

# Methicillin-resistant *Staphylococcus aureus* in HIV-infected patients

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**Abstract:** Concordant with the emergence of methicillin-resistant *Staphylococcus aureus* (MRSA) in the community setting, colonization and infections with this pathogen have become a prevalent problem among the human immunodeficiency virus (HIV)-positive population. A variety of different host- and, possibly, pathogen-related factors may play a role in explaining the increased prevalence and incidence observed. In this article, we review pathophysiology, epidemiology, clinical manifestations, and treatment of MRSA in the HIV-infected population.

**Keywords:** MRSA, *Staphylococcus aureus*, HIV, resistance

## Introduction

In persons infected with the human immunodeficiency virus (HIV), *Staphylococcus aureus* (*S. aureus*) infections account for significant morbidity.<sup>1-3</sup> *S. aureus* was recognized to colonize the anterior nares of HIV-infected patients with greater frequency than that of the general population dating back to the 1990s, leading authors to postulate that this higher colonization burden might translate into a higher incidence of infections.<sup>4,5</sup>

Methicillin-resistant *Staphylococcus aureus* (MRSA) was first reported in the 1960s and started to establish itself as a nosocomial pathogen with increasing prevalence rates among hospitals nationally and worldwide.<sup>6,7</sup> Originally associated only with health care-acquired infections, MRSA began to be recognized as an important cause of community-onset infections in the late 1990s.<sup>8-10</sup> Now recognized as community-acquired MRSA (CA-MRSA), the latter differs genotypically and phenotypically from health care-associated MRSA (HA-MRSA). CA-MRSA isolates carry much smaller staphylococcal cassettes (SCCmec types IV, V, or VII),<sup>11,12</sup> have different lineages (the predominant lineages by multilocus sequence typing are sequence types ST80 and ST30 outside the United States<sup>13-15</sup> and ST8 and ST1 in the United States),<sup>16,17</sup> and carry the *Panton Valentine leukocidin* (*PVL*) gene (which encodes for a *S. aureus* toxin that creates pores on host cell membranes),<sup>13</sup> From a clinical standpoint, CA-MRSA isolates most commonly involve skin and soft tissues,<sup>16</sup> tend to affect younger patients,<sup>18-23</sup> and are characteristically susceptible to a greater number of non- $\beta$  lactam antibiotics.<sup>22,24</sup> MRSA has thus established itself as a heterogeneous group of organisms with different epidemic potentials resulting in its constantly evolving epidemiology. This heterogeneity is also represented by different virulence potentials and complex interactions with susceptible hosts. HIV-infected patients are now recognized as one of these higher risk groups due to increased rates of both MRSA colonization and infections over the past decade. The organism's interactions and disease manifestations with

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the immunocompromised host are expected to be complex and diverse as the epidemiology of MRSA and that of HIV continue to change over time.

Herein, we review the pathophysiology, epidemiology, clinical manifestations, and treatment of MRSA in the HIV-infected population. It is important to note that specific issues related to colonization and infection may vary widely depending on the time period of the study, specific population studied, and the prevalence of antiretroviral treatment in the population, and to note that most of the available data are focused on CA-MRSA infections originating from North America where clonal group USA300 (ST8 by multilocus sequence typing) predominates.

## HIV and host defense against *Staphylococcus aureus*

Innate immunity represents the main host defense against *S. aureus*, with neutrophils being the primary cellular defense of the innate immune response.<sup>25,26</sup> Proper neutrophil function requires the coordination of many steps, including chemotaxis, phagocytosis, intracellular killing, and subsequent apoptosis.<sup>25</sup> Although not as well studied as cellular or adaptive immunity, the innate immune response in persons with HIV have revealed significant neutrophil dysfunction that may increase the risk of bacterial infections.

Chemotaxis involves the active recruitment of neutrophils to the site of infection and is the first step in bacterial eradication. An early study evaluating neutrophil chemotaxis in persons with HIV found a more than 45% reduction in chemotaxis in persons with AIDS-related complex vs healthy controls. In addition, the serum from persons with HIV inhibited chemotaxis in neutrophils from the controls,<sup>27</sup> suggesting that a serum molecule may be responsible for decreased chemotaxis in persons with HIV. In a subsequent study, the chemotactic index of neutrophils in children with asymptomatic HIV infection was 29.8% lower than that in healthy controls.<sup>28</sup> In these studies, decreased chemotaxis was predominantly seen in persons with early HIV disease. One possible explanation is that increased cytokine expression in late-stage HIV may increase random neutrophil migration.<sup>28</sup> In contrast to the more pronounced chemotaxis inhibition in early HIV disease described above, a longitudinal evaluation of neutrophil function in untreated HIV patients found an initial 19% decrease in chemotaxis that progressed to a 32% decrease after 3 years of follow-up.<sup>29</sup> In addition, the dysregulation of L-selectin expression (an adhesion molecule important in neutrophil binding to the endothelium) has been shown to increase with decreasing CD4 counts.<sup>30</sup>

Although data are limited, highly active antiretroviral treatment (HAART) may improve neutrophil chemotactic function. In a cohort of 18 HIV-infected persons with CD4 T-cell counts < 350/ $\mu$ L and diminished baseline neutrophil chemotaxis, chemotactic activity was found to be in the normal range in 72% after 9 months on HAART.<sup>31</sup>

