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MINIREVIEWES

Treatments and limitations for methicillin-resistant *Staphylococcus aureus*: A review of current literature

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Abstract

Methicillin-resistant *Staphylococcus aureus* (MRSA) has remained a major threat to healthcare; in both hospital and community settings over the past five decades. With the current use of antibiotics for a variety of infections, including MRSA, emerging resistance is a major concern. Currently available treatments have restrictions limiting their use. These issues include, but are not limited to, side effects, cross-resistance, lack of understanding of pharmacokinetics and clinical pharmacodynamics, gradual increment in minimal inhibitory concentration over the period (MIC creep) and ineffectiveness in dealing with bacterial biofilms. Despite availability of various therapeutic options for MRSA, the clinical cure rates remain low with high morbidity and mortality. Given these challenges with existing treatments, there is a need for development of novel agents for MRSA. Along with prompt infection control strategies and strict implementation of antibiotic stewardship, cautious use of newer anti-MRSA agents will be of utmost importance. This article reviews the treatments and limitations of MRSA management and highlights the future path.

Key words: Methicillin resistant; Methicillin-resistant *Staphylococcus aureus*; Antibiotics; Monotherapy

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Core tip: Methicillin-resistant *S. aureus* (MRSA) remains a major threat despite availability of multiple treatments. Limitations of the current anti-MRSA treatments demand more careful use of these agents. Using antibiotics in combination for MRSA treatment needs further evaluation. Multiple strategies including research and development of new antibiotics and antibiotic stewardship are necessary to contain the MRSA.

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INTRODUCTION

Staphylococci have been involved in human disease for centuries and were identified first as the cause of incurable boils. Sir Alexander Ogsto and Friedrich J Rosenbach identified, classified, and contributed to the nomenclature of *Staphylococci*[1]. *S. aureus* has since evolved as a major infectious pathogen being severely detrimental to the health of millions of patients. *S. aureus* possesses resistance mechanisms to standard agents. The first incidence of penicillin resistance was reported in 1942 which was identified to be due to inducible beta-lactamase. After introduction of methicillin in 1959, methicillin-resistant *S. aureus* (MRSA) was reported in 1961[2].

Burden of MRSA is high in middle-income countries like India. Amongst all *S. aureus* isolates, Indian Network for Surveillance of Antimicrobial Resistance group reported methicillin resistance in 41% of their isolates[3]. This high burden of MRSA in India is the cause of significant morbidity and mortality. Additionally, formation of biofilms in MRSA isolates is associated with increased virulence, pose a challenge in clinical management, and may also contribute to the development of resistance[4,5].

Current treatment strategies have limitations and improper source control may add to that, especially in severe MRSA infections. Thus, we aim to review the current treatment strategies, their limitations, and a way forward for effective management of MRSA infections.

CURRENT TREATMENT RECOMMENDTIONS FOR MRSA INFECTIONS

MRSA infections involve a wide disease spectrum. Common sites include skin/soft tissue, bone/joint, vascular line, native valve/prosthetic valve endocarditis, central nervous system shunt infections and meningitis/brain abscesses. The Infectious Disease Society of America (IDSA) provides treatment recommendations for MRSA infections[6] (Table 1).

Vancomycin dosing in MRSA

Vancomycin is one of the mainstays of therapy for MRSA infections. In adults, IV vancomycin at a dose of 15-20 mg/kg/dose (max 2 g/dose) every 8-12 h based on renal function is recommended with a loading dose of 25-30 mg/kg in seriously ill patients[7]. Therapeutic drug monitoring (TDM) is recommended to ensure adequacy of dosing, with most infections necessitating trough concentrations of 10-20 μg/mL, with concentrations at the higher end of this range (*i.e.*, 15-20 μg/mL) reserved for difficult to penetrate sites such as pulmonary and central nervous system. However, in skin and skin structure infections (SSTIs), trough monitoring may not be necessary and vancomycin in a dose of 1 mg every 12 h may be adequate[6].

LIMITATIONS OF CURRENT TREATMENTS: MONOTHERAPY

Table 1 Methicillin-resistant *S. aureus* treatment recommendations[6]

Infections	Antibiotic Treatment
Skin and soft tissue infections (SSTIs)	
Uncomplicated SSTIs	Clindamycin, trimethoprim-sulfamethoxazole (TMP-SMX), a tetracycline (doxycycline or minocycline) (A-II), linezolid
Complicated SSTIs	IV Vancomycin, Linezolid (oral or IV 600 mg twice daily), Daptomycin (4 mg/kg/dose IV once daily), Telavancin (10 mg/kg/dose IV once daily), Clindamycin (600 mg IV or PO 3 times a day)
Recurrent SSTIs	Nasal decolonization - mupirocin twice daily +/- topical body decolonization - skin antiseptic solution (*e.g.* chlorhexidine) or dilute bleach baths.
Bacteraemia and infective endocarditis	
Native valve endocarditis	Vancomycin; Daptomycin (6 mg/kg/dose IV once daily)
Prosthetic valve endocarditis	Vancomycin + Rifampin (300 mg PO/IV every 8 hour) followed by Gentamicin (1 mg/kg/dose IV every 8 hour)
Pneumonia	
Community acquired, or healthcare associated	IV vancomycin or linezolid (600 mg PO/IV twice daily) or clindamycin (600 mg PO/IV 3 times daily)
Bone and joint infections	
Osteomyelitis or Septic arthritis	Vancomycin; Daptomycin (6 mg/kg/dose IV once daily); TMP-SMX [4 mg/kg/dose (TMP component) twice daily] + Rifampin (600 mg once daily)
Device-related osteo-articular infections (early onset < 2 mo - prosthetic joint infections)	Vancomycin or Daptomycin (6 mg/kg/dose IV once daily) + Rifampin (600 mg once daily) followed by; Rifampin + fluoroquinolone / TMP- SMX / tetracycline / clindamycin
Device-related osteo-articular infections (early onset < 2 mo - spinal implant infections)	Initial parenteral therapy + Rifampin followed by prolonged oral therapy
CNS infections	
Meningitis, Brain abscess, subdural empyema, spinal epidural abscess, Septic Thrombosis of Cavernous or Dural Venous Sinus	IV Vancomycin +/- Rifampin; OR; Linezolid 600 mg PO/IV twice daily or TMP-SMX 5 mg/kg/dose IV every 8-12 hour

SSTIs: Skin and soft tissue infections; TMP-SMX: Trimethoprim-sulfamethoxazole; PO: Per oral; IV: Intravenous; CNS: Central nervous system.

An ideal anti-MRSA agent does not exist; desirable properties in anti-MRSA antibiotics include rapid bactericidal action, excellent penetration in tissue, consistent and predictable pharmacokinetics to support reliable dosing, low probability of resistance development, lower risk of side effects, and good microbiological and clinical cure rates. Biofilm formation with *S. aureus* is known and contributes to antibacterial tolerance by promoting bacterial persistence in biofilms.

Thus, identifying an ideal antibiotic which will also be active against biofilms can be a challenge. Table 2 enumerates some of the limitations of major existing anti-MRSA treatments.

Vancomycin monotherapy

Over the years of vancomycin use, resistance is now beginning to emerge in MRSA isolates[8]. Vancomycin has several limitations. First is the ratio of minimum bactericidal to inhibitory concentration (MBC: MIC ratio). A study from Sader *et al*[9] demonstrated that 20.1% of tested MRSA strains (n = 900) were vancomycin tolerant defined by MBC: MIC ratio of ≥ 32. This varied from 10.0% to 43.0% among different centres evaluated[9]. Secondly, the accessory gene regulator pathway is associated with regulation of quorum sensing and endotoxin production[10]. Development of polymorphisms or loss of function of accessory gene regulator (*agr*) pathway is associated with failure of vancomycin therapy[11]. Thirdly, the “MIC creep” phenomenon wherein there is a gradual reduction in susceptibility of *S. aureus* to vancomycin despite concentrations in the susceptible range (≤ 2 mg/L) can develop with continued use of vancomycin[8]. A study from California by Wang *et al*[12], demonstrated a gradual shift of MIC from ≤ 0.5 to 1.0 μg/mL over 5 years to vancomycin in MRSA strains (n = 6002). The proportion of isolates with MIC 1 μg/mL increased from 19.9% to 70.4% over study duration (Figure 1). Fourth concern is development of hetero-resistance to vancomycin (hVISA). In this phenomenon, from among the isolated MRSA, a subpopulation demonstrates intermediate level of vancomycin resistance, but the colony as a whole remains susceptible. The mechanisms for this remains unclear but may involve thickening of cell wall avoiding penetration of vancomycin, and alteration in *agr* pathway[10]. A study from Sader *et al*[9] involving nine hospitals in the United States showed hVISA prevalence of 13.4%. The development of hVISA was more common (45.6%) in MRSA isolates with MIC ≥ 1 mg/L. Fifth, the extensive protein binding of vancomycin leads to variable tissue

