Management of Methicillin-Resistant *Staphylococcus aureus* Bacteremia

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*Staphylococcus aureus* bacteremia and endocarditis are serious infections that demand prompt clinical attention to ensure good outcomes. Of foremost importance is identifying and managing the source of infection and any associated complications. Evaluation for the presence of cardiac involvement is essential because inadequately managed *S. aureus* endocarditis is life threatening. Thus, physicians must aggressively negotiate treatment paths, considering whether the *S. aureus* bacteremia is complicated, whether foreign sources of infection should be removed or replaced, and whether surgical intervention is necessary. Selection of an antibiotic treatment is also an essential factor for optimal management. The increasing prevalence of methicillin-resistant *S. aureus* (MRSA) infections has created a tremendous demand for effective and safe antimicrobial agents other than the historic anti-MRSA agent vancomycin.

The management of bacteremia caused by methicillin-resistant *Staphylococcus aureus* (MRSA) is a growing clinical challenge, as the rates of this infection continue to rise globally. A recent British study found that, between 1997 and 2004, the overall incidence of *S. aureus* bacteremia increased significantly among inpatients of 2 large hospitals and that this increase was primarily due to an increase in infections caused by MRSA [1]. *S. aureus*—and, increasingly, MRSA—is now the most common cause of infective endocarditis in most developed regions [2].

The impact of the increasing frequency of MRSA bacteremia is magnified by the poor outcome associated with this serious, common infection. A growing body of evidence now supports a worse overall outcome for patients with MRSA bacteremia, compared with that for similar patients with methicillin-susceptible *S. aureus* (MSSA) infection [3]. These findings highlight the importance of expedient and aggressive management of MRSA bacteremia. Successful management depends first and foremost on determining the extent of the infection and then on making appropriate decisions about the type and length of therapy. In this article, we address issues and controversies around the clinical management of *S. aureus* bacteremia and infective endocarditis and review the currently available therapies for MRSA bacteremia, as well as potential agents currently undergoing clinical trials.

**CLINICAL MANAGEMENT OF *S. AUREUS* BACTEREMIA**

**Assessment of the extent of infection.** Establishing the extent of infection is the most important aspect of the management of *S. aureus* bacteremia. The report of even a single positive blood culture result for *S. aureus* should prompt initiation of empirical antibiotic therapy, obtainment of follow-up blood cultures, and an investigation to determine the source and extent of infection. Common sources of *S. aureus* bacteremia include intravenous catheters and other intravascular devices, soft-tissue infections, and pneumonia (usually associated with receipt of mechanical ventilation) [4–7]. Approximately one-third of patients with *S. aureus* bacteremia will develop metastatic complications resulting either from hematogenous seeding of a distant site or from local extension of infection, and patients frequently have involvement of >1 site [4, 7, 8].
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Common sites of metastatic infection include bone and joints, especially when prosthetic material is present; the epidural space and intervertebral discs; heart valves; and intra-abdominal organs, such as the kidneys and spleen.

Factors associated with complicated \textit{S. aureus} bacteremia were examined in a cohort of 724 patients in whom complicated bacteremia was defined as the presence of at least 1 of the following factors: attributable mortality, metastatic infection at the time of initial hospitalization, embolic stroke, or recurrent infection within the 12-week follow-up period [4]. The strongest indicator of clinical complication was a positive result of follow-up blood culture at 48–96 h after the initial positive blood culture. Other independent predictors were community acquisition of infection, skin examination suggesting acute systemic infection, and persistent fever at 72 h after the first positive blood culture. Patients with any of these findings should be managed aggressively by ensuring both that all metastatic foci are identified and that therapy is given for an appropriate duration.

Identification of infected sites is critically important. A careful history and physical examination may reveal reports of focal pain or findings of point tenderness, joint effusions, new cardiac murmurs, or peripheral stigmata of endocarditis [9–11]. In addition, radiographic imaging studies performed on the basis of symptoms (e.g., MRI of the spine to rule out an epidural abscess or osteomyelitis in a patient with significant back pain) and an echocardiography of the heart to evaluate for endocarditis should be completed.