After chemotaxis, neutrophil phagocytosis and intracellular killing are vital steps in host defense against *S. aureus*.<sup>25</sup> Several studies have found decreased neutrophil phagocytosis of *S. aureus* in HIV-infected patients compared with healthy controls.<sup>32</sup> Studies demonstrating reduced bacterial phagocytosis and respiratory burst with decreasing CD4 counts and a significantly increased capacity of neutrophils to phagocytose *S. aureus* in early HIV suggest that phagocytosis may depend on the stage of HIV infection.<sup>33,34</sup> Paradoxically, no difference was found in the phagocytosis of *S. aureus* in asymptomatic and symptomatic HIV-infected patients vs controls, but phagocytosis by normal neutrophils was less efficient when bacteria were preopsonized with serum from HIV-infected persons, implying that defective opsonization may exist in HIV-infected persons.<sup>28</sup> Studies have also shown a reduced bactericidal capacity of neutrophils in HIV-infected persons. A >20% decrease in the intracellular killing of *S. aureus* was found in neutrophils from HIV-infected patients vs healthy controls.<sup>35</sup> In contrast to studies that show impaired phagocytic oxidative capacity in HIV-infected patients may be explained by reduced intracellular bacterial killing,<sup>35-37</sup> the impaired bactericidal capacity in this study was not explained by a defect in the production of reactive oxygen species.<sup>36</sup> As is true for the defects in chemotaxis and phagocytosis, there is evidence that this decreased bactericidal activity of neutrophils against *S. aureus* in HIV-infected patients is more pronounced with late-stage HIV disease,<sup>27,28</sup> and that bacterial killing by neutrophils from healthy controls can be decreased when *S. aureus* is pretreated with the serum of HIV patient, again revealing a possible defect of opsonization in patients with HIV.<sup>27,28</sup> The effect of HAART on neutrophil bactericidal function is still unclear.

Neutropenia is a well-recognized consequence of HIV infection and increases the risk of bacterial infections.<sup>38</sup> The etiology of neutropenia in HIV-infected persons is multifactorial with bone marrow invasion by opportunistic infections, treatment-related hematologic toxicities, and nutritional deficiency, all potentially playing a role.<sup>38</sup> Another mechanism may be increased neutrophil apoptosis, which has been shown to be accelerated in HIV-infected persons.<sup>39-41</sup> Pitrak et al<sup>40</sup> found that neutrophil viability in culture was markedly decreased after 18 hours in

patients with AIDS (58.8%) vs healthy controls (83.5%).<sup>40</sup> It is believed the oxidative stress of HIV may, in part, be responsible for accelerated neutrophil death.<sup>41</sup> Protease inhibitors (PIs) have been shown *in vitro* to inhibit neutrophil apoptosis,<sup>42</sup> thus suggesting PI use may potentially reverse some of the accelerated neutrophil apoptosis seen in HIV-infected persons.

Many other cells play an important role in host defense against *S. aureus*, including monocytes and B lymphocytes. Monocytes are involved in the phagocytosis of bacteria, the production of immunomodulating cytokines (many of which direct and organize neutrophil function), and the removal of apoptotic neutrophils. Studies have shown significant monocyte dysfunction exists in HIV-infected patients.<sup>32,33,43</sup> Moreover, the HIV Nef protein has been found to decrease monocyte chemotaxis and to inhibit the phagocytosis of apoptotic neutrophils, thus potentially contributing to an increased inflammatory state in HIV-infected persons.<sup>44,45</sup>

Finally, B lymphocytes produce antibodies that are an essential component of antibacterial immune responses and increase the efficiency of neutrophil phagocytosis. Since early on in the HIV epidemic, B-cell abnormalities and the production of dysfunctional antibodies have been recognized in HIV-infected persons and believed to increase the risk of bacterial infections.<sup>46,47</sup>

The demonstrated defects in innate immunity surely contribute to the high rates of *S. aureus* infections in persons infected with HIV. Further work is needed to evaluate

the effect of HAART on the recovery of the innate immune response against *S. aureus*.

## Epidemiology and clinical manifestations

### Colonization

The prevalence of colonization with *S. aureus* varies according to the population studied. Groups of patients with higher colonization rates have been identified, including patients with HIV infection.<sup>48–55</sup> For MRSA, specifically, colonization rates of 0%–17% have been reported for HIV-positive outpatients and 17%–31% for inpatients (Table 1). HIV has been identified as an independent risk factor for determining colonization with MRSA.<sup>48,49,52,56</sup> The reason for the higher colonization rates observed are unclear, but could include factors such as frequent contact with both health care and community settings and frequent exposure to antibiotics, leading to a greater likelihood of becoming colonized with resistant strains. Some authors argue that this increased susceptibility to colonization with *S. aureus* could be HIV-specific.<sup>57</sup> Some of the risk factors for colonization among HIV-infected patients suggest immunologic and virologic control, as well as the use of prophylactic Bactrim might be important protective measures.<sup>51,52,58,59</sup> However, higher colonization burdens have been shown for HIV-infected patients without evidence of immunosuppression, suggesting this association might be independent of CD4 T-lymphocyte counts.<sup>54</sup> In addition, sociodemographic and behavioral factors might also play an important role in establishing higher colonization rates among this patient population. Table 2