Table 2 Limitations of current anti-methicillin resistant *S. aureus* treatments

Treatment	Limitations
Vancomycin	Higher MBC: MIC ratio
	Polymorphisms or changes in gene function (*e.g. agr* pathway)
	MIC creep
	Development of hetero-resistance (hVISA)
	Variable tissue penetration
	AUC: MIC ratio
	Nephrotoxicity
	Red man syndrome
Teicoplanin	Therapeutic drug monitoring may be necessary
	Need to generate evidence on pharmacokinetics and clinical pharmacodynamics
Daptomycin	Resistance development
	Possible cross-resistance in hVISA
	Inactivation by alveolar surfactant
Linezolid	Serious adverse drug reactions *e.g.*, thrombocytopenia, optic neuropathy, peripheral neuropathy, lactic acidosis, monoamine oxidase inhibition
	MIC creep
	Limited efficacy in bacteraemia or endocarditis
TMP/SMX	High degree of resistance
	Limited efficacy in bacteraemia
	Thymidine salvage in presence of pus
Clindamycin	High rates of inducible and constitutive resistance
	Risk of *Clostridium difficile* infection
Tetracyclines	Limited utility in severe invasive infections
Tigecycline	Low serum levels with limited efficacy in bacteraemia
	Poor tissue penetration and AUC: MIC ratio
	Black box warning from the USFDA for all-cause mortality, Mortality Imbalance and Lower Cure Rates in VAP and pancreatitis
Quinupristin/ Dalfopristin	Limiting side effects like infusion-site inflammation, pain, and oedema, thrombophlebitis, arthralgia, myalgia, nausea, diarrhoea, vomiting, and rash
	Drug interactions with CYP3A4 inhibitors
Ceftaroline	Risk of agranulocytosis
Telavancin	Risk of nephrotoxicity
Oritavancin and Dalbavancin	Long half-life - delayed hypersensitivity if occurs may persist for weeks
	Clinical failure may get unnoticed if there is lack of daily follow-up evaluations
	Effectiveness in bacteraemia, pneumonia, bone and joint infections, and prosthetic infections has not been established
	Higher occurrence of osteomyelitis reported in clinical studies with oritavancin

AUC: Area under the curve; MBC: Minimum bactericidal concentration; MIC: Minimum inhibitory concentration; TMP/SMX: Trimethoprim-Sulfamethoxazole; USFDA: United States Food and Drugs Administration; VAP: Ventilator associated pneumonia.

penetration which can further be different in comorbidities like diabetes, meningitis, *etc*[10]. Sixth, the pharmacodynamics of vancomycin has been considered to be an important aspect in determining efficacy. The area under the curve (AUC) and MIC ratio of 400 or more is believed to provide therapeutic effectiveness for which vancomycin trough concentration should reach 15-20 mg/L especially in severe MRSA infections[7]. For achieving AUC: MIC ratio of 400 or more at MIC of 1 mg/L, dose of 3-4 mg/d is necessary. For MIC of 2 mg/L, achieving target AUC: MIC ratio is not possible even when higher doses are used. This can result in poor clinical and microbiological cure.

Nephrotoxicity is an important adverse effect associated with vancomycin. The reported incidence varies from nearly 14% in children to 35% in adults. In adults, trough concentration beyond 15 μg/mL is associated with increased risk of renal injury. Attaining AUC: MIC ratio of ≥ 400 is therefore harmful especially wherein the

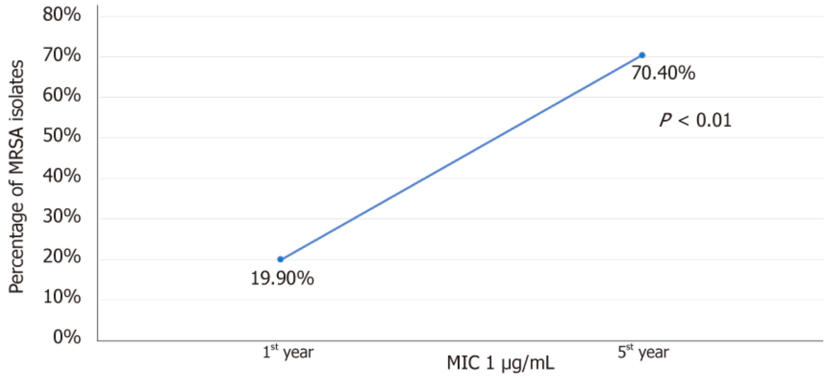

Figure 1 Minimal inhibitory concentration creep - Proportion of MRSA isolates with vancomycin minimal inhibitory concentration of 1 μg/mL[12].

isolate MIC is > 2 mg/L. In such cases, use of alternative agents is advised[13].

Daptomycin

Daptomycin, a branched cyclic anionic lipopeptide exerts bactericidal action *via* calcium-dependent modification in membrane potential causing leaking of intracellular ions and cell death[14]. It has shown similar efficacy to vancomycin in MRSA bacteraemia, endocarditis, complicated SSTIs, but not in pneumonia due to inactivation by alveolar surfactant[10]. However, point mutation in *MprF* gene (L431F substitution) identified in clinical isolates was associated with reduced negative cell membrane charge, thicker cell wall, and longer doubling time. This was found to confer increased resistance to daptomycin and vancomycin[15]. Daptomycin-non-susceptible (DAP-NS) phenotype has also been reported in MRSA infections. Among 2.4% DAP-NS strains (n = 208), one was sequence type 72 (ST72) and other four were ST5. Three of these strains were also found to be hVISA. The resistance mechanism in ST72 was charge repulsion, ST5 showed charge independent mechanisms. Changes in cell wall thickness were not found in any of the DAP-NS strains[16]. DAP-NS isolates were not sensitive to high-dose of daptomycin[17]. Increased MIC of daptomycin was found to be associated with increased mortality in patients with MRSA bacteraemia[18]. Finally, daptomycin has been associated with elevated creatine kinase and rhabdomyolysis, which is problematic in critically ill patients already at risk of such increases and sequalae thereof, such as renal injury[19].

Linezolid

Linezolid, a synthetic antibiotic, binds to ribosomal RNA on both 30S and 50S subunits and thereby inhibits protein synthesis. Additionally, it inhibits formation of initiation complex and reduce the rate of translation process[20]. Occurrence of serious adverse drug reactions like thrombocytopenia, optic neuropathy, peripheral neuropathy, lactic acidosis, and potential serotonin syndrome through monoamine oxidase inhibition have important therapeutic limitations resulting in poor adherence to therapy[21]. MIC creep with linezolid similar to that of vancomycin has also been reported[22]. Being a bacteriostatic agent, its first line use in severe invasive infections especially bacteraemia and endocarditis is avoided[10].

In persistent MRSA bacteraemia (> 7 d) despite therapy with glycopeptides like vancomycin or teicoplanin, shifting to linezolid failed to show superiority in microbiologic response, treatment success, and mortality compared to the patients who continued glycopeptides[23].

Limitations of other agents

Teicoplanin: TDM may be necessary in ascertaining the teicoplanin concentrations as daily dosages of 4 mg/kg have been reported to result in treatment failure compared to a 6 mg/kg dose. Also, trough concentrations of > 10, > 20, and > 30 mg/L have been reported to be necessary for successful treatment of *S. aureus* septicemia, MRSA endocarditis, and MRSA osteomyelitis, respectively[24]. Also, given its important role in MRSA management, there is more need to generate evidence on pharmacokinetics and clinical pharmacodynamics[24].

Trimethoprim-sulfamethoxazole (TMP-SMX): In MRSA infections, its utility is limited by development of resistance and poor efficacy[25,26]. Therefore, TMP-SMX is mainly confined to treatment of uncomplicated skin and skin structure infections from an MRSA standpoint[27].

Clindamycin: Clindamycin has bacteriostatic activity and high rates of inducible and constitutive resistance, limiting its utility for MRSA infections[28,29]. Further, risk of *Clostridium difficile* infection (CDI) might deter use of clindamycin as sole agent for MRSA as duration of exposure has been identified as an important determinant of CDI[30].

Tetracyclines: Tetracyclines such as doxycycline and minocycline are limited to uncomplicated SSTIs by community-acquired MRSA. Bacteriostatic activity and limited spectrum limits utility in severe invasive MRSA infections[10].

Fucidin (fusidic acid): Fusidic acid inhibits bacterial protein synthesis *via* action on RNA. As a topical agent, it has been used for treatment of skin infection, though there has been recent interest in rectifying its use in combination with rifampicin for infected joint prostheses. This however has been limited by significant drug-drug interactions resulting in ineffective fusidic acid exposure[31].