Many experts recommend that patients with \textit{S. aureus} bacteremia undergo transesophageal echocardiography, on the basis of several investigations that demonstrated the superior sensitivity of this diagnostic test for the detection of endocarditis among patients with \textit{S. aureus} bacteremia [9, 12, 13]. For example, one investigation found that 26 (25%) of 103 prospectively identified patients with \textit{S. aureus} bacteremia who underwent both trans-thoracic and transesophageal echocardiography had definite endocarditis on the basis of findings from transesophageal echocardiography, compared with only 7 (6.8%) when the findings from transthoracic echocardiography alone were considered [9]. In addition, transesophageal echocardiography is more sensitive than transthoracic echocardiography in identifying complications of endocarditis, such as intracardiac abscess and valvular perforation, processes that occur commonly in endocarditis due to \textit{S. aureus} [14]. Transesophageal echocardiography has 2 major purposes in the management of \textit{S. aureus} bacteremia: (1) the detection of significant cardiac complications associated with \textit{S. aureus} bacteremia and infective endocarditis in high-risk settings, such as for patients with prosthetic valves, permanent cardiac devices, prolonged bacteremia or fever, or cardiac conduction abnormalities, and (2) the intracardiac assessment of patients at low risk for endocarditis, in whom short courses of therapy are desired. In this latter setting, a transesophageal echocardiography of native valves that does not identify any findings of endocarditis makes the diagnosis of endocarditis unlikely, although other criteria, such as the absence of other metastatic foci, must be met before the decision is made to give a short course of therapy (see “Duration of antimicrobial therapy” subsection).

**Importance of eliminating the source and debulking the metastatic sites.** The removal of infected intravascular material and prosthetic devices is essential in the management of \textit{S. aureus} bacteremia, since recurrence is strongly associated with failure to do so. Among 244 hospitalized patients with \textit{S. aureus} bacteremia, 56% of the 23 patients from whom the infected foreign bodies were not removed experienced relapse of infection or death, compared with 16% of the 221 patients whose devices were removed or who did not have a device ($P<.01$) [15]. In patients with permanent pacemakers or implantable cardiac defibrillators and \textit{S. aureus} bacteremia, failure to remove the device was associated with increased risk of recurrent bacteremia or death (mortality rate, 52.4% with removal of device vs. 25% without removal) [16].

A more controversial issue concerns the role of surgery in the management of left-sided \textit{S. aureus} endocarditis. Traditionally, these patients have been given medical treatment unless they met established criteria for surgical intervention for endocarditis, including congestive heart failure, myocardial invasion, high risk for embolic complications, and failure to respond to antimicrobial therapy [17]. However, patients with \textit{S. aureus} endocarditis are likely to benefit from early surgical intervention [18–21]. In one study, early surgical intervention significantly improved survival rates among patients with \textit{S. aureus} native- or prosthetic-valve endocarditis but did not improve survival among patients with infection due to other pathogens [21]. Although the exact role, indications, and timing of early surgical intervention for \textit{S. aureus} endocarditis have yet to be determined, it is likely to be beneficial to many patients.

**Duration of antimicrobial therapy.** The duration of antimicrobial therapy depends on the extent of infection. Historically, all patients with \textit{S. aureus} bacteremia were given treatment with long courses (4–6 weeks) of therapy, largely because of concerns that endocarditis or other complications might be present but undiagnosed [22, 23]. Retrospective studies performed in the early 1990s suggested that 10–14 days of therapy was appropriate for patients with catheter-associated \textit{S. aureus} bacteremia in the absence of clinical evidence of early metastatic complications [5, 24]. In these 2 retrospective studies, late relapse occurred in 17% and 66% of patients given treatment for <10 days of therapy and in none of the patients given treatment for at least 10–15 days [5, 24]. However, it is important to note that the numbers of patients in each study were small and that...
the proportions of patients with MRSA bacteremia were not reported. A meta-analysis performed to address the efficacy of short-course therapy for catheter-associated *S. aureus* bacteremia found a pooled estimate of the rate of late complications to be 6.1% (95% CI, 2.0%–10.2%) in 11 studies [22]. However, the authors concluded that, because the studies included were not adjusted to protect against a variety of biases that could lead to inaccurate results, short-course therapy could not be recommended until a means existed to identify “low-risk” patients.