**Table 1** Prevalence of MRSA colonization in HIV-positive patients

Patient population	No. of HIV-infected patients	Median CD4 count of the cohort	HIV patients colonized with <i>S. aureus</i> , %	HIV patients colonized with MRSA, %	Reference
Outpatient <sup>a</sup>	100	450	49	2	157
Outpatient <sup>b</sup>	243	NA	NA	3.8	58
Outpatient <sup>c</sup>	100	NA	NA	2	158
Outpatient <sup>c</sup>	146	328	NA	10.3	59
Outpatient <sup>c</sup>	158	NA	27	4	65
Outpatient <sup>c</sup>	163	NA	21.5	3.1	159
Outpatient <sup>c</sup>	195	270	23	3	160
Outpatient <sup>c</sup>	111	NA	64.6 <sup>d</sup>	0	55
Outpatient <sup>c</sup>	900	NA	NA	8	79
In/outpatient <sup>c</sup>	178	NA	NA	34.8	161
Outpatient	162	205	30	6	51
Outpatient <sup>e</sup>	60	NA	76.7	17.4	162
Outpatient <sup>f</sup>	107	612	58.9 <sup>d</sup>	16.8 <sup>d</sup>	54
Inpatient	81	NA	NA	17	48
Inpatient <sup>g</sup>	239	NA	NA	31.4	53

**Notes:** <sup>a</sup>ID clinic; <sup>b</sup>Clinic for gay, lesbian and transgender patients; <sup>c</sup>HIV clinic; <sup>d</sup>Cumulative prevalence; <sup>e</sup>Patients with HIV infection attending a dermatology clinic; <sup>f</sup>MSM; <sup>g</sup>Children admitted to a hospital in South Africa with pneumonia.

**Abbreviations:** MRSA, Methicillin-resistant *Staphylococcus aureus*; HIV, human immunodeficiency virus; NA, not available; ER, emergency room.

**Table 2** Risk factors for colonization with MRSA in HIV-positive patients<sup>a</sup>

Risk factors for colonization with MRSA in HIV-positive patients (reference)	Studies that have found no association (reference)
High HIV viral load <sup>58</sup>	54,159
Low CD4 T-cell count <sup>51,52,58,59,79</sup>	54,55,159,160
Bactrim use (protective) <sup>58,59</sup>	160 <sup>b</sup>
Antibiotic use (other than Bactrim) <sup>3,51,52,54,79,160</sup>	
Hospitalization <sup>3,160</sup>	
Central venous catheter <sup>3</sup>	
Dermatologic disease <sup>3</sup>	
<b>No significant association found for the following risk factors (reference)</b>	
Intravenous drug abuse (IVDU)/recreational drug use <sup>54,159</sup>	
ARV treatment status <sup>54</sup>	
Prior MRSA infections <sup>54</sup>	
Use of sports/gym facilities/shared towels <sup>54</sup>	

**Notes:** <sup>a</sup>Does not take into account whether isolates are community-acquired MRSA (CA-MRSA) vs hospital-acquired MRSA (HA-MRSA); <sup>b</sup>Use associated to risk, likely because their outpatient strain was identical to their hospital strain and therefore strain was likely a HA-MRSA strain.

**Abbreviations:** MRSA, Methicillin-resistant *Staphylococcus aureus*; HIV, human immunodeficiency virus; ARV, antiretroviral.

summarizes independent risk factors that have been identified for colonization with MRSA in HIV-positive patients.

Not all studies have found HIV status as an independent risk factor for colonization.<sup>60</sup> Potential reasons to explain disagreement between studies include the presence of other unrecognized sites of colonization (patients might be colonized in the genital or perineal areas but not in the nasopharynx),<sup>61</sup> and intermittent colonization. The intermittent nature of colonization is illustrated in the study by Shet et al,<sup>54</sup> where the prevalence of MRSA colonization was 4.7% at the first visit, 8.7% at the second visit, and 11.8% at the third visit for a cumulative prevalence of 16.8%.<sup>54</sup> It has been estimated that up to 20% of true carriers can be missed when a single sample is obtained.<sup>55</sup> As far as persistence of colonization in HIV-infected patients who are known to be colonized, 38%–39% of patients have been reported to be persistent carriers, but up to 62% of patients will have a positive *S. aureus* nares culture if screened at three different points in time.<sup>55</sup>

Whether colonization with MRSA precedes MRSA infection is controversial.<sup>62</sup> Earlier to widespread reports of CA-MRSA, a prospective, multicenter study found that HIV-infected patients colonized with *S. aureus* were more likely to become infected.<sup>63</sup> In a study looking at patients not known to be HIV-infected with bacteremia, blood isolates matched nasal isolates in 82% of patients.<sup>64</sup> Among HIV-infected patients, the study by Szumowski et al<sup>58</sup> suggests an

association between perianal MRSA colonization and skin and soft tissue infections (SSTIs). Pulsed-field gel electrophoresis (PFGE) profiles for infecting and colonizing strains in a recent study showed identical macrorestriction profiles.<sup>54</sup> Furthermore, colonization with *S. aureus* has been identified as an independent risk factor for *S. aureus* infections in HIV-positive patients.<sup>54,63</sup>

In contrast, some published studies refute the role of prior colonization as necessary for MRSA infection. A point prevalence survey done in an HIV clinic reported that only 1 of 6 patients who had a MRSA SSTI during the previous 6 months was colonized with MRSA.<sup>65</sup> In this study, colonization at the time of infection was not assessed, so the absence of a temporal association is not certain. Similarly, in the case of MRSA bacteremia in HIV-infected children, *S. aureus* carriers did not have higher rates of *S. aureus* bacteremia than did noncarriers.<sup>53</sup> Some authors have therefore suggested that high-risk sexual behavior may be a more important risk factor for transmission than actual colonization.<sup>66</sup>