Tigecycline: Tigecycline has shown promise in MRSA infections equivalent to vancomycin[32]. It is effective in SSTIs and complicated intraabdominal infections[33]. However, high protein binding can result in low serum levels thereby limiting effectiveness in MRSA bacteraemia. Black box warning issued from the US Food and Drug Administration for all-cause mortality, mortality imbalance and lower cure rates in VAP and pancreatitis is a concern with tigecycline[34].

Quinupristin/Dalfopristin: Quinupristin/Dalfopristin is considered among the effective agents in *Staphylococcal* infections and may be effective in MRSA bacteremia[35]. However, occurrence of side effects like infusion-site inflammation, pain, and edema, thrombophlebitis, arthralgia, myalgia, nausea, diarrhoea, vomiting, and rash limit its use. Also, inhibition of cytochrome P450 3A4 with quinupristin/dalfopristin warrants caution with use of drugs metabolized through this enzymatic pathway[36]. Interference with other drugs metabolism may result in QTc prolongation with use of quinupristin/dalfopristin.

Ceftaroline: Ceftaroline is an effective agent for severe MRSA infections and provides clinical cure in nearly 74% cases. The major concern with this agent is development of agranulocytosis. Prolonged therapy (≥ 21 d) increases risk of leukopenia and therefore treatment with ceftaroline should be closely monitored in these situations[37].

Telavancin: It is another effective agent in MRSA with resistance to vancomycin, linezolid and daptomycin. However, nephrotoxicity is an important limitation. An increased mortality has been observed in hospital or ventilator associated pneumonia[38].

Oritavancin and Dalbavancin: These lipoglycopeptides have ultra-long half-life upwards of 346 h making them attractive as single-dose antibiotics. This and the inability to remove *via* dialysis, however also raises a concern as injury resulting from delayed hypersensitivity (if occurs) or other adverse effects may persist for weeks. It's effectiveness has not been established in bacteraemia, pneumonia, bone and joint infections, or prosthetic infections[39]. While these agents have potential for ambulatory infectious diseases management, particularly in areas of poor clinic access for frequent intravenous infusions, their utility in acute and critical care remains to be proven.

LIMITATIONS OF CURRENT TREATMENTS: COMBINATION TREATMENTS

With development of resistance and limitations of individual agents discussed above, combination therapy is suggested for most severe and invasive MRSA infections. The objectives are to broaden the coverage, prevent or reduce development of resistance, improve the effectiveness of individual agents, enhance capacity to penetrate biofilms, and to reduce toxin production[40].

Vancomycin + Rifampicin

Rifampicin is bactericidal to *S. aureus*, achieves high intracellular concentration, and penetrates biofilms. A systematic review in 2008 reported that *in-vitro* findings identified with rifampicin combination did not relate to *in-vivo* findings[41]. Another review in 2013 reported limited evidence to support adjunctive use of rifampicin in MRSA infections. The increased risk of drug interactions, adverse effects with rifampicin and development of rifampicin resistance are possibilities with use of rifampicin in combination[42]. Latter is especially important in Indian context where the rifampicin is the primary drug against tuberculous infection and burden of tuberculosis is enormous. Currently, IDSA guidelines recommend use of rifampicin in combination only in prosthetic valve endocarditis and in osteoarticular infections associated with prostheses[6]. Rifampicin should not be used as monotherapy for the treatment of MRSA infections.

Vancomycin + Gentamicin

In vitro studies have demonstrated increased bactericidal activity of vancomycin and animal studies have shown to shorten the duration of bacteraemia. Nephrotoxicity associated with gentamycin can add to the nephrotoxic potential of vancomycin[40].

Vancomycin + Quinupristin/Dalfopristin

Laboratory analyses have shown synergism with this combination[10]. However, clinical evidence is restricted to case reports.

Daptomycin + Rifampicin or Gentamicin

Similar to other combination treatments, the evidence from *in-vitro* studies shows synergistic activity with this combination as well[43,44]. However, clinical evidence is restricted to case reports[45-47]. In time-kill study, addition of gentamicin rather than rifampicin has been shown to provide synergism with daptomycin[48].

Daptomycin + Beta-lactams

With beta-lactams active against MRSA (*e.g.* ceftaroline), daptomycin has shown synergistic activity[49]. In MRSA strains from endocarditis, ceftaroline in addition to daptomycin also cleared daptomycin non-susceptible strains. Daptomycin at 6 mg/kg every 48 h was and ceftaroline at 200 mg every 12 h enhanced bacterial killing[50]. The finding from this single study demands further careful determination of optimal dosing regimen for effective utilization of active agents like ceftaroline. Another study reported rapid clearance of bacteraemia with addition of high dose nafcillin or oxacillin (2 mg IV every 4 h) to high-dose daptomycin (8-10 mg/d) in 7 cases of vancomycin and daptomycin resistant MRSA[51]. Though this points to enhanced efficacy of beta-lactams, further evaluation in prospective studies is necessary.

Daptomycin + Linezolid

An *in-vitro* study involving pharmacokinetic/pharmacodynamic model of biofilm for 3 d showed greater activity with combination of daptomycin and linezolid than either agent alone suggesting potential for biofilm associated MRSA infections[52]. However, there is lack of clinical studies to substantiate the findings of *in-vitro* studies.

Linezolid/Tedizolid + Rifampicin

In combination with rifampicin, time kill studies of linezolid did not show synergism or antagonism but linezolid prevented emergence of mutant resistance in rifampicin[53]. One major issue with this combination is that rifampicin can reduce the linezolid concentration which can be well below the MIC90 for *Staphylococci* and effect may persist longer than 3 wk even after withdrawal of rifampicin[54,55]. With tedizolid and rifampicin combination, activity is increased but synergy observed was not found to be universal[56].

Trimethoprim/Sulfamethoxazole + Rifampicin

Poor efficacy, development of resistance and side effects and drug interactions as mentioned above in their individual discussion, render this regimen redundant.

Triple antibiotic combination

The evidence is very limited for effectiveness and utility of triple drug combinations including beta-lactams, aminoglycosides, and vancomycin, barring isolated case reports[57].

FUTURE DIRECTIONS

Despite availability of multiple treatment options for MRSA, burden of MRSA remains substantial. While choosing an effective therapeutic strategy, multiple factors play a vital role in antibiotic selection. Development of resistance with anti-MRSA antibiotics has led to the use of antibiotics in combinations. There is no concrete evidence as to decide on specific combination neither there are any comparative data with different combinations. Success of new molecules like ceftaroline, tedizolid, and plazomicin should stimulate further research and development of new anti-MRSA therapies.

A number of anti-MRSA molecules are in different phases of development. But, to identify truly novel anti-MRSA agent that will act on new targets in the pathogen, there is need to invest further.

CONCLUSION

Current therapeutic management of MRSA is mainly focused on vancomycin and it still remains an effective therapy either alone or in combination. However, development of intermediate level of resistance, MIC creep, adverse effects, and vigilant TDM have been path-blockers for the sole use of vancomycin in MRSA. At present, selecting an individual agent that can provide the best synergy and minimal adverse effects remains the frontline therapeutic option against MRSA. Stimulating and supporting new and ongoing research for development of effective anti-MRSA therapies and implementation of infection control strategies are of urgent necessity. A collaborative action from policy makers, prescribers, and consumers is essential to safeguard the judicious use of newer agents in the management of MRSA infections.

