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ORIGINAL ARTICLE

Restricted vancomycin policy for staphylococcal late onset sepsis in a Portuguese neonatal intensive care unit

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Abstract

Introduction: Sepsis is a major cause of morbimortality in newborns and *Staphylococcus spp* are responsible for most cases of lateonset sepsis. Our unit adopted a conservative policy, using flucloxacillin and gentamicin as first line therapy, switching to vancomycin if isolation of methicillinresistant *Staphylococcus aureus* or clinical deterioration. We aim to evaluate the efficacy of our practice. **Methods:** Analysis of staphylococcal lateonset sepsis (2011-2020) in a neonatal intensive care unit. Demographic, clinical presentation, treatment and outcome were analyzed. Asymptomatic infants were excluded; consecutive positive blood cultures in the same episode of sepsis were counted once. **Results:** Fifty nine cases of lateonset sepsis by *Staphylococcus* were found with 109 positive blood cultures. Median gestational age 31 weeks, median birth weight 1.435g. Clinical presentation: bradycardia (53%, n = 31), lethargy/irritability (51%, n = 30), "ill appearance" (42%, n = 25). Isolated agents: coagulase negative *Staphylococci* 73% (n = 43), *Staphylococcus aureus* 27% (n = 16) methicillin-resistant 15% (n = 9) and methicillin-sensitive 12% (n = 7). Empirical therapy with flucloxacillin and gentamicin instituted in 90% (n = 53) of cases; mean duration of treatment 11.4 days (SD ± 3.6). Switch for vancomycin in 28.3% of cases (n = 15). Vancomycin avoided in 66% (n = 39). Due to clinical improvement initial therapy was maintained in 84.4% (n = 27) cases of coagulase negative *Staphylococci* resistant to flucloxacillin. We had one death (methicillin-resistant *Staphylococcus aureus* treated with vancomycin from day one). **Discussion:** Our conservative policy was associated with low mortality, even if *in vitro* resistance. **Conclusion:** It seems to be a safe approach, with most of the newborns showing a good outcome and duration of therapy within the recommendations. These outcomes support a restrictive use of vancomycin, preventing the emergence of resistance.

Keywords: Empirical therapy. Flucloxacillin. Invasive staphylococcal disease. Late onset sepsis. Vancomycin.

Política restrita de vancomicina para sepse estafilocócica de início tardio em uma unidade de terapia intensiva neonatal portuguesa

Resumo

Introdução: A sépsis neonatal tardia é uma causa importante de morbimortalidade, sendo os *Staphylococcus spp* responsáveis pela maioria dos casos. A nossa unidade adoptou a política de prescrever flucloxacilina e gentamicina como terapêutica de primeira linha nestes casos, alterando para vancomicina em caso de isolamento de *Staphylococcus aureus* resistente à meticilina ou de agravamento clínico. O objectivo deste estudo é avaliar a sua eficácia. **Métodos:** Análise das sépsis estafilocócicas tardias entre 2011 e 2020 numa Unidade de Cuidados Intensivos Neonatais; analisados dados demográficos, apresentação/evolução clínica e tratamento. Recém-nascidos assintomáticos excluídos; hemoculturas positivas consecutivas

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no mesmo episódio de sépsis, foram contabilizadas apenas uma vez. **Resultados:** Houve 59 casos de sépsis neonatal tardia a *Staphylococcus*, com 109 hemoculturas positivas. Mediana idade gestacional 31 semanas; mediana peso ao nascimento 1,435g. Apresentação clínica: bradicardia (53%, n = 31), letargia/irritabilidade (51%, n = 30), "sensação de doença" (42%, n = 25). Agentes isolados: *Staphylococcus* coagulase negativa 73% (n = 43), *Staphylococcus aureus* 27% (n = 16) (resistente à meticilina 56,2% (n = 9/16) sensível à meticilina 43,8% (n = 7/16). Instituída terapêutica empírica com flucloxacilina e gentamicina em 90% (n = 53) dos casos, duração média de 11,4 dias (DP ± 3,6). Alteração para vancomicina em 28,3% (n = 15) e evitado o seu uso em 66% (n = 39). Terapêutica inicial mantida em 84,4% (n = 27) dos casos de *Staphylococcus* coagulase negativa resistentes à flucloxacilina por melhoria clínica. Verificou-se um óbito (sépsis por *Staphylocccus aureus* resistente à meticilina tratado com vancomicina como primeira linha). **Discussão:** A política antibiótica descrita associouse a baixa mortalidade, mesmo nos casos de resistência *in vitro*. **Conclusão:** Aparenta ser uma abordagem segura, associada a boa evolução clínica, suportando o uso restritivo de vancomicina e contribuindo para a prevenção da emergência de resistências.

