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Review

How we deal with *Staphylococcus aureus* (MSSA, MRSA) central nervous system infections

Roberta Maria Antonello[1], Niccolò Riccardi[2,*]

[1]Azienda Sanitaria Universitaria Giuliano Isontina ASUGI, Trieste University Hospital, 34149 Trieste, Italy
[2]Infectious Diseases Unit, Department of Clinical and Experimental Medicine, University of Pisa, 56124 Pisa, Italy
*Correspondence: niccolo.riccardi@yahoo.it (Niccolò Riccardi)
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Abstract

Among central nervous system (CNS) infections (e.g., meningitis, brain abscess, ventriculitis, transverse myelitis), those caused by *Staphylococcus aureus* (SA) are particularly challenging both in management and treatment, with poor clinical outcomes and long hospital stay. It has been estimated that SA is responsible for around 1%–7% of meningitis (up to 19% in healthcare-associated meningitis). Recent neurosurgical procedures and immunocompromisation are major risk factors for SA CNS infections. Hand hygiene, surveillance nasal swabs and perioperative prophylaxis are crucial points for effective SA infections prevention. In case of SA-CNS infections, pending microbiological results, anti-methicillin-resistant SA (MRSA) antibiotic, with good CNS penetration, should be included, with prompt de-escalation as soon as MRSA is ruled out. Consultation with an expert in antimicrobial therapy is recommended as well as prompt source control when feasible. In this narrative review, we reviewed current literature to provide practical suggestions on diagnosis, prevention, management, and treatment of SA CNS infections.

Keywords: *Staphylococcus aureus*; Central nervous system; CNS; MSSA; MRSA; Management; Review

1. Introduction

Bacterial central nervous system (CNS) infections are serious infections requiring prompt evaluation and management [1]. Etiological causes of bacterial meningitis vary by group age; in fact, among neonates and children most cases are due to group B *Streptococcus agalactiae*, *Escherichia coli*, *Listeria monocytogenes*, *Haemophilus influenzae*, and *Streptococcus pneumoniae*. Among adults, *Streptococcus pneumoniae*, *Neisseria meningitidis*, and *Listeria monocytogenes* represents the most detected cause of community acquired bacterial meningitis. *Staphylococcus aureus* (SA) CNS infection with its multiple clinical presentations (e.g., meningitis, brain abscess) is a rare but life-threatening condition, often occurring post neurosurgical interventions and/or in immunocompromised patients [1,2].

Treatment and management are challenging because of the critical location and the reduced penetration of systemically administered antibiotics in the CNS due to the blood-brain barrier. In addition, in case of methicillin-resistant SA (MRSA), a worse outcome may occur due to limited therapeutic options and pathogen related factors, such as adhesin genes, immune evasion genes, hemolysin and toxins (e.g., pore-forming toxins, Panton-Valentine leukocidin toxin) [3,4]. Furthermore, SA easily forms biofilm, especially in case of foreign bodies, requiring therapy with anti-biofilm properties or, in some cases, combination of two effective anti-SA agents [5]. It is estimated that MRSA accounts for about one third of SA CNS infections, thus raising attention on the importance of an appropriate reasoned empiric antibiotic treatment pending antimicrobial susceptibility test results [2].

Hand hygiene, surveillance swabs and adequate perioperative prophylaxis are crucial, as well as antimicrobial stewardship programs, to limit morbidity and costs related to prolonged hospital stay [6].

Aim of this narrative review is to raise attention on SA CNS infections, offering clinicians practical tips on diagnosis, prevention, antibiotic treatment and management.

2. Methods

On October 25th 2021 we performed a PubMed/MEDLINE literature search. The complete search string was "((((((central nervous system infection[Title/Abstract]) OR (CNS infection[Title/Abstract])) OR ((brain abscess[Title/Abstract]) OR (cerebral abscess[Title/Abstract]))) OR (encephalitis[Title/Abstract])) OR (meningitis[Title/Abstract])) OR (myelitis[Title/Abstract])) OR (spinal cord[Title/Abstract])) AND (aureus[Title/Abstract])". 1350 papers were found. Of these, 245 were excluded because they were not written in English and 895 were excluded by title or abstract screening because they were not pertinent with the review's topic. Two hundred and ten papers were screened by full text and discussed by the Authors, who jointly made the final decision about which papers to consider for inclusion. Seventy-four papers were included in the present review. Their pertinent references were evaluated and eventually included in the manuscript.