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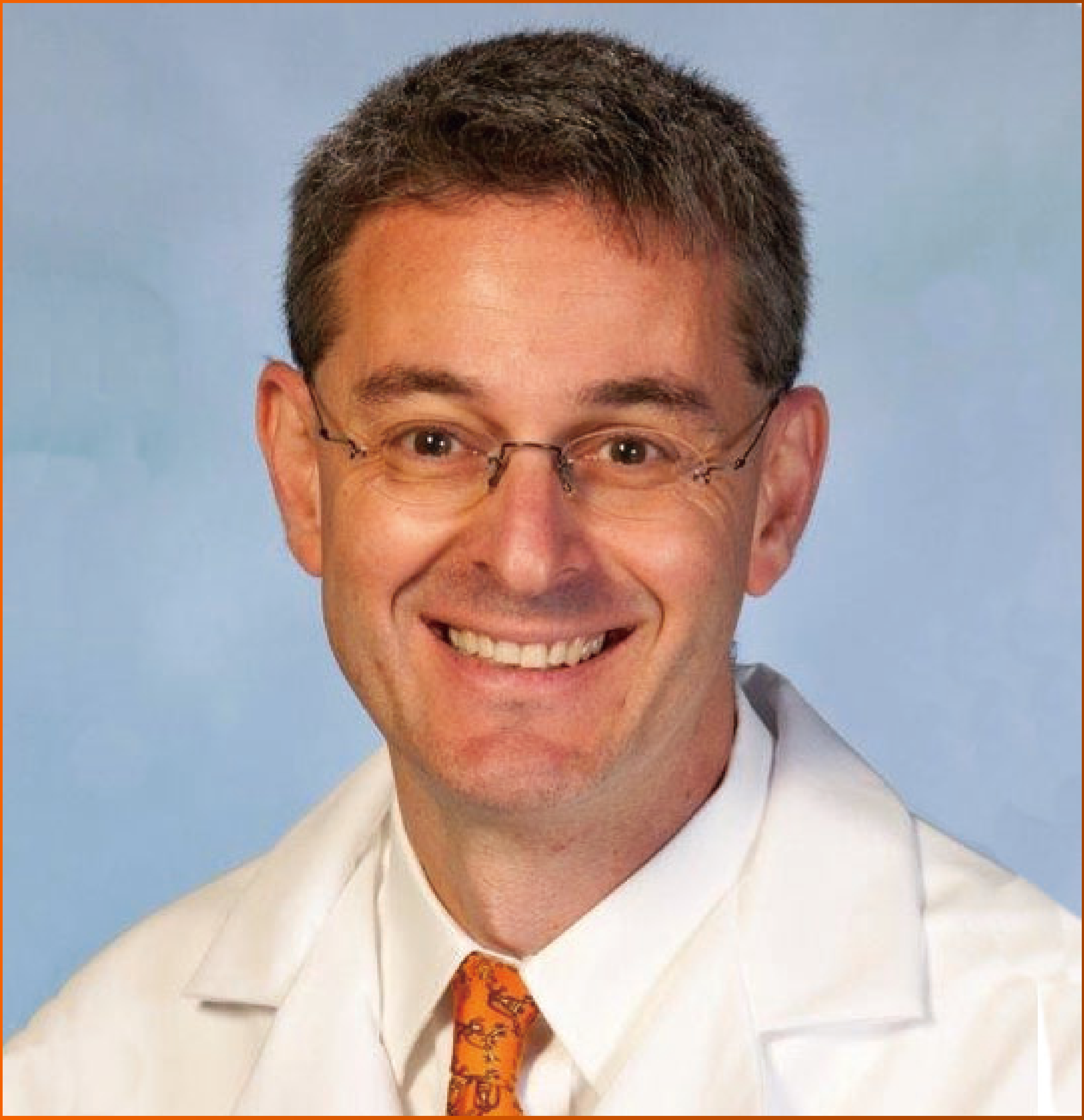

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EDITORIAL

Towards the worldwide eradication of hepatitis B virus infection: A combination of prophylactic and therapeutic factors

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Abstract

Hepatitis B virus (HBV) is still a global health problem, mostly because of the intermediate/high rates of HBV chronic carriers living in most Asian, African and eastern European countries. The universal HBV vaccination of new-borns undertaken in most nations over the last 3 decades and effective HBV antiviral treatments (nucleos(t)ide analogue with high genetic barrier to viral resistance) introduced in the last decade have shown their beneficial effects in inducing a clear reduction of HBV endemicity in the countries where they have been extensively applied. Great hopes are now placed on new antiviral and immunotherapeutic drugs that are now at an advanced stage of study. It is in fact already conceivable that the synergistic use of new drugs targeting more than one HBV-lifecycle steps (covalent closed circular DNA destruction/silencing, HBV entry inhibitors, nucleocapsid assembly modulators targeting viral transcripts) and of some new immunotherapeutic agents might eliminate the intrahepatic covalent closed circular DNA and achieve the eradication of HBV infection. In spite of this, a strong effort should be given to extensive educational and screening programs for the at-risk population and to the implementation of HBV vaccination in developing countries.

Key words: Hepatitis B virus; Chronic hepatitis B infection; Hepatitis B virus prevention; Vaccination

Core tip: The spread of hepatitis B virus (HBV) infection has recently decreased in several countries due to the universal HBV vaccination of new-born babies and to the extended use of HBV nucleos(t)ide analogues with high genetic barrier to viral resistance. However, HBV vaccination and extensive educational and screening programs for at risk populations should be implemented predominantly in developing

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countries. New drugs targeting more than one HBV-lifecycle steps and of some new immunotherapeutic agents are under investigation with the aim of obtaining the clearance of hepatocytic covalent closed circular DNA through their synergistic action.

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INTRODUCTION

Despite the universal vaccination campaigns against hepatitis B virus (HBV) undertaken in most nations over the last 3 decades, HBV is still a global health problem with about 257 million people chronically infected, at least 40% of world population being an HBV contact or carrier[1]. About half million deaths per year are due to complications of advanced chronic hepatitis, and 340000 are due to hepatocellular carcinoma (HCC)[2,3].

The level of HBV endemicity, evaluated on the prevalence of subjects with HBV chronic infection, varies significantly from one country to another and in some countries from one geographic area to another. The rate of hepatitis B surface antigen (HBsAg) chronic carriers ranges from 0.5% to 2% (low endemicity) in most countries of North and South America, Western and Central Europe, Australia and northern Africa, from 2.1% to 8% (intermediate endemicity) in most eastern European and central Asian nations and above 8% (high endemicity) in some eastern Asian and sub-Saharan African countries and in Alaska[4,5]. Ten HBV genotypes (HBV-GT) have been identified at present, and their geographical distribution is of great epidemiological interest because it is conditioned by both local diffusion and migratory flows[4-8]. HBV-GT-A predominates in North America, eastern Africa and northern/western Europe[9,10], HBV-GT-B and -C in Asia[11], HBV-GT-D in countries facing the Mediterranean sea[11-21], in the Middle-East and in southern Asia[5], HBV-GT-E in central-western Africa[4,19,22], genotype F in southern and central America[5], HBV-GT-G in France and in some region in the United States[5], HBV-GT-H in Latin America[5] and HBV-GT-I and -J in eastern Asia[5,10]. However, several cases of acute hepatitis related to HBV-GT typical of geographic areas with high or intermediate endemicity have occurred in western countries hosting migrant populations from those areas[6,23-32].

Promiscuous unprotected sexual activity is a main risk factor for acquiring HBV infection worldwide, while other main risk factors have a different impact in different geographical areas. In fact, HBV infection is most frequently acquired at birth from hepatitis B e-antigen (HBeAg) positive mothers or through household contacts in early childhood in countries with intermediate/high endemicity, with a high rate of progression to chronicity that helps to maintain the high levels of endemicity. On the other hand, in countries with low HBV endemicity like Western Europe, North America and Australia, the major risk factor for acquiring HBV infection is the sharing of needles and other equipment between intravenous drug users[33,34], which causes the infection to remain confined to this at-risk population.

Acute Hepatitis B onset occurs 45-180 d after HBV has been acquired with some constitutional symptoms followed by dark urine and jaundice in less than 10% of children aged less than 5 years and in more than 50% of adults. The symptomatic phase of the illness lasts about 15 d and even longer in adults. Immune-complexes related extrahepatic manifestation (membranous glomerulonephritis, necrotizing vasculitis and papular acrodermatitis) are rare events[35,36].

Fulminant hepatitis is due to an overreaction of the immune system; it develops in about 1% of the patients[37,38], leading to death in about three-quarter of them and requiring liver transplantation. The age-related difference in the clinical outcome of acute HBV infection is striking[39]. In fact, more than 95% of adult patients spontaneously recover and develop a long-lasting immunological protection against reinfection, provided by seroconversion to hepatitis B surface antibody (anti-HBs) and by cellular immunity, while only 2%-5% progresses to chronicity[40]; instead, 90% of new-borns and 30% of children aged 1-5 years progresses to chronicity[41]. The difference in the outcome between children and adults is based on the degree of reactivity of the cellmediated immunity, recognized as the true engine for eliminating HBV infection, low in new-borns and children and normal or high in teenagers and adults[42]. Risk factors for a more severe clinical course have been recognized in being a young adult or of female sex, in coinfection with hepatitis D virus (HDV), hepatitis C virus (HCV) or human immunodeficiency virus (HIV), in alcohol abuse and in intravenous drug use[43-53].

Once a patient has recovered and serum HBsAg cleared, a residual HBV replication persists, as evidenced by the detection of small amount of HBV-DNA inside the hepatocytes, a virologic condition named occult B infection[54-63].

Depending on the entity of HBV replication and on the effectiveness of the immune-response, chronic infection has a variable clinical presentation broadly grouped in either an asymptomatic stable HBsAg carriage, chronic hepatitis or liver cirrhosis with or without HCC[23,64,65]. Patients with chronic hepatitis progress to cirrhosis at a rate of 1%-5% per year[66]; and, in turn, HBV cirrhotic patients develop HCC at a median rate of about 3.7% per year[24,67-70].