## Infections

Rates of MRSA infections have increased over time among HIV-positive patients<sup>66–70</sup> and have been reported to be 6-fold to 18-fold higher than in the general population.<sup>70,71</sup> The proportion of MRSA relative to methicillin-susceptible *S. aureus* (MSSA) infections has also increased over the last several years among HIV-infected children and young adults (from 17% to 100% of all *S. aureus* infections at the end of an 8-year follow-up period).<sup>72</sup> In retrospective reviews, 7% of outpatient HIV cohorts developed CA-MRSA infections over prolonged follow-up (8–13 years).<sup>69,70</sup> Similarly, in an asymptomatic cohort of HIV outpatients followed over a year, 9% developed MRSA infections in contrast to 0% of the uninfected controls.<sup>54</sup> In a dermatology practice over 3 years, 51% of CA-MRSA SSTIs were in HIV-positive patients.<sup>73</sup> For SSTIs, specifically, the incidence of CA-MRSA among HIV-infected patients was reported to have significantly increased from 2000 to 2007 with USA300 MRSA accounting for 86% of the isolates.<sup>71</sup> Not only HIV-positive patients are more likely to have community-onset *S. aureus* infections but also are more likely to have a nosocomial infection caused by *S. aureus* than HIV-negative patients.<sup>74</sup>

Whether HIV-infected patients are at increased risk of infections because of higher colonization rates or due to other social, environmental, behavioral, biologic, HIV host-specific risk factors, or a combination of all these is still unclear. Risk factors for MRSA infections have been more extensively studied for SSTIs in HIV-infected patients. Some authors

postulate that CA-MRSA SSTIs are more tightly related with sexual behavior or drug-using behavior than they are with HIV.<sup>75,76</sup> Evidence supporting the association with high-risk sexual practices includes a higher incidence of these infections in men who have sex with men (MSM),<sup>77</sup> their distribution predominantly in the genital or perianal areas,<sup>70,75</sup> the association with a history of other sexually transmitted diseases,<sup>70,75</sup> and the protective use of condoms.<sup>75</sup> It has also been suggested that the colonization patterns in CA-MRSA infection are different from those in non-CA-MRSA infections.<sup>78</sup> This could offer a plausible explanation to the higher frequency of SSTI observed in this patient population, assuming a direct relationship with high-risk sexual practices.

Whether the risk for SSTI is increased among HIV patients with lower CD4 T-cell counts is debated: some studies have found a significant association,<sup>66,69,70,79</sup> whereas others have not.<sup>58,75</sup> Overall, reported mean CD4 counts at the time of presentation with SSTIs specifically have been well above 200 cells/mm<sup>3</sup> (mean CD4 counts: 457,<sup>68</sup> 445,<sup>69</sup> 560<sup>72</sup>). However, in favor of the role of immunosuppression, outbreaks have been reported in patients with extremely low CD4 counts (CD4 T-cell count < 10 in 66%),<sup>80</sup> and 85% of *S. aureus* infections have been reported to occur in patients with CD4 counts less than 100 cells/mm<sup>3</sup> with this risk increasing over time.<sup>63</sup>

As would be expected, an elevated HIV viral load has been identified as a risk factor not only for infection<sup>66</sup> but also for recurrence.<sup>69,81</sup> Of course, patients with higher degrees of immunosuppression are more likely to be in contact with the health care system, or, alternatively, immunosuppression might represent a marker for other associated conditions or behaviors. However, both low CD4 counts<sup>66,70,79,82</sup> and elevated HIV viral load<sup>66,69,70</sup> have been found to be independent risk factors for MRSA infections. Other risk factors for MRSA infections in HIV-positive patients are listed on Table 3.

## SSTI

Mirroring what is observed in the general population,<sup>3,58,66,72,75,76</sup> most MRSA infections in HIV-positive patients represent SSTI, which account for up to 83%–90% of the MRSA infections observed in HIV outpatients,<sup>58,66,70</sup> and 30%–45% in inpatients.<sup>3,82</sup> Likewise, the etiology of SSTI in HIV-infected patients has been documented to be MRSA in 37%–93% of patients;<sup>68,70,83</sup> the vast majority of these are due to CA-MRSA.<sup>70</sup> In fact, the presence of a SSTI predicts infection with a specific clone identified by PFGE, the USA300 clone.<sup>79</sup> The most common type of SSTIs are

**Table 3** Risk factors for MRSA infections in HIV-positive patients

Risk factors for MRSA infections in HIV-positive patients (reference)	Studies that have found no association (reference)
Low CD4 count <sup>66,70,79,82</sup>	75
Elevated HIV viral load <sup>66,69,70</sup>	
Recent use of $\beta$ -lactam antibiotics <sup>70</sup> or antibiotic use <sup>3,79</sup>	
History of syphilis <sup>70</sup>	
Bactrim use (protective) <sup>66,70,75</sup>	69 <sup>a</sup>
Injection drug use, type of sexual practice (MSM), or both <sup>66</sup>	82
Sex partners with skin infections <sup>75</sup>	
Use of a condom (protective) <sup>75</sup>	
Methamphetamine use <sup>75</sup>	
Use of a public hot tub or sauna <sup>75</sup>	
Routine hands on contact with customers at work <sup>75</sup>	
Cumulative hospital stay <sup>3,82</sup>	
Invasive procedures in the previous year <sup>82</sup>	
Central venous catheter <sup>3</sup>	
Dermatologic disease <sup>3</sup>	

**Note:** <sup>a</sup>n = 1.

**Abbreviations:** MRSA, Methicillin-resistant *Staphylococcus aureus*; HIV, human immunodeficiency virus; MSM, men who have sex with men.