A more recent post hoc analysis of a randomized, clinical trial of patients with *S. aureus* bacteremia and infective endocarditis examined the effect of duration of therapy on outcomes [25]. Forty-six patients had catheter-associated *S. aureus* bacteremia, as well as negative findings of trancesophageal echocardiography and no other foci of infection identified, whereas 189 patients had non–catheter-associated *S. aureus* bacteremia or endocarditis. In both patient groups, success rates among patients who received <14 days of antibiotic therapy were significantly lower than those among patients who received a longer duration of therapy [25] (figure 1).

In the current era, in which patients with *S. aureus* bacteremia are older and have more serious underlying diseases and in which rates of MRSA infection are higher, these results suggest that longer courses of therapy may now be needed, even for catheter-associated *S. aureus* bacteremia. If a 14-day course of therapy is considered for catheter-associated *S. aureus* bacteremia, we believe that the patient must have the implicated catheter removed and then must meet the following clinical characteristics: (1) endocarditis should be excluded with trancesophageal echocardiography, (2) the patient should have no implanted prostheses (e.g., prosthetic valves, cardiac devices, or arthroplasties), (3) “follow-up” cultures of blood specimens drawn 2–4 days after the initial blood cultures were obtained must be negative for *S. aureus*, (4) the patient should defervesce within 72 h after initiation of effective antistaphylococcal therapy, and (5) the patient should have no localizing signs or symptoms of metastatic staphylococcal infection.

**ANTIBIOTIC OPTIONS FOR MRSA BACTEREMIA**

The antimicrobial agents currently available in the United States for the treatment of complicated and uncomplicated MRSA bacteremia are noted in table 1 and are discussed in this section.

**Agents with Established Efficacy**

**Vancomycin.** Vancomycin has been the mainstay of therapy for MRSA bacteremia and endocarditis for the past 40 years, and its use has cured countless patients. Recently, however, physicians using vancomycin have been concerned because of a general impression of its suboptimal performance for the treatment of serious staphylococcal infections. Vancomycin has been associated with slower bacterial clearance and worse response rates among patients with MSSA bacteremia and endocarditis, compared with those associated with antistaphylo-coccal β-lactam agents [36–40], and its use in the treatment of MRSA bacteremia and endocarditis has been associated with prolonged duration of bacteremia [37, 39, 41–42].

Reports of vancomycin treatment failure in patients infected with isolates that do not show evidence of vancomycin resistance by use of conventional microbiologic testing have increased over the past decade. Some patients are infected with heteroresistant MRSA, in which subpopulations of the organisms have MICs for vancomycin that are indicative of reduced susceptibility (4–32 μg/mL). For these patients, heteroresistance is associated with a high bacterial load and an initially low serum level of vancomycin, which in turn may lead to the induction or selection of heteroresistant strains and the failure of vancomycin treatment [43]. The frequency of heteroresistance among isolates in the United States appears to be low, occurring in only 3 of 22 isolates in a study of patients with persistent (≥10 days; *n* = 11) or recurrent (≥30 days; *n* = 11) MRSA bacteremia [44]. For patients with fully susceptible MRSA isolates, vancomycin MICs of 2 μg/mL are associated with sporadic clinical failure and worse clinical outcomes [45–47].

Given the association between higher vancomycin MICs and poor response to therapy, it has been hypothesized that higher doses of vancomycin may improve patient outcomes, even though no studies have demonstrated this. Nevertheless, current guidelines for the treatment of MRSA bacteremia and endocarditis recommend vancomycin troughs of 10–15 μg/mL [17]. Troughs at this level are best obtained by a vancomycin
Table 1. Currently available antibiotics for treatment of methicillin-resistant Staphylococcus aureus (MRSA) bacteremia.