The wide spread of HBV infection, its frequent evolution into chronicity with the possibility of developing liver cirrhosis and HCC and its progression to death in patients who do not undergo a successful liver transplantation have called for extensive HBV vaccination campaigns and effective therapeutic measures.

USE OF HBV VACCINATION IN REDUCING THE SPREAD OF HBV INFECTION

Introduced in 1982, HBV vaccination is the most effective measure to prevent HBV infection[71]. One dose of the currently used HBV vaccine contains 5 μg of recombinant HBsAg produced in in yeast *Saccharomyces cerevisiae* with recombinant DNA technology and adsorbed on amorphous aluminium sulphate hydroxyphosphate. Hepatitis B vaccine is given as a three-dose series. Post-vaccination testing is required, and a person with suboptimal response (serum titters of antibody to HBsAg < 10 mIU/mL), like immunocompromised persons and those with advanced renal disease[71], should receive a fourth dose or be revaccinated[71-75]. HBV vaccination provides a protective production of antibody to HBsAg > 10 mIU/mL in about 95% of subjects and is more effective in children and young adults than in adults over 40. In adults, about 90% reach anti-HBs protective levels, and females respond to HBV vaccine better than males[76,77]. It has also been documented that vaccine induced anti HBV immunity lasts at least 3 decades[78-81] and is presumably life-long.

HBV vaccination had been initially recommended for infants born to HBV-infected mothers and for adults at risk for acquiring HBV infection (sexual partners or household contacts of HBsAg-positive persons, subjects with more than one sexual partner, males having sex with males; injection drugs users; incarcerated persons; health care workers and public safety employees at risk for exposure to blood or blood-contaminated body fluids; adults with diabetes mellitus; persons with advanced renal disease, persons with chronic liver disease not HBV-related, pregnant women who are at risk during pregnancy, HIV-infected persons; international travellers to regions with high or intermediate levels of HBV endemicity and any adult seeking protection from HBV infection)[71-73]. HBV vaccination offered to young or adult subjects at risk of infection has not been particularly effective, since it is estimated that only 20%-30% of those in need have accepted vaccination, and, consequently, no evident reduction in HBV endemicity has been obtained. Worthy of mention, the prevalence of acceptance of HBV vaccination in healthcare workers (HCWs) ranges from 15% in African countries to nearly 75% in the United States[82-87]. In addition, half of HBV vaccinated subjects completed the vaccination schedule, resulting in a lower production of anti HBs and, consequently, in a risk of lower level and lower duration of protection. Several reasons contribute to the poor acceptance of a necessary vaccination, like little information on the usefulness or effectiveness of the vaccine, poor confidence in its effectiveness, fear of adverse reactions, lack of availability and cost of vaccine in some countries[88-91]. That being the case, countless decades would have been necessary to reach the worldwide eradication of HBV infection.

A more effective vaccination strategy was therefore chosen in most countries. The universal vaccination of all new-born babies has shown beneficial effect wherever it has been correctly applied, with a clear reduction of the levels of HBV endemicity. Worthy of mention, prior to the introduction of the national HBV vaccination program in 1984, approximately 15%-20% of the Taiwanese adult population were HBsAg positive[92,93]. The effectiveness of this program was demonstrated by the significant decrease in the incidence rate of HBV chronic carriers and the rate of mother-to-child HBV vertical transmission[94-98]. An example of this favourable effect is the strong decrease in the rate of HBsAg positivity in university students of this country, which was decreased from 9.7% in those born before 1974 to less than 1% in those born after 1992[99].

After an 8-year application of universal HBV vaccination of new-borns in Saudi Arabia, the HBsAg prevalence in children aged 1-12 years dropped from 6.7% in 1989 to 0.3% in 1997[100]. In Gambia, a clear reduction in newly acquired HBV infections, HBsAg carrier rate and HBV-related mortality was observed 14 years after the introduction of HBV vaccination in children[101]. Also, in Alaska, the implementation of HBV vaccination induced a decrease in the HBsAg carrier rate[102].

The impressive reduction in HBV endemicity in countries where universal vaccination against HBV has been applied is in stark contrast to the persistence of high HBV endemicity persisting in developing countries where HBV vaccination programs have been poorly applied. An example of this contrast was recently observed by us in a cohort of migrants who came from countries of sub-Saharan western Africa to Europe. In this cohort, migrants born in western African countries where HBV vaccination has been not sufficiently applied showed an HBsAg positivity ranging from 9.7% to 22.5%, whereas those born in Nigeria showed the beneficial effects of a universal HBV vaccination of new-borns well applied from 2 decades. Those from Nigeria had a global rate of HBsAg positivity of 4.1% and age-related rates of 3.5% in subjects less than 25 years, 4.1% in those aged 26-40 years and 17.9% in those aged over 41, a cohort effect underscoring a tendency of HBV endemicity towards reduction.

Concluding on this point, there remains much to be done to get a proper extended application of all the possible prophylaxis measures aimed at reaching the eradication of HBV infection. Firstly, HBV universal vaccination programs of new-born babies should be extensively applied and never discontinued in all world countries. Secondly, extensive information campaigns will have to be undertaken so that people at risk of HBV infection may receive instructions on how this infection spreads and how to prevent it and then be encouraged to undergo screening and, if exposed to infection, to HBV vaccination[103]. Thirdly, a permanent program of screening and vaccination of migrants from areas of intermediate or high endemicity must be applied in all host nations. These remedies, however, will not be enough as there are, as of now, some hundreds of millions of infected subjects able to transmit the infection worldwide.

Mainly due to individual factors (*e.g.*, immunogenetic conditions, advanced age, obesity, smoking or chronic diseases such as celiac disease, diabetes, HIV infection, advanced kidney disease, autoimmune diseases), 5%-10% of the adult population does not respond or responds insufficiently to anti-HBV vaccine (anti-HBs titres < 10 mIU/mL). For non-responders, the pathway to improve the immunogenicity of the vaccine adjuvant has been followed and an oligonucleotide of the cytosine phospho-guanosine, a Toll-like 9 agonist receptor potent stimulator of the vertebrate innate immune system, has been used as an adjuvant for a recombinant two-dose hepatitis B vaccine (administered at wk 0 and 4). Recently approved for use in adults, initial data have shown a higher percentage of protected subjects compared to alum-adjuvanted vaccines[71,73,74,79,81].

USE OF THE ANALOGOUS NUCLEOS(T)IDES IN ABOLISHING THE INFECTIVITY OF HBV CHRONIC CARRIERS

The pharmacological suppression of HBV replication in HBV chronic carriers is another opportunity for health authorities to undertake an effective path towards the eradication of HBV infection. Although a sustained eradication of intrahepatic covalent closed circular DNA (cccDNA) as well as integrated cccDNA is currently not feasible, long term suppression of viral replication with HBV DNA serum clearance may be easily obtained with long-term administration, maybe life-long, of high genetic barrier to resistance nucleos(t)ide analogues tenofovir disoproxil fumarate (TDF), entecavir (ETV) or tenofovir alafenamide (TAF). These drugs have improved the outcomes of HBV-related chronic hepatitis by lowering the rate of transition to liver cirrhosis and reducing the risk of HCC development, but the clearance of serum HBsAg is only achieved in a small portion of treated patients[104].

Treatment with interferon in its pegylated form (PEG-IFNα), extensively used as monotherapy in the past, will become obsolete because of its poor efficacy and of the frequent occurrence of badly endured and sometimes severe adverse reactions during long-term treatment. In HBsAg/HBeAg positive patients, the seroconversion to anti-

HBe was obtained only in 29%-32% of patients after 1-year PEG-IFN treatment and to anti-HBS only in 3%-5%[105,106]. In HBeAg-negative patients, a favourable response with stable normalization of serum alanine aminotransferase and serum HBV DNA reduced below 400 copies/ml was obtained only in 15% of cases treated for 12 mo, with HBsAg loss in about 4%[107].

The first generation nucleos(t)ide analogues lamivudine, adefovir and telbivudine have become obsolete because their low genetic barrier is unable to prevent the formation of viral resistant strains. In addition, the sequential use of ETV to treat lamivudine resistance increases the risk of ETV resistance. A switch to tenofovir has been demonstrated to be effective in patients with confirmed lamivudine, telbivudine, adefovir or ETV resistance.

Long-term therapy with nucleos(t)ide analogues with high genetic barrier to viral resistance (ETV, TDF) is required to obtain a stable suppression of HBV replication[108]. These drugs are highly recommended as first-line therapy because HBV resistance is a rare event in nucleoside-naïve patients during a 5-year treatment with ETV and no resistance with a 7-year treatment with TDF[109]. Histological evaluation after a long-term treatment with ETV or TDF showed an impressive improvement in liver necroinflammation and fibrosis scores in most patients[110,111]. In addition, compared with controls, a significant reduction in the incidence of HCC has been observed in HBsAg positive cirrhotic patients undergoing a long-term therapy with ETV or TDF[112-117].