abscesses followed by cellulitis, furunculosis, impetigo, folliculitis, and carbuncles.<sup>70,75</sup> Contrary to what would be expected, the majority of patients with MRSA SSTIs (specifically with CA-MRSA SSTIs) do not seem to have immunologic or virologic parameters consistent with AIDS at the time of infection.<sup>84</sup> The location of SSTIs has been reported to be the lower extremity in 21%–32%, buttocks/scrotum/anogenital region in 26%–40%, upper extremity in 10%–20%, face in 3%–13%, and trunk in 3%–10%.<sup>69,70,75</sup> Infections usually resolve with treatment<sup>68</sup> and are rarely complicated by pneumonia or osteomyelitis.<sup>72</sup> Bacteremia is also an infrequent complication but has been reported in 0%–7% of patients.<sup>68,70,72</sup> The rates of patients requiring hospitalization are similar to those of the general population.<sup>70</sup> In contrast, recurrence of infection is quite common (10%–71%), which in some cases has been reported to occur at twice the rate of the general population.<sup>70</sup> Recurrence usually occurs at a median of 4–4.5 months,<sup>68–70,72,76,81</sup> and does not seem to be related to initial antibiotic susceptibility and antibiotics received for the initial SSTI;<sup>81</sup> more frequently, recurrences happen at a different site of the original infection.<sup>72</sup> Risk factors for recurrence include lower CD4 cell counts, higher HIV RNA levels, lack of incision and drainage at the time of initial MRSA infection,<sup>69</sup> whereas risk factors for infection (specifically with a CA-MRSA isolate) include residence in alternative housing (ie, shelters), residence in high-risk zip codes, and younger age.<sup>71</sup>

Although the majority of reported SSTIs in HIV-infected patients are due to CA-MRSA, there are limited data with specific isolate typing or looking at the role of staphylococcal toxins that are known to be commonly associated with these isolates, such as PVL.<sup>85</sup> Of the few studies for which typing is available, Skiest et al<sup>68</sup> found 88% and 100% of MRSA isolates carried SCCmec type IV and PVL, respectively; Graber et al found 87% of all MRSA isolates were USA300 (which usually carries SCCmec type IV and PVL);<sup>17,81</sup> and Ramsetty et al found that 89% of the MRSA isolates causing both infection and colonization in HIV outpatients were USA300.<sup>79</sup> Srinivasan et al<sup>72</sup> reported a lower prevalence of infections with the USA300 MRSA isolate (52% PVL positive, USA300) among 31 HIV-infected children and young adults with MRSA infections, 87% of which were SSTIs. Only this last study attempted to determine whether PVL-positive MRSA strains caused increased morbidity in the HIV-positive population compared with PVL-negative MRSA strains. In addition to finding that the proportion of patients with PVL-positive MRSA infections did not increase over time (despite the fact the proportion of overall MRSA infections did relative to MSSA), they found that PVL-positive MRSA infections were significantly associated with more SSTI but not with increased morbidity or a higher risk of complications compared with PVL-negative MRSA infection.<sup>72</sup>

## Invasive infections

Cases of *S. aureus* or MRSA necrotizing cellulitis, pyomyositis,<sup>86</sup> necrotizing fasciitis,<sup>87,88</sup> pneumonia,<sup>2,3,89</sup> bacteremia,<sup>3</sup> endocarditis,<sup>63,88,90</sup> purulent pericarditis with cardiac tamponade,<sup>91</sup> and even perinephric abscess<sup>2</sup> have all been reported in HIV-positive patients. With few exceptions,<sup>63,82</sup> invasive infections (ie, bacteremia, endocarditis, pneumonia, etc) are not as common as SSTIs, usually accounting for <20% of MRSA infections overall.<sup>3,66,70,72</sup> Bacteremias have been reported to account for approximately 10%–41% of MRSA infections, pneumonias for 6%–30%, and deep soft tissue infections, endocarditis, and other invasive infections accounting for even lower percentages, but these numbers vary depending on the type of cohort (inpatient vs outpatient).<sup>66,82</sup> Regardless, these deep-seated infections can be a significant cause of morbidity and mortality in this patient population. For HIV-positive patients with *S. aureus* bacteremia, for example, mortality rates of up to 67% have been reported and patients are twice as likely to die compared with HIV-positive patients without this invasive infection.<sup>63</sup> The outbreak reported by Smith et al,<sup>15</sup> additionally suggested that this increased morbidity and mortality might be related

to immunosuppression because all cases occurred among patients with low CD4 counts (67% with CD4 counts < 10) and 83% had invasive disease (3 of 6 patients with bacteremia and 2 of 6 with pneumonia). In contrast, despite finding a two fold increased mortality rate in HIV-positive patients with an MRSA infection compared with other HIV-positive inpatients, a study from Italy did not find this to be a statistically significant mortality difference.<sup>82</sup>

Whether improved HIV control will result in reduced risk of MRSA infections and/or recurrences is argued by some<sup>69</sup> but remains to be proved in future studies.

## Bacteremia

*S. aureus* is the most frequent cause of both community and hospital-acquired bacteremia in HIV-positive patients,<sup>2,92–94</sup> and MRSA can explain 32%–67% of cases of *S. aureus* bacteremia in this patient population.<sup>2,67,82,95–97</sup> At large urban centers, the prevalence of HIV among patients with MRSA bacteremia can be up to 22%.<sup>98</sup> Prior to the widespread emergence of MRSA in the community, the incidence of MRSA bacteremia in HIV-positive patients was thought to be declining.<sup>95</sup> Burkey et al<sup>67</sup> reported an increasing incidence just a few years later. This recent increasing incidence temporally coincides with increasing reports of MRSA from the community.