<table>
<thead>
<tr>
<th>Agent type and name [reference]</th>
<th>Usual dosage* [reference]</th>
<th>Adverse effect(s)</th>
<th>Comment(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Agent with established efficacy</td>
<td></td>
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<tr>
<td>Vancomycin [28]</td>
<td>15–22.5 mg/kg iv every 12 h [26, 27]</td>
<td>“Red man” syndrome; neutropenia; thrombocytopenia</td>
<td>Slowly bactericidal; treatment failures reported despite MICs in susceptible range</td>
</tr>
<tr>
<td>Daptomycin [29]</td>
<td>6 mg/kg iv every 24 h (although not FDA approved, dosages of 8–12 mg/kg can be considered in some cases)</td>
<td>Elevated CPK level</td>
<td>Bactericidal; cannot be used for pneumonia; emergence of resistance during therapy reported</td>
</tr>
<tr>
<td>Agent for salvage therapy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Linezolid [30]</td>
<td>600 mg po/iv every 12 h</td>
<td>Bone marrow suppression, particularly thrombocytopenia; irreversible sensory motor polyneuropathy and optic neuritis associated with therapy for &gt;28 days; serotonin syndrome when coadministered with serotoninergic agents; lactic acidosis</td>
<td>Bacteriostatic; oral form with excellent bioavailability; many treatment failures have been reported</td>
</tr>
<tr>
<td>Quinupristin/dalfopristin [31]</td>
<td>7.5 mg/kg iv every 12 h</td>
<td>Myalgia and arthralgia; pain/inflammation at infusion site; thrombophlebitis</td>
<td>Bactericidal with susceptibility to both components of drug; side effects are a limitation to clinical use, but infusion-site reactions are improved with administration via central catheter</td>
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<tr>
<td>Trimethoprim-sulfamethoxazole [33]</td>
<td>10–15 mg/kg/day in 2 or 3 divided doses [32]</td>
<td>Rash; hypersensitivity reactions (e.g., erythema multiforme)</td>
<td>Bactericidal</td>
</tr>
<tr>
<td>Clindamycin [34]</td>
<td>600–900 mg iv every 6–8 h</td>
<td>Clostridium difficile diarrhea</td>
<td>Bacteriostatic; not indicated for monotherapy given history of failures in treatment of MSSA bacteremia/endocarditis</td>
</tr>
<tr>
<td>Tigecycline [35]</td>
<td>100 mg iv once, then 50 mg iv every 12 h</td>
<td>Nausea and vomiting</td>
<td>Bacteriostatic; serum levels may be inadequate to treat bacteremia; activity against anaerobes and many gram-negative organisms</td>
</tr>
</tbody>
</table>

NOTE. CPK, creatine phosphokinase; FDA, US Food and Drug Administration; iv, intravenous; MSSA, methicillin-susceptible S. aureus; po, by mouth.

* For adults with normal renal function.

dosage of 15 mg/kg every 12 h, rather than the traditional dosage of 1 g every 12 h. The ideal vancomycin trough level continues to be an area of active investigation [46, 48].

Some clinicians advocate the use of rifampin in combination with vancomycin or other agents for the treatment of S. aureus infections, because rifampin is highly active against staphylococci and has excellent tissue penetration. However, this practice has not been shown to improve outcomes in patients with MRSA bacteremia or native-valve endocarditis and has been associated with significant adverse effects, such as increased levels of transaminases and drug interactions [41, 49]. In addition, in one study [49], resistance to rifampin developed among isolates in 21% of patients with S. aureus native-valve endocarditis who were given treatment with rifampin in combination with other agents. Therefore, if rifampin is used for the treatment of S. aureus bacteremia or endocarditis, we recommend waiting until cultures of the patient’s blood have cleared S. aureus before addition of rifampin, to minimize the risk of development of resistance [50].

The use of 3–5 days of low-dose synergistic gentamicin with vancomycin for the treatment of MRSA bacteremia and native-valve endocarditis has not been shown to improve patient outcomes, although it appears to reduce the duration of bacteremia by ~1 day in patients with MSSA native-valve endocarditis [51, 52]. On the basis of these data, the American Heart Association’s guidelines for the treatment of S. aureus native-valve endocarditis consider low-dose use (e.g., 1 mg/kg intravenously 3 times daily for 3–5 days for patients with normal renal function) as optional [17]. However, the potential for nephrotoxicity with this practice may be higher than previously appreciated. In a recent randomized, controlled trial that compared daptomycin monotherapy with combination therapy (low-dose, short-course gentamicin plus either antistaphylococcal penicillin or vancomycin), patients who received combination therapy were significantly more likely to develop renal dysfunction than were those who received daptomycin [42]. On the basis of this evidence of potential harm and the failure to convincingly demonstrate clinically significant benefit, we recommend not using synergistic gentamicin, particularly with vancomycin, in the management of most cases of S. aureus bacteremia and native-valve endocarditis. If the decision is made to use synergistic gentamicin for the management of
MRSA bacteremia or endocarditis, susceptibility testing should be done, since many MRSA isolates are resistant to gentamicin. In addition, gentamicin should be used with extreme caution in patients with renal impairment and in elderly patients.