Table 1. Principal risk factors and diagnostic tools for *S. aureus* central nervous system infections.

Risk factors	Diagnostic tools
Recent surgery	Physical examination
SA bloodstream infection	Blood examination
SA infection (e.g., infective endocarditis, pneumonia, aortic graft infection)	CSF examination
Infectious of contiguous site (e.g., otitis)	CSF serology
Presence of foreign bodies	PCR on CSF or intraoperatory specimens
MRSA colonization	Cultures (CSF, blood, pus)
Immunocompromisation	Neuroradiology
Diabetes mellitus	Nuclear medicine
Cancer	-
Dialysis	-

SA, *Staphylococcus aureus*; MRSA, methicillin-resistant *S. aureus*; CSF, cerebrospinal fluid; PCR, polymerase chain reaction.

The manuscript was organized in the following major chapters: "Epidemiology and risk factors"; "Clinical presentation"; "Diagnosis"; "Prevention and prophylaxis"; "Reasoned antibiotic treatment and management".

3. Epidemiology and risk factors

3.1 Epidemiology

SA CNS infections incidence greatly depends on the setting and the geographical region of investigation. For instance, the number of meningitis that are caused by SA is around four times higher in Europe than in Africa or America (different microbiological detection methods and publication bias should always be considered) [7]. 1%–7% of meningitis are reported to be caused by SA, with up to 19% in healthcare associated meningitis and up to 41% of brain abscesses [7–10]. In children, SA is reported to cause up to 32% of acute CNS infections [11,12].

3.2 Risk factors

SA can infect the CNS through three main paths: contiguous spread from nearby body sites, haematogenous dissemination (including septic vegetations on heart valves), and during surgical intervention (Table 1). Surgical interventions represent a risk factor both in case of direct involvement of the CNS and in case of ophthalmic or otolaryngologic procedures [13]. In post-operative CNS infections, cerebrospinal fluid (CSF) leak and external ventricular drainage are adjunctive risk factors [14]. Emergency surgical procedures expose the patient to a greater risk of SA infection compared to elective surgery [15].

Immune deficits, both innate and acquired, are known risk factors for CNS infections sustained by uncommon pathogens, including Gram positive bacteria [16]. Despite this, CNS infections sustained by SA have been described also in immunocompetent patients without any known risk factors [17]. Furthermore, immunomodulation occurring in pregnancy has been occasionally reported as a risk factor for the spreading of SA to CNS from contiguous sites [18].

Diabetes mellitus, cancer and dialysis are reported to be adjunctive risk factors as well as negative prognostic factors [19,20]. Foreign bodies are a risk factor for bacterial infection, both in case of neurosurgical devices (e.g., deep brain stimulator), but also in case of central venous catheters, and dialysis equipment [21,22]. Of note, patients carrying a ventriculoperitoneal shunt should always be considered at higher risk of intra-abdominal bacterial migration to CNS and SA is occasionally reported as the causative agent of CNS infections also in this peculiar scenario [23]. Mariano *et al*. [24] described the case of a young woman with MRSA endocarditis and meningitis occurring after a nape piercing removal, underlying the importance of careful local hygiene after any invasive procedures.

In addition, neurologic complications of infective endocarditis should be kept in mind. Patients suffering from SA infective endocarditis may experience bacterial dissemination to the CNS, as SA vegetations are typically large and friable and therefore with a high embolic potential [25]. Among endocarditis, those caused by SA are reported to account as an independent risk factor for neurologic complications [26]. Cardiac vegetations causing septic emboli to CNS, microabscesses and mycotic aneurysms, potentially leading to ischemic or hemorrhagic stroke, are described in literature [27]. Risk factors for endocarditis and SA bacteremia (e.g., intravenous drug abuse), are risk factors for SA CNS infections as well [27].

Finally, special attention is required for peculiar settings: due to the limited diagnostic options, delay in prompt diagnosis and treatment of MRSA CNS infections in prisons and shelters, as well as in long-term facilities, is associated with death or severe sequelae [6,28].