After SSTIs, bacteremia is the most frequently observed infection among HIV-infected patients. Along with IVDA,<sup>67</sup> end-stage renal disease,<sup>67</sup> low CD4 T-cell count (<200 cells/ $\mu$ L),<sup>67,95</sup> use of  $\beta$ -lactam antibiotics,<sup>95</sup> and previous hospital admissions,<sup>95</sup> HIV infection has been identified as an independent risk factor for MRSA bacteremia.<sup>99</sup> Hospitalized patients with HIV have been reported to be almost 17 times more likely to have *S. aureus* bacteremia compared with HIV-negative patients.<sup>96</sup>

The source of bacteremia varies depending on the time the study was conducted and the patient population, perhaps in addition to other factors. In the pre-HAART era, cases of *S. aureus* bacteremia were more frequently community-acquired, reported among intravenous (IV) drug users, and commonly associated with endocarditis.<sup>2</sup> In more recent studies (coinciding with widespread reports of CA-MRSA), the source for *S. aureus* bacteremia was somewhat different: SSTI in 15%–31% of cases, a catheter in 17%–54% of cases, use of IV drugs (or endocarditis) in 3%–49%, and unknown in approximately 19%.<sup>96,97</sup> Significant immunosuppression can be observed among patients with bacteremia, with mean CD4 counts at the time of bacteremia of 52–130 cells/ $\text{mm}^3$  and 94% of the patients being categorized as AIDS in one of the

studies.<sup>96,97</sup> Paradoxically, CD4 counts and viral loads have not been shown to be independent predictors for poor outcomes. In fact, the absence of HAART has been associated with a lower mortality.<sup>97</sup> Whether outcomes of HIV-infected patients with *S. aureus* bacteremia are influenced by the isolate's resistance profile (MRSA vs MSSA) is another matter of debate: 2 studies suggest this is not the case,<sup>96,97</sup> but a recent study suggests both HIV infection and methicillin resistance can increase at least the odds of *S. aureus* bacteremia recurrence by almost 5 and 2 times, respectively.<sup>100</sup> Rates of objective outcomes, such as mortality, have not been found to be significantly higher in HIV-infected patients compared with HIV-negative patients with *S. aureus* bacteremia.<sup>101</sup> In HIV-infected patients with *S. aureus* bacteremia, overall mortality rates are 10%–67%, and approximately 40% for MRSA specifically.<sup>58,63,97,101</sup>

From a clinical standpoint, little data are available differentiating the clinical presentations of bacteremia in HIV-infected and uninfected patients. Mean duration of fever, percentage of bands, neutrophils, and number of platelets are similar between HIV-infected and uninfected patients with *S. aureus* bacteremia, but HIV-infected patients do have significantly lower white blood cell counts on admission.<sup>96</sup> Complications of bacteremia may include metastatic seeding, pneumonia, endocarditis (which can be observed in up to 20% of patients), relapse or recurrence of infection (observed in up to 17% of patients), sepsis, shock, and overall can be observed in approximately 13% of patients.<sup>96,97</sup>

## Endocarditis

The most common etiologic agent of endocarditis among HIV-infected patients, whether IV drug users or not, is *S. aureus*.<sup>90,102,103</sup> The incidence, epidemiology, clinical presentation, and outcomes of infective endocarditis (IE) were evaluated in HIV-infected outpatients followed at one center. Though the study was not limited to cases with *S. aureus*, it was by far the most common etiologic organism representing 69% of the cases; of these, 28% were methicillin-resistant. The incidence of IE in HIV-infected patients was found to be significantly higher than that of the general population. The majority of cases occurred among male, African-American IV drug users in their 40 years of age with median CD4 counts of 68 cells/mm<sup>3</sup>. These demographics did not differ from HIV-infected controls without IE except for the following identified risk factors: IV drug use, CD4 count < 50 cells/mm<sup>3</sup>, and HIV RNA > 100,000 copies/mL.<sup>90</sup> Fever, chills, shortness of breath, and myalgias were the most common presenting symptoms. Over 50% of the patients

in this cohort had died at 1 year, but the type of organism was not found to be an independent predictor of mortality. At 1 year, 16% of patients had recurrences, and 66% of the recurrences were due to *S. aureus*.<sup>90</sup>

A second study looking at 133 cases of *S. aureus* endocarditis (of whom 38% were HIV-positive drug abusers) from one center over a 22-year period found that HIV-negative patients with *S. aureus* IE were more likely to have dyspnea, cutaneous signs, neurologic lesions, and even a higher mortality. This can be explained by the fact that HIV-positive patients were more likely to be drug abusers and therefore to have right rather than left-sided endocarditis, which is associated with a more favorable prognosis.<sup>104</sup> Of note, only 6% of the isolates were methicillin-resistant. Reports of IE caused by CA phenotype isolates (ie, USA300) among HIV-positive patients are still limited.<sup>105</sup>

## Pneumonia

As is the case for the general population, MRSA pneumonia among HIV-positive patients can be health-care associated, secondary to bacteremia, or community-acquired. MRSA is a common pathogen for nosocomial pneumonia in HIV-positive patients (25% of cases due to *S. aureus*, 65% of these methicillin-resistant) and has been identified as an independent risk factor for mortality among HIV-positive patients.<sup>106</sup> CA-MRSA pneumonia has been recognized as an emerging entity concurrent to the emergence of CA-MRSA, presenting usually after a viral prodrome with varying degrees of lung necrosis which manifest as shortness of breath, sepsis, and hemoptysis.<sup>107</sup> It was initially recognized mainly among healthy patients,<sup>107</sup> but in more recent reports, nearly 50% of the cases were among immunocompromised patients and 43% of the patients in this group were HIV-positive.<sup>89</sup>