A 5-year ETV treatment induced HBV DNA serum clearance in more than 90% of HBeAg positive patients with chronic hepatitis[118], and a similar rate was obtained with TDF[109]. Seroconversion to anti-HBe was obtained in about 20% of patients after 1-year of ETV or TDF therapy[118,119].

HBsAg loss occurred in 11.8% of HBeAg-positive patients after 7 years of TDF treatment, more frequently in Caucasians than in Asians[109]. Consolidation therapy is recommended after the loss of HBsAg[120].

TAF is an oral second-generation prodrug of TDF with a high genetic barrier to viral resistance. Although TDF and TAF show similar rates of cure[121-123], switching from TDF to TAF provides improvement in bone density and renal function, a favourable effect in a log-term treatment[124,125].

Currently, new drugs are being tested that are aimed at eradicating chronic HBV infection: HBV entry inhibitors, capsid inhibitors, short interfering RNA and targeting cccDNA[126-132]. Briefly, a blockade of HBV entry in experimental cells was obtained using a pre-S acylated peptide of the large HBsAg protein, and further studies on chronic HBV and HDV infection are ongoing[133]. In some experimental models it has been shown that the AB-423 capsid inhibitor is able to direct erroneously capsid assembly to inhibit pregenomic RNA encapsidation and consequently to reduce cccDNA concentrations in liver cells[128-138].

Several antisense short interfering RNAs targeted towards HBsAg transcripts have achieved mRNA degradation in pre-clinical or clinical evaluation. Among these, ARC 520 is of interest. It is directed towards HBV RNA transcripts and reduces the synthesis of HBV DNA and viral proteins[138]. Regarding cccDNA targeting, several DNA cleavage enzymes have been tested in experimental models and preliminary data seem encouraging[132].

In addition, experimental studies are underway to develop new drugs or therapeutic vaccines that may regulate the immune-system dysfunction in hepatitis B[139-150].

CONCLUSION

The universal HBV vaccination of new-borns has produced significant results in countries where, responding to the demand of the World Health Organization, it has been correctly applied. Nevertheless, in several developing countries, socio-economic reasons have impaired the application of HBV vaccination, delaying the achievement of a global reduction in HBV endemicity. Also, the vaccination on a voluntary basis of adults at risk of HBV infection has failed to contribute to the project of a progressive reduction of the levels of endemicity. This being the case, we believe that an additional 2-3 decades of extensive application of the universal HBV vaccination will be needed to achieve a substantial reduction of HBV spread.

Another aspect of the ambitious project to eradicate HBV infection is the extensive information campaign on how to acquire the infection and how to prevent it. So far, information campaigns have been occasional and limited to certain risk categories in many countries and therefore have not substantially contributed to the reduction of HBV endemicity.

Good news comes from the therapeutic management of chronic hepatitis B. In fact, the new nucleos(t)ide analogues (ETV, TDF and TAF) that effectively suppress HBV replication may be used for a very long period with no risk to induce viral resistance. In addition, new drugs for the complete eradication of HBV replication, thus ensuring a complete cure, are currently being developed and will be very likely be available in the next decade.

The set of data reported here suggests that prolonged extended application of the universal HBV vaccination of new-borns and the utilization of the high genetic barrier to resistance nucleos(t)ide analogues and, in the near future, of some drugs today in experimental development will allow for, in the next 2-3 decades, a strong reduction of HBV endemicity and possibly the eradication of HBV infection.

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CASE REPORT

Serratia marcescens and other non-AACEK GNB endocarditis: A case report and review of literature

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Abstract

BACKGROUND

Non-*Aggregatibacter aphrophilus, Aggregatibacter actinomycetemcomitans, Cardiobacterium hominis, Eikenella corrodens, Kingella spp*. (non-AACEK) gram-negative bacilli (GNBs) are an infrequent and challenging cause of endocarditis associated previously with mainly intravenous drug use. Currently, this pathology has increasingly become a healthcare-associated issue. Current guidelines do not clearly define the management of non-AACEK GNB endocarditis due to a lack of prospective trials. We review characteristics, outcomes and treatment of non-AACEK GNB endocarditis, in particular *Serratia marcescens* endocarditis.

CASE SUMMARY

We describe the case report of a 46-year-old man who presented to the emergency department with high-grade fever and a purulent exudate on an intracardiac device site. *Serratia marcescens* mitral valve endocarditis as a consequence of complicated generator pocket infection was diagnosed. The patient was treated with complete device removal and a long course of broad-spectrum antibiotics for 6 wk after surgery with intravenous piperacillin-tazobactam and ciprofloxacin, which was later switched to oral ciprofloxacin and

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sulfamethoxazole-trimethoprim. The patient had complete resolution of symptoms and inflammatory parameters at the end of the treatment and at follow-up.

CONCLUSION

Long-term dual-antibiotic therapy containing a beta-lactam is indicated for most non-AACEK GNB endocarditis, whereas valve surgery may not be necessary in all patients.

Key words: Non-AACEK gram-negative bacilli endocarditis; *Serratia marcescens*; Healthcare-associated; Intravenous drug use; Case report; Dual-antibiotic therapy

Core tip: While gram-negative bacillus (GNB) Non-*Aggregatibacter aphrophilus, Aggregatibacter actinomycetemcomitans, Cardiobacterium hominis, Eikenella corrodens, Kingella spp*. (non-AACEK) endocarditis has been associated with mainly intravenous drug use, the role of healthcare-associated contact has been highlighted in two prospective observational studies. Our aim was to review the characteristics and management of non-AACEK GNB endocarditis, especially in the case of *Serratia marcescens*. This bacterium has become a rare cause of endocarditis, but community acquisition still has an important role in this disease. We discuss treatment options, supporting long-term dual-antibiotic treatment as the preferred option for most patients with non-AACEK GNB endocarditis, whereas valve surgery does not seem to be necessary in all patients.

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INTRODUCTION

Gram-negative bacillus (GNB) non-*Aggregatibacter aphrophilus, Aggregatibacter actinomycetemcomitans, Cardiobacterium hominis, Eikenella corrodens, Kingella spp*. (non-AACEK) bacteria are a rare cause of infectious endocarditis. The International Collaboration on Endocarditis (ICE) prospective study from Morpeth *et al*[1]. showed that among 2761 patients with definite endocarditis, only 49 (1.8%) had endocarditis due to non-AACEK GNB[1]. The recent Italian Endocarditis Study (SEI) from Falcone *et al*[2] reported a slightly higher incidence of 3.3% (58 patients) among 1722 patients studied. The most prevalent bacteria found in these observational prospective studies about GNB non-AACEK endocarditis were *Escherichia coli* (29 and 31%), *Pseudomonas aeruginosa* (19 and 22%) and *Klebsiella pneumoniae* (10%). In contrast, *Serratia marcescens* is less common and represents between 3.5% and 8% of endocarditis pathogens[1,2].

Historically, in the 1970s and 1980s, GNB non-AACEK endocarditis was associated with nosocomial exposure and IVDU[3-7]. *Serratia marcescens* was a predominant cause of community-acquired endocarditis, as highlighted by Mills *et al*[3] and Cooper *et al*[4]. In their reviews, individuals with a history of IVDU accounted for 88 and 89%, respectively, of patients with *Serratia marcescens* endocarditis. Currently, GNB non-AACEK endocarditis has become a healthcare-associated (HCA) issue[1,2]. Morpeth *et al*[1] were first to describe that association in a prospective observational study: 57% of non-AACEK GNB endocarditis cases were HCA (nosocomial and non-nosocomial), predominantly in individuals undergoing non-dental invasive procedures and in patients with intracardiac devices (ICDs). Falcone *et al*[2] reported that 44.7% of GNB non-AACEK endocarditis cases were HCA (nosocomial and non-nosocomial), but for most patients, the acquisition was community acquired (55.2%), which was again associated with the presence of an ICD (OR = 3.6) but also with immunosuppression (OR = 5.16). In both studies, the most important source of infection was the genitourinary tract[1,2].

Currently, mortality related to GNB non-AACEK endocarditis has decreased from between 30% and 68% in the 1980s[3-7] to between 13% and 24%[1,2]. Cardiac valve surgery is not associated with better outcomes except for in those individuals presenting with complications (heart failure, cardiac abscess, fistula, dehiscence and valve perforation). The multidrug resistance patterns of the bacteria seem to play an important role in the in-hospital mortality rate (HR = 21.89)[2].