4. Clinical presentation

Clinical presentation depends on the exact localization of infection (e.g., encephalitis, brain abscess, empyema, meningitis). Despite this, common abnormalities on physical examination are present in most cases: fever with

chills, tachycardia, hypotension and general malaise are commonly found [29]. However, these signs may also be absent and the patient can be hemodynamically stable [30]. The mental status may be altered and the Glasgow Coma Scale (GCS) score may be low [14]. Signs of meningeal irritation (e.g., Brudzinski sign, Lasegue sign) are commonly present in case of meningeal involvement, as well as vomit and nuchal rigidity [31]. Other neurological symptoms, such as seizures, hallucinations, confusion, vision loss, and neurological deficits should alway be carefully evaluated [31].

Meningitis is a medical emergency requiring immediate antibiotic prescription and supportive therapy. SA meningitis is reported in most cases as post neurosurgical complication, but due to anatomical proximity, meningitis may occur as a threatening complication of ocular/orbital infections and otitis [32]. It has also been described as a complication of a furuncle whose cultures grew MRSA [33]. Spontaneous MRSA meningitis in an otherwise healthy patient has also been described [31,34]. Cerebrovascular complications of meningitis (e.g., intracranial haemorrhage, cerebral infarction, cavernous sinus thrombosis) are rarely described [35,36]. Spinal epidural phlegmon and in general spinal cord involvement have occasionally been reported and are associated with poor outcomes [30,37]. Pneumocephalus, defined as the presence of gas in the cranial cavity, is another extremely rare complication of SA meningitis [38]. Meningitis and brain abscesses can occasionally be present simultaneously, also without known predisposing factors [39].

Abscesses are focal suppurative processes that can be parenchymal, subdural or in continuity with adjacent structures [40] (Fig. 1). Post neurosurgical brain abscesses can occur weeks to months after surgical intervention (up to two years later) [9]. Intraventricular extension is associated with high mortality rates (up to 80%), which are doubled compared to abscesses non involving ventricular space [41]. Multifocal brain abscesses as a complication of endophthalmitis following ophthalmic procedures or chorioretinitis were reported also in immunocompetent patients [17,29]. Gan *et al*. [42] described a brain abscess caused by MRSA occurring in an otherwise healthy infant as a conjunctivitis complication. A patient suffering from brain abscess should always be investigated for immunodeficiency, and in case of infants also for specific congenital immune deficits [43]. Epidural spinal abscesses can compress the spinal cord and nerve roots, resulting in motor and sensory lateralized deficits. Okada *et al*. [44] described the case of a middle-age man with an epidural abscess involving the entire spine who had undergone sacral epidural block two weeks before presentation, presenting with signs of meningeal irritation but no neurological deficits.

Pyogenic ventriculitis consists of suppurative fluid in the cerebral ventricles and it can occur both as a post neurosurgical complication, especially in external ventricular drains carrier, or as primary pyogenic ventriculitis complicating community-acquired meningitis [45]. Primary ventriculitis is an extremely rare condition, with less than 10 cases described. Signs and symptoms are extremely variable and signs of meningeal irritation and focal neurological deficits are often absent [46,47].