## Necrotizing fasciitis

Overall, *S. aureus* was an infrequent cause of necrotizing fasciitis but is now recognized as an emerging clinical syndrome.<sup>88</sup> Of 19 cases of CA-MRSA necrotizing fasciitis reported in the literature, only 11% were HIV-positive patients.<sup>87</sup> Data on the incidence and prevalence of this entity among HIV-positive patients are therefore limited to very few case reports, which impedes conclusions on comparative severity and clinical presentations.<sup>87,88</sup> However, in general, it has been suggested that necrotizing fasciitis caused by CA-MRSA may be less virulent than similar infections caused by other organisms.<sup>88</sup>

## HIV and treatment of MRSA

Little data suggest that the treatment of MRSA infections in HIV-infected patients should be any different than the treatment in noninfected patients. Below, we briefly review the limited data about treatment of these infections.

### Treatment of MRSA SSTIs

A recent study in HIV-positive patients suggests that the antibiograms of MRSA isolates are showing lower susceptibility rates to antibiotics, such as clindamycin, erythromycin, and ciprofloxacin, to which MRSA isolates have classically been susceptible.<sup>54</sup> Concordant with this, a study looking at the MSM population in Boston and San Francisco found a high rate of resistance to clindamycin, tetracycline, and mupirocin among MRSA isolates independent of HIV infection.<sup>77</sup> A similar study in MSM from New York reported a high rate of resistance to tetracycline (23%), clindamycin (63%), and erythromycin (93%) in CA-MRSA isolates.<sup>108</sup> In fact, recurrent infections with MRSA have been associated with resistance among initially susceptible isolates in MSM<sup>77</sup> and in HIV-infected patients.<sup>69</sup>

A number of oral agents such as trimethoprim-sulfamethoxazole (TMP-SMZ), clindamycin, tetracyclines such as doxycycline, rifampin (in combination with other agents), and linezolid have been used to treat MRSA-associated SSTIs in HIV and non-HIV patients. Despite the extensive use of the above-mentioned agents, there are no prospective controlled trials of most of these drugs prescribed to treat MRSA SSTIs. Small areas of skin infection with a drainable focus are usually cured by incision and drainage alone in adults<sup>17</sup> and children.<sup>109,110</sup> However, reported success to therapy has been 95% of patients with CA-MRSA SSTI who received an active antibiotic compared with 87% in those who did not.<sup>111</sup> Large lesions, associated cellulitis, and presence of systemic symptoms like fever may warrant the use of a systemic antibiotic<sup>17,112</sup> despite the lack of supporting evidence from prospective controlled trials.<sup>113</sup> Addition of systemic antibiotics has also been advocated with advanced immunodeficiency.<sup>114</sup>

TMP-SMZ remains one of the most common drugs used to treat uncomplicated SSTIs due to MRSA despite the paucity of randomized, controlled trials that support its efficacy in such infections. TMP-SMZ was found to have a greater bactericidal activity against MRSA *in vitro* than linezolid, rifampicin, minocycline, and clindamycin<sup>115</sup> and was considered as an acceptable alternative to vancomycin for the treatment of systemic MRSA infections by Markowitz et al.<sup>116</sup> Increased rates of clinical response in SSTIs have

been reported with the use of TMP-SMZ.<sup>117</sup> Clinicians should be aware that TMP-SMZ resistance among MRSA isolates in HIV-infected patients has been reported.<sup>50,118</sup> The use of prophylactic TMP-SMZ may select for this resistance<sup>50,118,119</sup> although resistance has also been reported without a history of prior TMP-SMZ use.<sup>70</sup> Fortunately, overall TMP-SMZ resistance in HIV-infected patients remains infrequent.<sup>77</sup>

Clindamycin can potentially inhibit toxin production including PVL<sup>120,121</sup> and is used to treat MRSA infections.<sup>122</sup> Inducible clindamycin resistance has to be ruled out by performing a D-test because a number of isolates that are erythromycin-resistant have shown to be clindamycin-resistant despite appearing initially susceptible.<sup>123</sup> The incidence of clindamycin resistance in the United States varies. In a study of SSTIs in HIV-infected patients in Dallas, 10% of CA-MRSA isolates were resistant to clindamycin.<sup>68</sup> Srinivasan et al<sup>72</sup> reported a 19% incidence of clindamycin resistance in MRSA isolates from children and young adults with HIV infection at St. Jude Children's Research Hospital. A study of CA-MRSA SSTIs in MSM in New York has found that 63% of the isolates were resistant to clindamycin.<sup>108</sup> Moreover, a more recent study of SSTIs in otherwise healthy HIV-positive patients in New York found that 42.9% of all MRSA isolates were resistant to clindamycin.<sup>54</sup> Given the possible increasing rate of resistance of MRSA isolates, clindamycin should be used with caution if local antibiograms suggest local high-grade resistance of MRSA isolates.