Daptomycin. Daptomycin is a concentration-dependent, bactericidal cyclic lipopeptide that was approved by the US Food and Drug Administration (FDA) in 2006 for the treatment of S. aureus bacteremia and right-sided endocarditis. In a prospective, randomized trial of 235 patients with S. aureus bacteremia or endocarditis, daptomycin at a dosage of 6 mg/kg daily was found to be as effective as standard therapy, consisting of initial low-dose gentamicin plus either vancomycin or an antistaphylococcal penicillin [42]. Eighty-nine patients (38%) had infection due to MRSA, and, in this subgroup, daptomycin was at least as effective as vancomycin (figure 2), with successful treatment outcome in 20 (44.4%) of 45 patients given daptomycin, compared with 14 (31.8%) of 44 patients given vancomycin [42]. This finding, although not statistically significant, was similar across all diagnoses, with the exception of left-sided endocarditis, which was not cured in patients in either treatment group.

Patients in the daptomycin arm of the study were more likely to experience therapy failure due to persisting or relapsing infection than were those in the comparator arm (15.8% vs. 9.6%, respectively). Of the 19 patients who experienced failure of therapy with daptomycin due to persisting or relapsing infection, 6 had isolates with emergence of reduced susceptibility to daptomycin during the study, and, of those 6 patients, 5 had MRSA infections (3 with complicated bacteremia with deep-seated infection and 2 with left-sided endocarditis) [42, 53]. The finding of the emergence of reduced susceptibility to daptomycin raises some concerns about its use for the treatment of MRSA left-sided endocarditis and bacteremia in which a deep focus of infection has not been surgically debrided, and it underscores the importance of a careful evaluation of patients with S. aureus bacteremia for the presence of endocarditis or other metastatic sites of infection. Since daptomycin dosages of up to 12 mg/kg daily for 2 weeks have been found to be safe in healthy volunteers, it has been suggested that higher doses of daptomycin should be tried for seriously ill patients [54, 55]. Whether higher doses will be more effective and will reduce the risk of the emergence of resistance is unknown. Of note, daptomycin is not indicated for patients with pneumonia, because it is inactivated by pulmonary surfactant [56].

Agents for Salvage Therapy

The use of the agents discussed below for the treatment of MRSA bacteremia or endocarditis should be considered only if a patient has experienced treatment failure with or is unable to tolerate standard agents. Consultation with an infectious disease specialist is recommended to optimize the choice of an agent or a combination of agents, as well as the dosing regimen.

Linezolid. Linezolid is a bacteriostatic oxazolidinone with activity against MRSA. It has not been systematically studied and does not have FDA approval for use for the treatment of MRSA bacteremia. Successful use of linezolid for the treatment of MRSA bacteremia has been reported [57], including in 6 (50%) of 12 patients with bacteremia or endocarditis due to S. aureus with reduced susceptibility to vancomycin who received linezolid alone or in combination with rifampin and/or fusidic acid [58]. However, many treatment failures also have been reported [59–61].

A meta-analysis of the subgroup of 144 patients with S. aureus bacteremia in 5 studies that compared vancomycin with linezolid for the treatment of nosocomial pneumonia, skin and soft-tissue infection, or other S. aureus infections showed no difference in rates of clinical cure between vancomycin and linezolid (25 [36%] of 70 cases vs. 28 [38%] of 74 cases, respectively) [62]. Among the 53 patients with MRSA bacteremia and for whom data were available for analysis, clinical cure occurred in 14 (56%) of 25 patients who received linezolid and in 13 (46%) of 28 patients who received vancomycin. However, these results must be considered hypothesis generating rather than definitive, because the patients did not have long-term follow-up and represent a small subset of patients in the clinical trials.