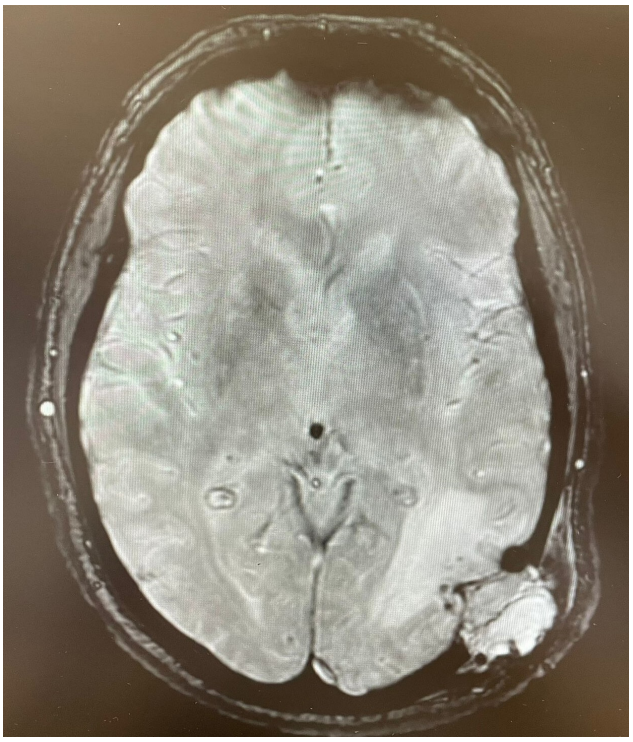

Fig. 1. MRSA abscess occurring after left occipital craniotomy. MRI sequences show a mixed-content (purulent and transudative/phlogistic) harvest in correspondence with the surgical site. The purulent extracranial compartment displaces the contiguous soft tissue ("mass effect") and it is interconnected with satellite infectious lesions in the parietal parasagittal posterior region. Meningeal enhancement and vasogenic edema in the left occipital region are also described.

SA acute transverse myelitis is a rare condition with few cases reported and it is often associated with poor outcomes [48,49]. It usually occurs soon after an infection involving another site, suggesting an immune-mediated effect [50,51]. Neurological deficits are often present and osteomyelitis can occur simultaneously [48].

Mild encephalitis/encephalopathy with reversible splenial lesions (MERS) is a rare clinico-radiological syndrome first described in 2004 and occasionally reported due to SA bacteraemia [52].

5. Diagnosis

5.1 Physical examination

Medical history should always be assessed carefully, paying particular attention to the immune system status, recent surgery, other signs and symptoms that may suggest

the site of origin of infection. Physical examination should also exclude a concomitant infective endocarditis, sinusitis, otitis, mastoiditis, and oral cavity poor hygiene suggestive of odontogenic foci [42,53]. Previous MRSA colonization should also be asked.

5.2 Blood examination

Blood tests usually show elevated inflammation markers, with leukocytosis (most neutrophils) and elevated C reactive protein (CRP) and procalcitonin levels (>2 ng/mL) [10,44]. Blood cultures may be of support in identifying the causative agent, although they turn positive only in about one third of cases [54].

5.3 Lumbar puncture

Lumbar puncture is crucial for the diagnosis of CNS infections. In case of SA meningitis, CSF examination commonly reveals high levels of white blood cells (most neutrophils), elevated protein level and hypoglycorrhachia [31,44]. Normal CSF glucose levels are occasionally reported [33,55]. Of note, presentation of CSF in SA meningitis is common to that of other bacterial meningitis. This should always be kept in mind not to miss differential diagnosis pending microbiological results. CSF examination can result within normal ranges, especially in case of brain abscesses [14]. CSF Gram stain and cultures identify the causative agent in most cases [31], allowing antimicrobial susceptibility testing and targeted antibiotic therapy. Serology on CSF and antigen testing can raise suspicion on the causative agent pending culture results, and can rapidly distinguish, besides CSF examination, between bacterial, viral or fungal CNS infections. Polymerase chain reaction (PCR) and its variants (e.g., multiplex PCR, microarray assay) performed on significant samples (e.g., CSF, drained pus) is a valid rapid diagnostic option with good specificity and sensitivity [56,57]. PCR can also distinguish between MSSA and MRSA using specific primers for nuclease gene and Mec gene, respectively [56]. In case of drainage of an abscess, pus cultures may lead to the diagnosis in case of inconclusive lumbar puncture test or blood culture results.

5.4 Neuroradiology

Imaging investigation is of support on clinical suspicion, with specific features according to the localization of infection. Computed tomography (CT) has a good sensitivity in detecting brain abscesses, usually presenting with a thin, regular enhancing capsule, but it has some problems in making differential diagnosis (e.g., brain tumours) [41]. With regards to meningitis or ventriculitis, CT scan is often normal and the imaging evaluation requires magnetic resonance imaging (MRI) sequences [45]. Of note, also standard MRI sequences may result inadequate in diagnosing CNS infections [45]. On the other hand, diffusion-weighted MRI sequences have a higher sensitivity in diagnosing ventriculitis and meningitis [45]. In case of meningitis, diffusion-weighted MRI often shows multiple subarachnoid hyperintense lesions, mainly distributed in the frontal lobe region [58]. Diffusion-weighted MRI is able to differentiate brain abscesses from neoplasia in most cases, but differential diagnosis remains challenging [59]. Magnetic resonance spectroscopy is reported to discriminate also between aerobic and anaerobic brain abscesses [60]. Differential diagnosis of brain abscesses includes brain tumours and neuroinflammation, therefore an accurate diagnosis at an early stage is fundamental to define the best approach [41]. As an example, Pham *et al*. [61] reported the extremely rare condition of an infected intradural dermoid cyst mimicking a brain abscess on MRI. Imaging techniques are sometimes employed also for etiological diagnosis and source control purposes, as in the case of CT- or MRI-guided biopsies or drainage [62].