Long-acting tetracyclines have been used to treat MRSA-associated infections. Clinical cure was achieved in 83% of patients with tetracycline-susceptible MRSA infections in a study by Ruhe et al.<sup>124</sup> The same study found a similar response rate after review of the literature of 85 patients.<sup>124</sup> Importantly, recent studies have found increasing resistance to tetracyclines among MRSA USA300 isolates in Boston and San Francisco.<sup>125,126</sup>

Linezolid is a bacteriostatic agent that can be given orally to treat MRSA SSTIs and is approved for that indication. One study found that linezolid was equivalent to vancomycin in treating complicated SSTIs.<sup>127</sup> In a randomized trial treating diabetic foot infections, linezolid was at least as effective as aminopenicillin/β-lactamase inhibitors.<sup>128</sup> Resistance to linezolid has been reported, but it has not been a clinically significant problem to date.<sup>129</sup> Linezolid, like clindamycin, can inhibit toxin production by MRSA isolates that may be helpful in the case of severe SSTIs.<sup>120</sup> Linezolid use has been associated with myelosuppression, including thrombocytopenia and anemia, which are often reversible after drug discontinuation.<sup>130</sup> Neurotoxicity, mainly

peripheral and ocular neuropathy, has also been reported in patients receiving linezolid for more than 28 days.<sup>130–132</sup>

Finally, rifampin is sometimes used in combination with other agents although one study found the addition of rifampin to TMP-SMZ to be antagonistic.<sup>115</sup>

## Treatment of invasive infections

Available parenteral agents for treatment of invasive MRSA infections, such as bacteremia, pneumonia and complicated SSTIs, include vancomycin, linezolid, daptomycin, tigecycline, and quinupristin-dalfopristin in HIV and non-HIV patients. Vancomycin has been the agent of choice for treating invasive MRSA infections for years. However, resistance among some MRSA isolates and poor tissue penetration of vancomycin have raised recent concern when treating severe MRSA infections.<sup>133–136</sup> Moreover, there have been reports of treatment failure due to heteroresistant MRSA, in which a subpopulation of MRSA would have a high MIC and reduce susceptibility to vancomycin.<sup>137</sup> In addition, there is a correlation between vancomycin minimum inhibitory concentrations (MICs) and treatment outcomes.<sup>138,139</sup> Patients with MRSA bacteremia in one study had better outcomes when the isolates MIC was 0.5 µg/mL compared with those with 1–2 µg/mL.<sup>138</sup>

Linezolid can be administered either orally or IV to patients with MRSA infections. In a randomized open-label trial of patients with presumed MRSA infections including SSTIs and pneumonia, the clinical cure rates were 73.2% and 73.1% in the linezolid group and the vancomycin group, respectively.<sup>140</sup> Despite this, whether linezolid may be superior to vancomycin in the treatment of MRSA pneumonia is still controversial, and the optimal treatment of nosocomial and CA-MRSA pneumonia is not clearly defined due to the lack of prospective trials.<sup>141</sup> Linezolid is not FDA approved for treatment of MRSA bacteremia or endocarditis. It has been used in such cases with some reports of success<sup>140,142</sup> or failure,<sup>143,144</sup> and its efficacy in treatment of MRSA bacteremia or endocarditis has yet to be established.

Daptomycin is a bactericidal drug that is FDA approved for treatment of *S. aureus*, including MRSA SSTI bacteremia, and right-sided endocarditis. Daptomycin had similar efficacy to vancomycin in treatment of patients with complicated SSTIs due to MRSA.<sup>145</sup> In a randomized trial by Fowler et al<sup>146</sup> in patients with *S. aureus* bacteremia with or without endocarditis, daptomycin was not inferior to standard therapy consisting of initial low-dose gentamicin with either antistaphylococcal penicillin or vancomycin. Importantly,

*S. aureus* isolates with heteroresistance to vancomycin may exhibit daptomycin nonsusceptibility despite the lack of previous exposure to daptomycin.<sup>147</sup> Daptomycin should not be used for the treatment of MRSA pneumonia because the drug is inactivated by pulmonary surfactant causing clinical failures.<sup>148</sup> Of note, daptomycin use has been associated with elevated creatine kinase, myopathy, and even rhabdomyolysis in some cases.<sup>146,149</sup>

Tigecycline is available as an IV drug for treatment of SSTIs, including MRSA SSTIs, and has been shown to be noninferior to vancomycin in some studies.<sup>150,151</sup> However, its use has been limited, and the number of patients of MRSA infections receiving tigecycline has been small. In addition, cases of tigecycline-induced pancreatitis have been reported in the literature.<sup>152,153</sup> Quinupristin-dalfopristin has been used for salvage therapy in MRSA infections in patients who are intolerant or failing standard therapy,<sup>154,155</sup> but its use may be limited by the frequent adverse events, such as arthralgias and myalgias.<sup>156</sup>

In summary, several agents are available for treatment of SSTI and more serious infections due to MRSA, but few comparative studies are available and no studies have specifically evaluated the use of these agents in HIV-infected patients.

## Conclusion

As the epidemiology of *S. aureus* (and MRSA specifically) continues to evolve, both colonization and infections with this organism have become increasingly common in the HIV-positive population. Behavioral, social, environmental, biologic, HIV host-specific risk factors, and, probably, a combination of all these play a significant role in explaining the increased prevalence and incidence observed. The organism's interactions with the immunocompromised host are complex, and involve defects in innate immunity.

Little data suggest that the treatment of MRSA infections in HIV-infected patients should be any different than the treatment in noninfected patients. Finally, whether improved HIV control will result in reduced risk of MRSA infections or recurrences remains to be proved in future studies.

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## Disclosure

None of the authors in this manuscript have any conflicts of interest to disclose.

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