Palavras chave: Doença invasiva estafilocócica. Flucloxacilina. Sépsis neonatal tardia. Terapêutica empírica. Vancomicina.

Keypoints

What is known
- *Staphylococcus spp* are responsible for most cases of therapy for late onset sepsis.
- Given the possibility of fulminant clinical course, many NICUs choose vancomycin and gentamicin as a first line therapy for LOS.
- However, guidelines regarding the empirical antibiotic regimen for suspected staphylococcal infection are lacking.

What is added
- Flucloxacillin and gentamicin as first-line LOS seems to be a safe approach.
- Vancomycin, as a first-line therapy does not significantly improve survival, even if *in vitro* resistance to flucloxacil-lin is found.
- This selective use of vancomycin policy is of great importance to avoid the emergence of resistances.

Introduction

Late-onset sepsis (LOS), a major cause of morbimortality in preterm infants (PT), is defined as an infection occurring 72 hours after birth and, in in-hospital patients, is primarily attributed to hospital pathogens[1-4].

In recent years, *Staphylococcus aureus* (*Staph. aureus*) represent around 10% of LOS, while coagulase negative *Staphylococci* (CoNS) are responsible for 30% to 60% of LOS[5,6]. Difficulties might be encountered when defining whether a CoNS isolated from blood cultures represents a true infection or contamination. It should be considered a true infection if it is associated with clinical and laboratory findings of infection and there are at least two positive blood cultures with identical CoNS organisms[7].

Clinical presentation of neonatal sepsis is often nonspecific and diagnosis should be based in adjunctive laboratory data[3,4,8,9]. Given the possibility of fulminant clinical course, antibiotic therapy must be instituted as soon as a LOS is suspected. Even though noticeable variation in the chosen regimen can be found[3]. A recent Cochrane review concluded that there is insufficient evidence in favor of any particular antibiotic regimen for the empirical treatment of suspected LOS[2].

Taking the increasingly b-lactam resistance in consideration, some Neonatal Intensive Care Units (NICUs) administer vancomycin and gentamycin as empirical therapy whenever LOS is suspected. Clinicians should consider that recommendations favor their discontinuation after 48 hours, unless clinical or laboratory signs of infections or the resistance profile supports its ongoing use[1,4,5,8,10,11]. In order to avoid emergence of vancomycin-resistant *Staph. aureus* and CoNS and *Enterococci*, the Centers for Disease Control and Prevention published a recommendation guideline cautioning for the prudent use of vancomycin[12].

Usually, when blood culture results become available, if the organism identified is a methicillin-susceptible *Staphylococcus aureus* (MSSA), treatment should be narrowed or continued with an antistaphylococcal penicillin[1]. Otherwise, if the organism identified is methicillin-resistant *Staphylococcus aureus* (MRSA) treatment with vancomycin is consensually recommended[1].

To prevent emergence of vancomycin-resistant pathogens, we adopted a conservative policy using flucloxacillin and gentamicin as first-line therapy, restricting vancomycin use. Several other studies reported the safety of NICU vancomycin restriction[7,10,13,14]. In our unit, when we identify CoNS we maintain the treatment with

flucloxacillin and gentamicin even when *in vitro* resistance to flucloxacillin is found, if the newborn is clinically improving. If the organism identified is MRSA or ifthere's clinical deterioration, we switch to vancomycin. The aim of this study is to describe the clinical presentation of staphylococcal LOS and to evaluate the efficacy and safety on the use of flucloxacillin and gen-tamicin as empirical therapy in these situations.