5.5 Nuclear medicine

Nuclear medicine is gaining ground in recent years on CNS infections diagnosis. Photon emission tomography CT (PET CT) is highly sensitive in detecting meningeal enhancement [22]. CNS evaluation is challenging because the brain is a high glucose metaboliser also under physiological conditions, therefore the best radiopharmaceutical should be carefully evaluated.

6. Prevention and prophylaxis

It is estimated that 30–50% of adults are colonized with MRSA though totally asymptomatic, therefore screening programs (e.g., nasal swabs, skin swabs) are crucial to identify patients at higher risk of MRSA invasive infection [6,63]. As most MRSA invasive infections occur in patients without a history of MRSA colonization, besides in patients being colonized with MRSA, prophylaxis for SA should be carefully evaluated in every immunocompromised patient undergoing neurosurgery [64,65]. Time is a critical issue: screening should be performed as close to the operation date as possible, but in time to perform decolonization and/or preoperative prophylaxis. Optimal preoperative prophylaxis should be administered 30 to 60 min before the incision and prophylactic antimicrobial agents should be discontinued within 24 h of the procedure [6]. Due to organizational issues, pre-procedural screening is sometimes impossible to be performed in emergency interventional procedures, thus partially explaining the higher mortality rates in these patients [15,20]. With this in mind, high-risk patients undergoing elective surgical procedures should be screened at regular intervals. In case of MRSA colonisation, decolonisation aims at reducing MRSA at sub-detection levels. The best prophylactic regimen (topical, systemic or combination regimen) should be evaluated according to the procedure the patient is going to attend [6]. Short and ultra-short prophylaxis regimens are encouraged. First-generation cephalosporins (e.g., cefazolin) are usually administered 30 min before surgery if surveillance