European[8], American[9] and British[10] guidelines do not specifically define treatment of GNB non-AACEK endocarditis due to a lack of prospective studies. They recommend long-term (6 wk) combined bactericidal antibiotic treatment associated with surgery[8-10]: Beta-lactams should be the cornerstone of the antibiotic regimen and combined with aminoglycosides (AGs). Sulfamethoxazole-trimethoprim or fluoroquinolones (FQs) could also be added to beta-lactams or reinforce the combined regimen with a BL and an AG[8,9]. In the ICE study[1], most patients (57%) were treated equally with a combination of a BL and either an AG or FQ. Eight percent of the patients were treated with a triple antibiotic therapy, whereas 14% received a monotherapy regimen consisting of a BL[1]. In the more recent Italian Endocarditis Study (SEI)[2], 30% of the patients were treated with BL monotherapy, while 61% received combination therapy consisting of a BL and an AG in 34% and BL with FQ in 18%. Triple therapy and regimens containing sulfamethoxazole-trimethoprim were administered in only 4% of cases[2]. In both studies, there was no comparison of mortality with regard to each antibiotic regimen chosen, but combination therapy did not show superiority compared to monotherapy[2].

Serratia marcescens is a gram-negative rod belonging to the family *Enterobacteriaceae*. This ubiquitous bacterium is a human opportunistic pathogen and has been implicated in septicaemia, ventilator-associated pneumonia, meningitis, endocarditis, and urinary tract and HCA wound infections[1,2,11-13]. This bacterium has the ability to proliferate in moist environments (such as disinfectants, intravenous solutions and different medical materials) and has therefore been responsible for nosocomial outbreaks[14]. *Serratia marcescens* has multiple pathogenicity and virulence factors: adhesins, lipopolysaccharides, fimbriae and siderophores, which facilitate host penetration, adherence to solid surfaces and resistance to serum killing[13,14]. *Serratia marcescens* carries a chromosomally encoded AmpC-type beta-lactamase that confers inducible resistance to beta-lactams when exposed to them[12]. It then readily hydrolyses penicillins and cephalosporins, including those of the third generation, and is responsible for the reduced activity of other beta-lactams[12]. This pathogen is also capable of acquiring mobile genetic elements encoding resistance determinants, such as extended-spectrum beta-lactamases or metallo beta-lactamases[14].

Since the 1990s, the English literature has only reported 15 cases of *Serratia marcescens* endocarditis in adults: In addition to 6 cases reported in the prospective studies discussed earlier[1,2], 9 case reports, including our case, have been published (Table 1). The mean age of the patients in the case reports is 53 years. In 4 of the 9 patients (44.4%), endocarditis was HCA[15-17]. It was community-acquired in the remaining 5 patients (55.6%), mainly due to IVD use[12,18-21]. Other risk factors identified were immunosuppression (44.4%), venous catheter presence (33.3%), recent cardiac surgery in one case and ICD presence in 2 patients. All patients were treated with combination beta-lactam-containing antibiotic regimens except for 3 patients treated with monotherapy: One patient received ceftriaxone, another meropenem, and the last was treated with ciprofloxacin. Only 2 patients benefited from valve replacement surgery. The patient with ICD-related endocarditis and our patient underwent percutaneous pacemaker extraction. Mortality in this series of case reports was 22%, with death attributed to massive heart failure with surgery contraindicated due to the presence of cerebral abscesses in one case and the second due to cerebral haemorrhage.

CASE PRESENTATION

A 46-year-old man was admitted to the cardiology unit for suspicion of an intracardiac device (ICD) infection 4 mo after implantation. He suffered from congenitally corrected transposition of the great arteries with complete atrioventricular bloc, for which a bicavitary pacemaker had been placed in 1994. The patient developed cardiac insufficiency a few months before admission with non-sustained ventricular tachycardia. For these reasons, the pacemaker was upgraded into a defibrillator with resynchronisation. One month after that surgery, an incision site infection was diagnosed. Microbiological culture of the sample was positive for *Serratia marcescens*, and he was treated with local wound care.

Four days prior to his admission in our hospital, the patient presented to the emergency department of another hospital with high-grade fever (39°C), chills and a

Table 1 ***Serratia marcescens*** **endocarditis in adults since 1990**

Ref.	Age (yr)	Risk factors	Acquisition	Treatment and duration (wk)	Valve surgery	Outcome (follow-up)
Ena *et al*[15], 1991	29	IVDU	CA	Ciprofloxacin (4 IV + 1 po)	Y	Survived (13 mo)
Körner *et al*[18], 1994	50	Lymphoma, chemotherapy, CVC	HCA	Azlocillin/gentamycin (6 IV)	N7	Survived (5 mo)
Baggish *et al*[19], 2007	43	Splenectomy	CA	Cefepime (6 IV) and gentamycin (2 IV)	Y	Survived (1 yr)
De Silva *et al*[20], 2009	67	ICD	CA	Meropenem and gentamycin (NM), then ciprofloxacin (2 po)	N (ICD extraction)	Survived (6 mo)
Hadano *et al*[16], 2012	85	Diabetes, corticosteroids	HCA	Ceftazidime (6 IV) and gentamycin (5 d)	N	Died
Lyall *et al*[17], 2013	65	Post-Bentall + coronary bypass surgery	HCA	Meropenem and ciprofloxacin and gentamycin (NM)	N	Survived
Phadke *et al*[12], 2016	46	IVDU, HIV	CA	Meropenem (NM)	N	Died
Meyer *et al*[21], 2018	42	IVDU	CA	Ceftriaxone (6 IV)	Y	Survived
Current case, 2018	46	ICD	HCA	Piperacillin-tazobactam IV and ciprofloxacin po (5), then ciprofloxacin and trimethoprim/sulfamethoxazole (3 po)	N (ICD extraction)	Survived (6 mo)

IVDU: Intravenous drug use; CA: Community acquired; IV: Intravenous; Y: Yes; CVC: Central venous catheter; HCA: Healthcare associated; N: No; NS: Not specified; ICD: Intracardiac device; NM: Not mentioned; po: Per os.

purulent exudate on the ICD site. Further clinical examination was without peculiarity. Chest X-ray and electrocardiogram evaluation revealed no abnormalities. Remarkable laboratory findings included a white blood cell count of 11900/µg (normal between 4000 and 10000/µg), a C-reactive protein level of 203 mg/L (normal < 10 mg/L), and normal renal and hepatic function. Empiric antimicrobial therapy was started with vancomycin and ceftazidime. On the second day of hospitalization, two pairs of blood cultures performed in the emergency department both yielded *Serratia marcescens*, as did a culture of the purulent exudate swab. Antimicrobial susceptibility testing showed the following results: Resistance to amoxicillin-clavulanate, cefuroxime and colistin and sensitivity to temocillin [minimal inhibitory concentration (MIC) ≤ 8 µg/mL], piperacillin-tazobactam (MIC ≤ 4 µg/mL), ceftazidime (MIC ≤ 0.012 µg/mL), cefotaxime (MIC ≤ 0.25 µg/mL), meropenem (MIC ≤ 0.25 µg/mL), gentamycin (MIC ≤ 1 µg/mL), amikacin (MIC ≤ 2 µg/mL), ciprofloxacin (MIC ≤ 0.25 µg/mL), and sulfamethoxazole-trimethoprim (MIC ≤ 20 µg/mL). According to these results, the antibiotic treatment was changed to piperacillin-tazobactam (4 g every 6 h) on day 3 of hospitalization.

On admission in our hospital, on day 4, the physical examination revealed a temperature of 38.5°C, blood pressure of 112/75 mmHg, pulse of 95 beats/min, surgical site infection with pain, purulent exudate at the ICD site and no abnormal heart murmur. While blood culture performed at that time of admission revealed no more bacterial growth, a transoesophageal echocardiography (TEE) exam showed a vegetation of 16 mm x 8 mm on the defibrillator lead (Figure 1). Although the cardiac valves seemed undamaged, oral ciprofloxacin (500 mg every 12 h) was added to piperacillin-tazobactam on day 6. Furthermore, on day 7, wound debridement was performed, and the defibrillator lead was removed. Because TEE showed persistent images of vegetation on the old pacemaker leads on day 12, a decision was made to finally remove all material (ICD and pacemaker leads), with the exception of the epicardial lead, which was carefully cleaned and connected to a new provisional single chamber pacemaker. All perioperative samples and leads cultured were positive for *Serratia marcescens*. Despite the removal of all intracardiac material, a TEE carried out on day 20 revealed the presence of vegetation appended to the mitral valve, albeit without valve dysfunction. Finally, the diagnosis of ICD-related mitral valve endocarditis was made.