Methods

Our NICU has been open since the 1st of January of 2011. It is a new general hospital that serves a population of 355,723 habitants. In our NICU we admit newborn infants with 28 or more gestational weeks; 44% are preterm (data from 2018 to 2021). We have the possibility of performing long term invasive ventilation. Since pediatric surgery is not available at the hospital, usually we do not admit surgical cases. Thirty-three-point six percent (33.6%) of our patients have a central venous catheter (venous umbilical or peripheral inserted central catheter) with a median stay of 3.7 days (1 to 22 days). Ten percent (10%) of patients have invasive ventilation (median 3.2 days) and 31% have non-invasive ventilation (median 5.2 days) data from 2018 to 2021.

We carried out a retrospective descriptive analysis of institutional records of all infants admitted to our NICU with *Staphylococci* isolated from blood culture, identified through microbiology laboratory records, between January 1st, 2011, and December 31st, 2020. Verbal consent from the caregivers was obtained.

Confirmed LOS was defined as clinical sepsis occurring more than 72 hours after birth; newborns with LOS with at least one positive blood culture for *Staphylococci* were enrolled. So far, we have not been using as a diagnosis criterion for LOS, 2 positive blood cultures. Repeated blood cultures with the same agent during the same episode of sepsis were counted once. Infants who did not have clinical of sepsis and in whom *Staph. aureus* or CoNS were isolated, and blood cultures with multiple agents, were assumed as contamination and excluded (Fig. 1).

We analyzed the following variables: gender, GA, birth weight, presence of central catheters; clinical presentation (fever, hypothermia, cyanosis, apnea, bradycardia, respiratory distress, feeding difficulties, abdominal distension, lethargy/irritability, hypotonia and ill appearance), isolated microorganism and susceptibility to antimicrobial agents, type and duration of antibiotic exposure and clinical outcome[15]. All antibiotic dosing were prescribed according to the latest recommendations. The statistical analysis was performed using *Microsoft Excel*® and SPSS®.

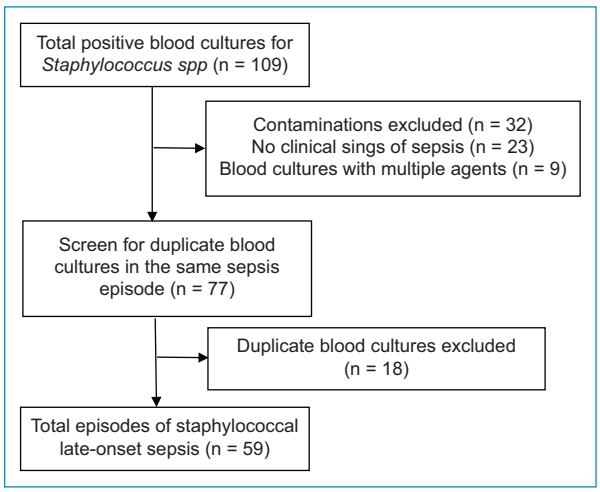

Figure 1. Flow diagram of the patient's selection process.

Results

Over the 10-years period, there were 2005 admissions to the neonatal unit. There were 380 episodes of confirmed LOS. The annual rate of LOS was between 12.6 and 29.02 episodes per 100 admissions, with an overall mean of 18.95 episodes (SD ± 5.08) per 100 admissions. There were 109 positive blood cultures for *Staphylococcus* in 90 newborns. Thirty-two were considered contamination and were excluded.

Of the remaining 77 positive cultures, 18 were got in the same episode of the 59 cases of LOS. CoNS accounted for 73% (n = 43) of the episodes, and *Staph. aureus* for 27% (n = 16). Distribution of agents per year is shown in Fig. 2. The most identified CoNS spp were *S. epidermidis* (67%), *S. haemolyticus* (14%) and *S. hominis* (5%). Eighty one percent (81%) (n = 35/43) of CoNS and 53,3% of *Staph. aureus* were resistant to flucloxacillin and 60% (n = 26/43) of CoNS and 33% of *Staph. aureus* were resistant to gentamicin. Resistance to vancomycin was not found.

The median GA and birth weight were respectively 31 weeks (limits 28 to 41) and 1.435g (limits 750 to 3.365). In 59% (n = 35) of cases, the sepsis occurred while a central catheter was in place. Episodes of catheter-associated sepsis occurred more frequently with umbilical catheters (51.4%, n = 18) than with peripherally inserted central catheters (37.1%, n = 13) – the median time between placement of the catheter and the beginning of sepsis were 2 days (1-7). The remaining episodes could not be attributed to a specific catheter.