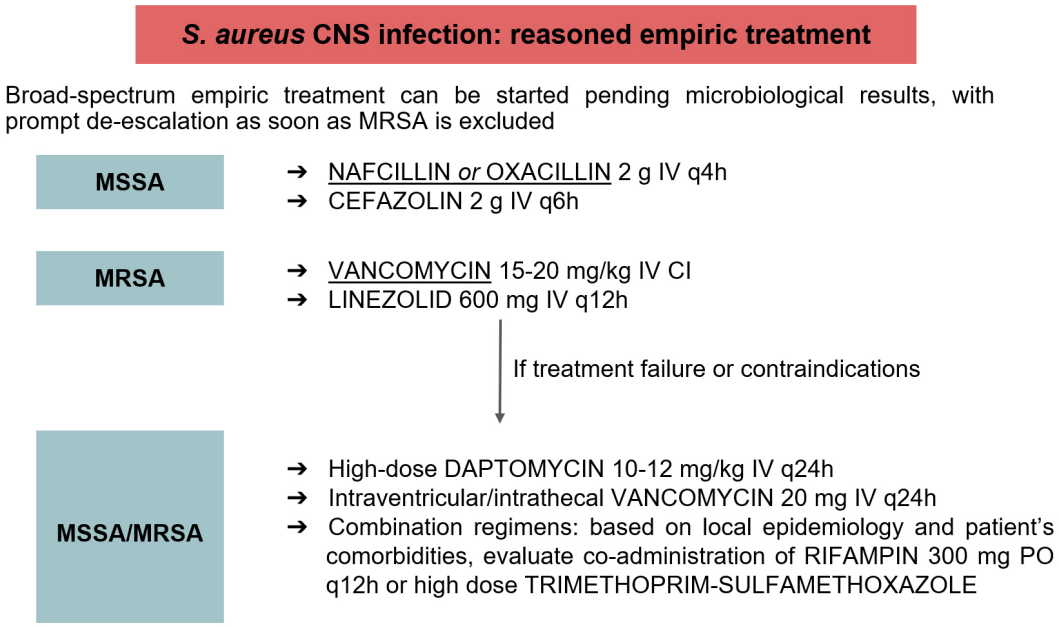

Fig. 2. *Staphylococcus aureus* central nervous system infections: diagnosis and reasoned empiric antibiotic therapy. First-choice treatments are underlined. Drug dosages refer to adults without renal or hepatic impairment. The choice of treatment should always take into consideration allergies and comorbidities of the patient. Advice from an expert in antimicrobial therapy is recommended. CI, continuous infusion; CSF, cerebrospinal fluid; CNS, central nervous system; IV, intravenously; MSSA, methicillin susceptible *S. aureus*; MRSA, methicillin susceptible *S. aureus*; PCR, polymerase chain reaction; PO, orally; SA, *Staphylococcus aureus*.

nasal swabs did not detect MRSA. On the contrary, vancomycin is preferred in case of known MRSA colonization or β-lactam allergy [66]. If hair removal is necessary, razor blade use is discouraged and electric clipping or depilatory cream should be used instead [67]. Antimicrobial stewardship programs regarding both preoperative and postoperative prophylaxis based on local epidemiology are advisable.

Beside surgical prophylaxis, general behaviours to reduce MRSA spreading should be adopted in both medical and surgical wards. Hand washing is the most effective preventive measure [68]. In addition, patients' belongings should be personal and not shared, waste and laundry appropriately managed, and surfaces should be periodically cleaned [6].

7. Reasoned antibiotic treatment

Taking in account patients' comorbidities (e.g., chronic renal failure) and possible drug-drug interactions (DDIs), empiric treatment should cover MRSA with antibiotics with good CNS penetration and, as soon as MRSA has been ruled out, prompt de-escalation to anti-MSSA treatment should be carried out (Fig. 2).

First line antibiotics for MRSA CNS infections are vancomycin 15–20 mg/kg intravascular (IV) continuous infusion, with dose adjustment according to renal function, to achieve preferred target AUC24 of 400–600 μg/mL or trough concentration of 15–20 μg/mL and linezolid 600 mg every 12 h (always paying attention to possible DDIs) [69–71]. Based on antimicrobial susceptibility test (AST), de-escalation to nafcillin or oxacillin 2 g IV every 4 h represents a good anti-MSSA option [72]. In a recent systematic review, cefazolin was found to be non inferior to antistaphylococcal penicillins in treating MSSA bacteremia and it was associated with inferior nephrotoxicity: due to good CNS penetration, cefazolin may be considered as an alternative option for MSSA CNS infections [72,73]. Limited data are available about ceftaroline, a fifth generation cephalosporin with anti-MSSA/MRSA activity, in *S. aureus* CNS infections; however, in animal models and few human case reports, a good CNS penetration and treatment outcome have been reported [74,75].

In a recent randomized control trial, high dose trimethoprim-sulfamethoxazole did not achieve non-inferiority to vancomycin in the treatment of severe MRSA infections and its use is only limited as companion drug to anti-MSSA/MRSA first-line antibiotics [76].

High-dose daptomycin (10–12 mg/Kg) may be considered as salvage therapy for MSSA/MRSA CNS infection in patients that have failed or have contraindication to first line agents [77].

Combination therapy with two active agents (e.g., rifampin 300 mg every 12 h or high dose trimethoprim-sulfamethoxazole) may be used when no source control can be applied or microbiological/clinical failure of monother-

apy [78]. Furthermore, intraventricular/lumbar intrathecal administration of vancomycin 20 mg daily may be considered for refractory cases [79]. Whatever the antibiotics chosen, treatment duration should be tailored on patient's clinical, radiological and surgical resolution (treatment lasting less than two weeks are strongly discouraged).

Finally, source control, that is the measures adopted to control the foci of infection (e.g., abscess drainage, removal or substitution of ventriculo-peritoneal shunt) should be applied whenever possible [80].

In case of treatment failure, combined surgical and antibiotic therapy reassessment should be performed to ensure adequate source control.

8. Conclusions

SA CNS infections are burdened by high morbidity and mortality. Prompt diagnosis and combined effective source control and antibiotic treatment are mandatory to increase the likelihood of good outcomes.

Author contributions

RMA—literature search, manuscript draft; NR—conception and design, manuscript draft, manuscript revision. All authors read and approved the final manuscript.

Ethics approval and consent to participate

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Conflict of interest

The authors declare no conflict of interest.

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