In addition, a recent European randomized clinical trial that compared linezolid with vancomycin, oxacillin, or dicloxacillin for the treatment of seriously ill patients with catheter-associated bloodstream infections and catheter-site infections was terminated early because patients in the linezolid arm had a higher chance of death than did those in any comparator arm.
[63, 64]. This difference was seen among patients with infections due to gram-negative organisms alone or with infections due to a mix of gram-negative and gram-positive organisms but not among patients with infections due to gram-positive organisms; thus, it is unclear whether the use of linezolid for the treatment of documented catheter-associated infections due to gram-positive organisms is effective. Nevertheless, we believe that this agent should not be used routinely for the treatment of MRSA bacteremia.

**Other potential salvage agents.** Quinupristin-dalfopristin, a streptogramin antibiotic, has been studied for salvage therapy in patients with MRSA infection, including 43 patients with bacteremia and endocarditis; the majority of bacteremia cases was associated with secondary sources, such as bone and joints or soft tissue [65]. The overall clinical success rates were 70.5% for patients with bacteremia and 54.4% for patients with endocarditis; success rates for bacteremia and endocarditis were much lower in the subgroup in which a documented bacteriological response was required for eradication (55.6% and 0%, respectively). Clinical use of quinupristin-dalfopristin has been limited by adverse events associated with its use, such as myalgia, arthralgia [66], and infusion-site reactions.

Trimethoprim-sulfamethoxazole was compared with vancomycin in a randomized control trial evaluating treatment of *S. aureus* infections in 101 injection drug users [32]. In this study, more than half of the patients had an intravascular infection that included tricuspid-valve endocarditis, thrombophlebitis, pseudoaneurysm, or bacteremia. Cure rates were 86% for patients given treatment with trimethoprim-sulfamethoxazole and 98% for patients given treatment with vancomycin, although all 47 patients with MRSA infection in both arms were cured. These results and those from a recent study that demonstrated that trimethoprim-sulfamethoxazole was rapidly bactericidal against MRSA isolates in vitro make this drug a plausible agent for a salvage regimen for the treatment of MRSA bacteremia and endocarditis [67].

Clindamycin should not be considered for monotherapy for *S. aureus* bacteremia or endocarditis, since its use for such conditions is associated with a high risk of treatment failure and relapse [68]. Tigecycline, a bacteriostatic glycyclcline antibiotic, has shown in vitro activity against MRSA; however, no clinical studies have evaluated it for use in the treatment of bacteremia or endocarditis. Peak serum concentrations of tigecycline do not exceed 1 μg/mL, which may limit its utility in the treatment of bacteremia [69].

**Future Agents**

Three lipoglycopeptide agents—dalbavancin, telavancin, and oritavancin—are currently under evaluation for the treatment of MRSA infection. Dalbavancin, which can be given in weekly doses because of its prolonged half-life, has been prospectively studied in patients with catheter-related bloodstream infections caused by gram-positive bacteria [70]. Although treatment was successful (20 [87%] of 23 patients who received dalbavancin experienced treatment success, compared with 14 [50%] of 28 patients who received vancomycin), very few patients with MRSA bacteremia were enrolled in the study. Telavancin has been shown to be effective for skin and skin-structure infections caused by MRSA [71], and a phase 2 study evaluating its use for uncomplicated *S. aureus* bacteremia has just been completed [72]. No clinical data are available regarding the use of oritavancin for the treatment of MRSA infection in humans.

Ceftobiprole and ceftaroline are broad-spectrum cephalosporins with activity against MRSA because of a high affinity for penicillin-binding protein 2a. The prospect of a β-lactam agent with activity against MRSA is intriguing, given the efficacy of β-lactam agents in the treatment of MSSA infection; however, no data regarding the efficacy of ceftobiprole or ceftaroline for the treatment of MRSA bacteremia and endocarditis are available.

**CONCLUSIONS**

The prevalences of MRSA bacteremia and endocarditis are increasing in the United States and abroad. Effective therapy requires an aggressive effort to identify and, when indicated, to debulk the source of infection and the associated metastatic foci, as well as the appropriate selection of an antimicrobial treatment regimen. Despite the active development of some promising agents, the current armamentarium for the treatment of MRSA bacteremia and endocarditis is inadequate for meeting the growing clinical need. Novel strategies and agents, both for treatment and for prevention of disease, are needed.

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