The dual antibiotic treatment was continued intravenously until 23 d after whole ICD removal. Blood analysis showed normalization of the CRP level and white blood count, and the patient was discharged with oral ciprofloxacin (750 mg every 12 h) and sulfamethoxazole-trimethoprim (800/160 mg every 12 h). Antibiotics were stopped on day 42 after ICD extraction, while TEE showed disappearance of the valvular vegetation (Figure 2). The patient is asymptomatic 10 mo after the completion of treatment and repeated TEE has not shown recurrence of endocarditis.

FINAL DIAGNOSIS

Serratia marcescens ICD-related mitral valve endocarditis.

TREATMENT

Complete device removal associated with dual broad-spectrum antibiotic treatment with piperacillin-tazobactam and ciprofloxacin switched to oral sulfamethoxazole-trimethoprim and ciprofloxacin for 6 wk after complete device removal.

OUTCOME AND FOLLOW-UP

Cure, no recurrence at 1, 3 and 10 mo.

DISCUSSION

Although it has been shown that GNB non-AACEK endocarditis has increasingly become a concern of healthcare contact, community acquisition of *Serratia marcescens* endocarditis still remains an important issue with regard to previous and recent data[1,3,4,22]. IVD use and immunosuppression seem to be the most important risk factors for *Serratia marcescens* endocarditis. It is noteworthy that our case is the second case report of ICD-related endocarditis due to *Serratia marcescens*, but the prospective ICE and SEI studies do not detail risk factors for each bacterium[1,2]. In accordance with actual guidelines[8-10], we support a long-term dual-antibiotic treatment regimen containing a broad-spectrum beta-lactam in *Serratia marcescens* endocarditis, considering the presence of inducible AmpC-type beta-lactamase in these bacteria. As there is a risk of clinical failure, cephalosporins, including third-generation cephalosporins, must be avoided. Piperacillin-tazobactam given in our patient was shown to be as effective as meropenem or cefepime in AmpC-type beta-lactamase-producing *Enterobacteriaceae*[23]. Monotherapy with a beta-lactam should not be the first choice in GNB non-AACEK endocarditis; even if Morpeth *et al*[1] showed no difference in comparison to a combined antibiotic regimen with regard to mortality, the long-term outcome was not reported in this study. In a series of case reports, monotherapy was effective in two of three patients, but the long-term outcome of one patient who received ceftriaxone is unknown[12,15,21]. Even if most guidelines suggest combining a beta-lactam with aminoglycosides, its use must be outweighed because of potential nephro- and audiotoxicity, and the duration should be limited to 2 wk[10]. We chose to combine piperacillin-tazobactam with ciprofloxacin, a drug with good tissue penetration. Our patient was discharged with oral ciprofloxacin and sulfamethoxazole-trimethoprim after a total duration of 5 wk of IV combination antibiotic treatment (3 wk after ICD removal). This aspect of management could be debated. However, a recent study from Iversen *et al*[24] showed non-inferiority in patients suffering from endocarditis with a stable condition in which IV antibiotics were switched to oral treatment after 2 wk. As GNB endocarditis patients tend to have more cardiac complications (abscesses, larger vegetation size) than patients with endocarditis due to other pathogens[1,2], guidelines suggest that surgical management be considered early in the course of the disease[8-10]. While complete and early removal of an ICD is highly recommended in ICD-associated endocarditis[8,25], valve repair or replacement surgery in non-AACEK GNB endocarditis did not show better outcomes than medical treatment alone, except for in those patients who presented with cardiac complications[1]. The case series also showed good clinical outcomes even in the absence of valve surgery in 71% of cases. We therefore propose that valve surgery be discussed on an individual basis.

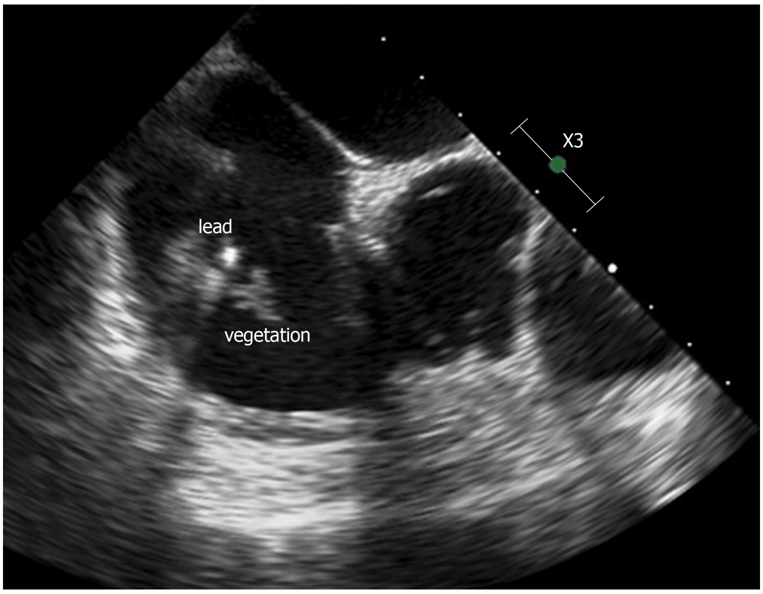

Figure 1 Transoesophageal echocardiography showing a defibrillator lead vegetation of 16 mm × 8 mm.

CONCLUSION

Globally, healthcare contact, immunosuppression and ICD presence are the major risk factors for GNB non-AACEK endocarditis[1,2]. This condition is of growing concern since people survive longer (at home) with more comorbidity than previously. *Serratia marcescens*, even if it has become an infrequent cause of GNB non-AACEK endocarditis, still should be suspected in the case of community-acquired endocarditis, especially in cases of IVDU. GNB non-AACEK endocarditis represents a challenging issue for clinicians since there are no clear guidelines[8-10]. The increase in multidrug resistant bacteria will certainly complicate treatment as well as outcomes even more. Awaiting further studies and in accordance with actual guidelines, we support treatment with a dual-antibiotic regimen containing broad spectrum beta-lactams in *Serratia marcescens* endocarditis, while valve surgery should be discussed early in the course of the disease on a case-by-case basis within a multidisciplinary team. Additional insights through prospective randomized trials about treatment in GNB non-AACEK endocarditis are urgently needed.

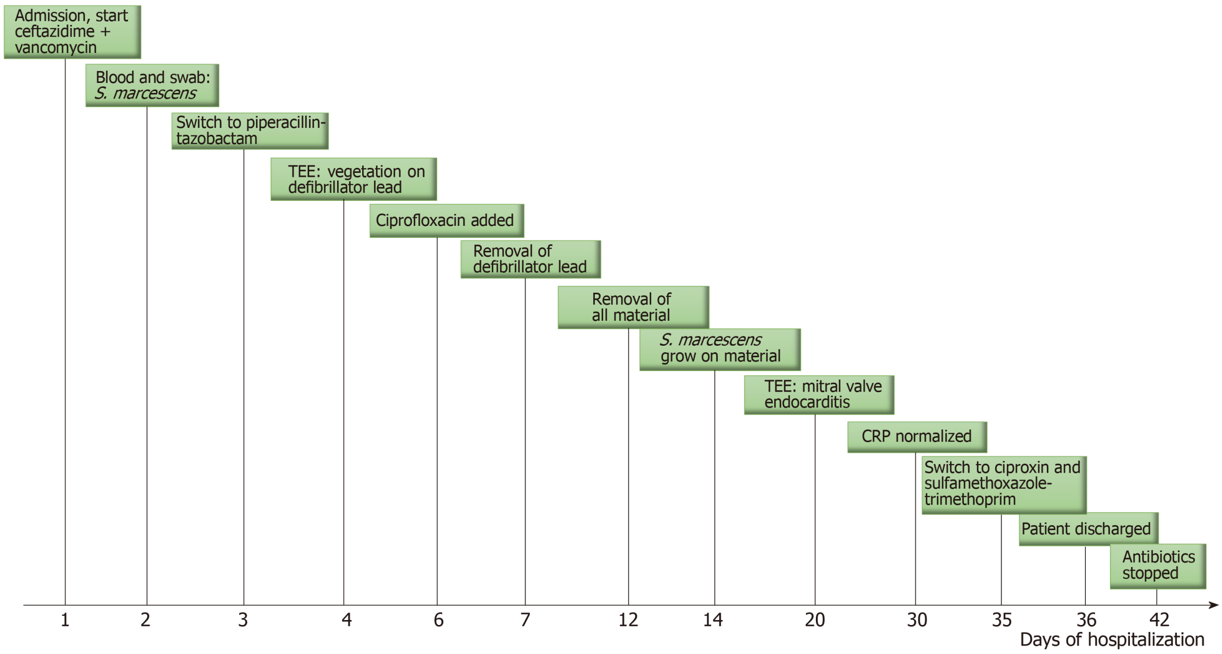

Figure 2 Timeline of the events occurring during the patient's hospitalization.

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