Clinical signs are shown in Table 1. The clinical presentation was similar regardless of whether the infection was due to *Staph. aureus* or CoNS.

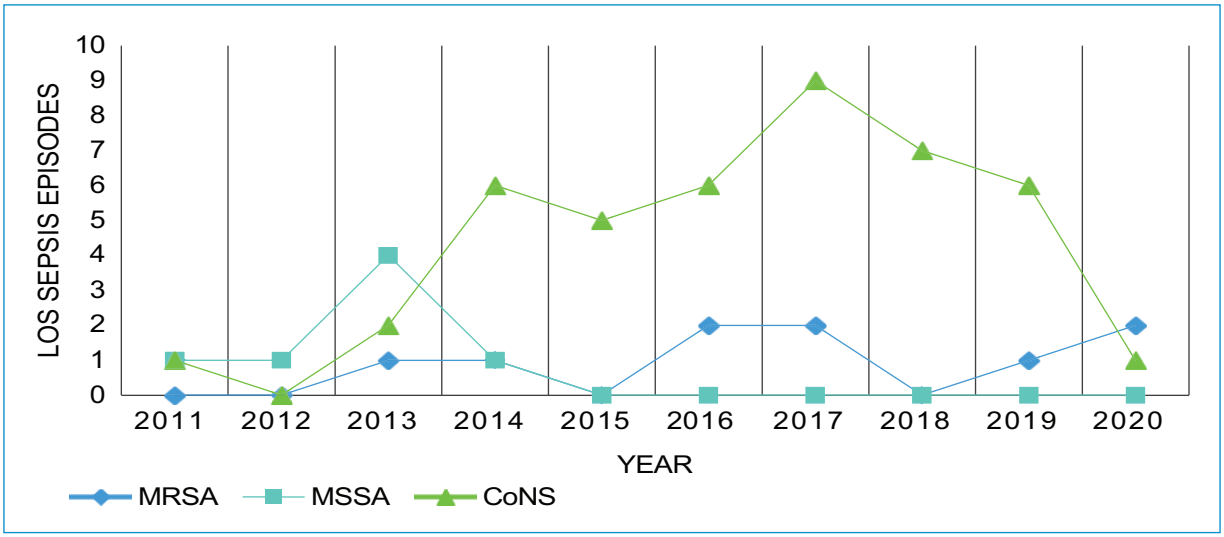

Figure 2. Graphic showing the annual distribution of late-onset sepsis caused by *Staphylococcus spp.*

Table 1. Characteristics of infants with *Staphylococcus aureus* and coagulase negative *Staphylococci*

Variables	*Staph. aureus* (n = 16)	CoNS (n = 43)	Total (n = 59)
Male [n, (%)]	6 (38%)	21 (49%)	27 (45.8%)
Median gestational age [weeks (range)]	32 (28-39) weeks	31 (28-41) weeks	31 (28-41) weeks
Median birth weight (range)	1,150 (1,150-1,750) grams	1,400 (750-3,365) grams	1,435 (750 to 3,365) grams
Central catheter in place [n (%)]	8 (50%)	27 (63%)	35 (59.3%)
Signs and symptoms [n (%)]			
– Fever	2 (13%)	5 (12%)	7 (11.9%)
– Apnea	2 (13%)	8 (19%)	10 (16.9%)
– Hypoxemia	4 (25%)	6 (14%)	10 (16.9%)
– Respiratory distress	1 (6%)	5 (12%)	6 (10.1%)
– Bradycardia	9 (56%)	22 (51%)	31 (52.5%)
– Lethargy / irritability	6 (38%)	24 (56%)	30 (50.8%)
– "Ill appearance"	7 (44%)	18 (42%)	25 (42.4%)
– Feeding difficulties	5 (31%)	9 (21%)	14 (23.7%)

CoNS: coagulase negative *Staphylococci.*

First-line empirical therapy with flucloxacillin and gentamicin was instituted in 90% (n = 53) of cases. Subsequently antibiotic switch for vancomycin was performed in 28.3% of cases (n = 15), due to isolation of MRSA (n = 6), absence of clinical improvement (n = 5), persistence of positive blood culture *S. haemolyticus and S.* epidermidis (n = 2), sepsis to a new agent (n = 1) and according to the antibiotic sensitivity test (n = 1), although this last infant was clinically stable. Mean duration of this regimen was 15.85 days (SD ± 6.05).

