow up period and is associated with a reduction in the rate of surgical site infections by 45% [31].

The effectiveness of mupirocin was confirmed in a recent prospective randomized trial which showed a reduction in the risk of hospital-associated *S. aureus* infections by 60% after decolonization of nasal and extra-nasal sites in surgical patients, with mupirocin and chlorhexidine gluconate soap [32]. However, randomized controlled trials have failed to show a benefit of mupirocin in non-surgical patients [33]. No trials with mupirocin have been reported in patients with cancer.

This study has several limitations. It is retrospective, and although conducted in a large pediatric comprehensive cancer center, the numbers of patients with colonization and infection were small. Further, the association between colonization with methicillin-susceptible *S. aureus* and infection was not studied. Prospective cohort studies which follow cancer patients with and without *S.aureus* colonization to accurately determine the prevalence of infection are needed.

In conclusion, an increasing prevalence of colonization with MRSA in the nares and rectum has been observed in children with cancer at our institution. Colonization with MRSA, particularly both in the nares and rectum, and with PVL-positive strains was associated with infection. *S.aureus* is currently a leading cause of blood stream infections in patients with cancer [34]. A complication rate of 33%, with an attributable mortality of 15%, was seen in a study of non-neutropenic adults with cancer and *S.aureus* bacteremia [35]. In a single institutional study, progressive cancer was an independent risk factor for MRSA surgical site infections [36]. Elimination of MRSA is of critical importance in patients with oral cancer [37], limb-salvage procedures and head and neck cancer with increased morbidity as a consequence of established infection [38]. The benefit of temporarily eliminating MRSA colonization in a subset of cancer patients especially those with isolates carrying the PVL genes, merits further study.

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Table I
Risk of MRSA infection with colonization

Characteristic	2000-2001	2006-2007	Both periods
Patients tested	810	925	1735
Patients colonized	5	27	32
Patients not colonized	805	898	1703
Patients infected and colonized	5	13	18
Patients infected but not colonized	3	22	25
RR of infection ^a	268.3	19.7	38.3
95% CI	86.72 - 830.24	11.13 - 34.71	23.36 - 62.84
Characteristic	2000-2001	2006-2007	p-value
Prevalence of colonization ^b	0.62% (5/810)	2.92% (27/925)	0.0003
Prevalence of infection ^c	0.99% (8/810)	3.78% (35/925)	0.0002

MRSA, methicillin-resistant *Staphylococcus aureus*; RR, relative risk; CI, confidence interval;

^a Relative risk of infection is the ratio of risk of infection occurring in patients with colonization versus patients without colonization;

^b Prevalence of colonization is the proportion of patients with MRSA colonization among all admitted patients who were screened for MRSA in that time period;

^c Prevalence of infection is the proportion of patients diagnosed with MRSA infection either at or during admission among all patients admitted to the hospital and screened for MRSA in that time period.

Table II
Comparison of MRSA colonization in the nares / rectum or in both sites with infection

32 MRSA patients				
Site of Colonization	Infection (n=18)	No infection (n=14)	Total (n=32)	p-value
Colonization both nares and rectum	8(100)	0	8	0.004
Colonization rectum or nares	10(42)	14(58)	24	
24 MRSA patients colonized only in one site				
Site of Colonization	Infection (n=10)	No infection (n=14)	Total (n=24)	p-value
Colonization nares	8(53)	7(47)	15	0.2
Colonization rectum	2(22)	7(78)	9	

MRSA, methicillin-resistant *Staphylococcus aureus*. Data are number (%) of patients, unless otherwise indicated.

Table III
Comparison of genotypes between colonizing and infecting MRSA isolates

Colonizing isolate	<i>spa</i> type	PFT	HA/CA	Infecting isolate	<i>spa</i> type	PFT	HA/CA
1C	t008	300	CA	1I	t008	300	CA
2C	t008	300	CA	2I	t008	300	CA
3C	t008	300	CA	3I	t008	300	CA
4C	t008	300	CA	4I	t008	300	CA
5C	t008	300	CA	5I	t008	300	CA
6C	t008	300	CA	6I	t008	300	CA
7C	t008	300	CA	7I	t008	300	CA
8C	t2940	600		8I	t2940	600	
9C	t002	100/800	HA	9I	t002	100/800	HA
10C	t002	100/800	HA	10I	t4533	100/800	HA
11C	t002	100/800	HA	11I	t008	300	CA
12C	t216	1000	CA	12I	t008	300	CA
13C	t045	100/800	HA	13I	t118		

PFT, pulsed-field type; HA, hospital-acquired; CA, community-acquired; C, colonizing isolate; I, infecting isolate; MRSA, methicillin-resistant *Staphylococcus aureus*.