Five patients (8.5%) started with vancomycin and gentamicin as first-line therapy. All of them had severe clinical symptomatology, such as arthritis, severe respiratory distress, high fever, lethargy/irritability, ill appearance or severe bradycardia (CoNS = 1; MRSA = 3; MSSA = 1). Mean duration of this regimen was 17.4 days (SD ± 5.1). Laboratory findings of infants who performed antibiotic switch and in those treated with firstline vancomycin and gentamicin are shown in Table 2. One infant started on flucloxacillin and amikacin.

We avoided the use of vancomycin in 66% (n = 39) of the total cases (6 corresponding to MSSA and 33 corresponding to CoNS), maintaining the initial therapy with flucloxacillin and gentamicin in 84.4% of cases (n = 27) due to unequivocal clinical improvement,

Table 2. Mean laboratory values of infants who performed antibiotic switch and in those treated with first line vancomycin and gentamicin

	Infants performing antibiotic switch	Infants treated with first line vancomycin
Hemoglobin (g/dL)	13.4 (SD ± 2.52)	11.5 (SD ± 2.03)
Leucocyte count (x10^9/L)	10,418 (SD ± 8,001.1)	33,388 (SD ± 7,267)
Platelets (x10^9/L)	140.466 (SD ± 105.02)	216.2 (SD ± 53.2)
C-reactive protein (mg/dL) at diagnosis	3.92 (SD ± 3.01)	3.85 (SD ± 3.2)
Maximum C-reactive protein (mg/dL)	6.46 (SD ± 2.85)	5.29 (SD ± 2.81)

SD: standard deviation.

despite CoNS resistance to flucloxacillin. The mean antibiotic duration in those cases was 11.4 days (SD ± 3.6) – for *Staph aureus*. the mean duration was inferior 13.1 days.

One death was recorded in a 28-week GA second twin infant treated with vancomycin and gentamicin since becoming symptomatic on day 6 of life. She developed a fulminant MRSA sepsis and subsequently died on day 8 of life.

Discussion

Our study provides a description of the epidemiology, presenting clinical features, treatment and outcome of neonatal staphylococcal sepsis.

We found a mean of 18.95 episodes of LOS (SD ± 5.08) per 100 admissions. These results highlight the importance of following the principal principles and strategies of control of hospital-acquired infection and antibiotic stewardship, such as intensive reinforcement of infection control practices, universal surveillance on admission, accurately identifying patients who need antibiotic therapy, using local epidemiology to guide the selection of empiric therapy, strictly cohorting patients, adjusting antibiotics when cultures results become available, monitoring for toxicity, optimizing the dose, route, and duration of therapy and develop an interdisciplinary antimicrobial stewardship policy[4,13,16,17].

International series, as well as our data, suggest that despite historical importance of *Staph. aureus* in LOS[5], CoNS have emerged as the most frequent isolated pathogen, such as *S. epidermidis, S. haemolyticus* and *S. warneri*[5]. In our study we found mainly *S. epidermidis* (67%) and *S. haemolyticus* (14%). Increase in CoNS sepsis incidence is believed to be related to improved survival, prolonged hospitalization of premature infants and increasing need for invasive procedures[6]. However, an overestimation of CoNS sepsis rates is possible because a positive blood culture can reflect catheter or culture contamination rather than true infection[6], this is why it is recommended to perform two blood cultures. MRSA is an increasing concern, representing up to 55% of *Staph. aureus* infections in NICUs, with wide geographical variations[6]. In our unit the prevalence of MRSA sepsis was 15% (9 cases in 59 sepsis) and 56,3% of *Staph aureus* were MRSA (9 MRSA in 16 *Staph aureus*). Manifestations of staphylococcal infections are frequently indistinguishable from neonatal sepsis caused by other organisms. However, CoNS have an insidious evolution and *Staph aureus* a sudden beginning with rapid evolution, similar to Gram-negative sepsis[6]. Yet, in our study, clinical findings were nonspecific and similar between CONS and *Staph aureus* with bradycardia (53%) standing out as the most frequently observed sign, followed by lethargy/irritability (51%) and an "ill appearance" description (42%) as reported in previous studies[3]. As expected[3], fever was a rare symptom, occurring in only 12% of cases.

Antibiotic resistance is a worldwide problem especially in NICUs[1,18]. Consequences of antibiotic overuse include rise of antibiotic-resistant organisms, altered intestinal microbiome, increased risk of necrotizing enterocolitis, hospital-acquired infections and mortality[11]. The empirical antibiotic regimen for suspected staphylococcal infection is not universally accepted and guidelines are lacking[6]. The choice depends on clinical characteristics and local susceptibility patterns[6]. Increasing resistance of CoNS to β-lactam antibiotics has prompted many NICUs to use vancomycin for initial treatment of LOS, if staphylococcal infection is suspected. This is an important risk factor for the emergence of vancomycin-resistant organisms, causing life-threatening infections[11,14]. Our unit LOS protocol includes empirical therapy with flucloxacillin and gentamicin. When the causative

microorganism is identified, treatment is adjusted according to clinical evolution and considering the susceptibility profile. With this policy we avoided the use of vancomycin in 64.4% of cases[19]. This decision is in accordance with the latest evidence that recommends restricting vancomycin use to prevent the emergence of vancomycin-resistant organisms[12]. Avoiding empiric vancomycin therapy until culture results and susceptibilities are known is a reasonable approach, mainly because of the low rate of fulminant sepsis, favorable outcome from invasive staphylococcal disease (ISD) infections in general and a low rate of MRSA infections[2,7,8,11,13]. Recent reviews of LOS in NICU showed that CoNS infections are rarely fulminant and that duration of sepsis did not change when clinicians stopped using empirical vancomycin therapy and that the empirical use of vancomycin as a first line therapy did not significantly improve survival, even when *in vitro* resistance to flucloxacilin is found[6,10].

In our unit we tend to maintain flucloxacillin and gentamicin in CoNS even when resistance *in vitro* is found. In our study the resistance of CoNS to flucloxacillin was 78%. Nevertheless, like other studies[11,14], we documented clinical improvement in more than half of the infants. We only switch to vancomycin if the organism identified is MRSA or if there's clinical deterioration, which was observed in 23% of the cases. Our data showed that this has been a safe approach, and in the 10 years reviewed in this study, there was only 1 death in an infant who started vancomycin from the first day of clinical sepsis, subsequently known to be caused by MRSA. However, before these recommendations can be generalized, cooperative research groups should determine the distribution of pathogens causing fulminant sepsis, as there may be regional differences that might alter specific recommendations[2]. Prospective studies are required to evaluate the long-term effect of vancomycin restriction on NICU patient safety and microbial ecology, particularly among institutions with higher rates of MRSA infections[10].

Our study presents several limitations: first it is a retrospective study with a small size sample (n = 59); secondly these are results from a single NICU that only admits 28 weeks gestational age infants and above and therefore cannot be generalized. Thirdly, laboratory parameters were not collected from all sepsis cases analyzed.

Future research needs to assess cost-effectiveness and the impact of antibiotics in different settings such as developed or developing countries and lower gestational age groups. Studies regarding *in vitro* sensitivity tests, in newborns with clinical improvement, would also be important to reinforce a conservative antibiotic policy.

The conservative LOS treatment policy adopted in our unit, selecting flucloxacillin and gentamicin as first line therapy, found a low mortality, despite a high prevalence of Staphylococcal *in vitro* resistances. It seems to be a safe approach for CoNS sepsis as we have only carried out antibiotic switch in the few cases with clinical worsening. These data agree with a more selective use of vancomycin, trying to stop the emergence of resistance.

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Conflicts of interest

None.

Ethical disclosures

Protection of human and animal subjects. The authors declare that the procedures followed were in accordance with the regulations of the relevant clinical research ethics committee and with those of the Code of Ethics of the World Medical Association (Declaration of Helsinki).

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors have obtained the written informed consent of the patients or subjects mentioned in the article. The corresponding author is in possession of this document.

Use of artificial intelligence for generating text. The authors declare that they have not used any type of generative artificial intelligence for the writing of this manuscript, nor for the creation of images, graphics, tables, or their corresponding captions.

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