Original Research Article

A comparative Study of parenteral versus oral antibiotics in the treatment of severe pneumonia in children under five years of age

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Abstract

Introduction: Pneumonia is a disease known to mankind from antiquity. Pneumonia is an acute inflammation of the pulmonary parenchyma that can be caused by various infective and non-infective origins, presenting with physical and radiological features compatible with pulmonary consolidation of a part or parts of one or both lungs. **Objective:** This study is aimed to compare parenteral versus oral antibiotics in the treatment of severe pneumonia in children under five years of age. **Materials and Methods:** This is a prospective observational comparative study. This study was conducted in the department of pediatrics, MGM hospital, Kakatiya Medical College, Warangal. A total of 268 patients were recruited for the study as per the inclusion and exclusion criteria of the WHO guidelines for community acquired pneumonia. **Results:** A total of 268 children have been enrolled in the present study. Treatment Failure rate in oral amoxicillin group is 12.6% and in Inj. ampicillin plus amikacin group is 11.1%. The difference in treatment outcome in the two treatment groups is NOT statistically significant. A total of 17 out of 134 children in oral amoxicillin group have progressed to treatment failure which amounts to a failure rate of 12.68%. More than half (7/15) of the children who progressed cumulatively to treatment failure in the inj ampicillin plus amikacin group have developed at least one of the signs of WHO defined very severe pneumonia. **Conclusion:** In the present study it has been observed that there is no statistically significant difference in the failure rate in oral amoxicillin group and Inj. Ampicillin plus Inj. Amikacin group, suggesting similar outcome for severe pneumonia treated with oral amoxicillin and Inj. Ampicillin plus Amikacin.

Keywords: Severe Pneumonia, Oral Amoxicillin, Inj Ampicillin plus Inj Amikacin

Introduction

Pneumonia is a disease known to mankind from antiquity. Pneumonia is an acute inflammation of the pulmonary parenchyma that can be caused by various infective and non-infective origins, presenting with physical and radiological features compatible with pulmonary consolidation of a part or parts of one or both lungs [1]. Pneumonia signifies a pulmonary inflammatory process.

The most significant andstriking feature of which is consolidation. Community-acquired pneumonia (CAP) is defined as pneumonia acquired outside hospital or healthcare facilities. Clinical diagnosis is based on a group of signs and symptoms related to lower respiratory tract infection with presence of fever >38ºC (>100ºF), cough, dyspnea, expectoration, pleuritic chest pain and physical examination may reveal focal areas of bronchial breathing and crackles. The frequency of each symptom is quite variable [2-9]. Pneumonia continues to be the biggest killer worldwide of children under five years of age. Although the implementation of safe, effective and affordable interventions has reduced pneumonia mortality from 4 million in 1981[10] to just over one million in 2013 [11-12].

Pneumonia still accounts for nearly one-fifth of childhood deaths worldwide**.** Community-acquired pneumonia is the leading cause of under-five morbidity and mortality in developing countries. One explanation for this higher mortality associated with pneumonia in developing countries is the high prevalence of a

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bacterial etiology in up to 74% in some studies [13]. In India, pneumonia caused nearly 175,000 child deaths in 2013 [14]**.** In the early 1980s, the global burden of childhood mortality due to pneumonia led the World Health Organization (WHO) to develop a pneumonia control strategy suitable for countries with limited resources and constrained health systems as these countries are responsible for a disproportionate 90% of the pneumonia related deaths [15].

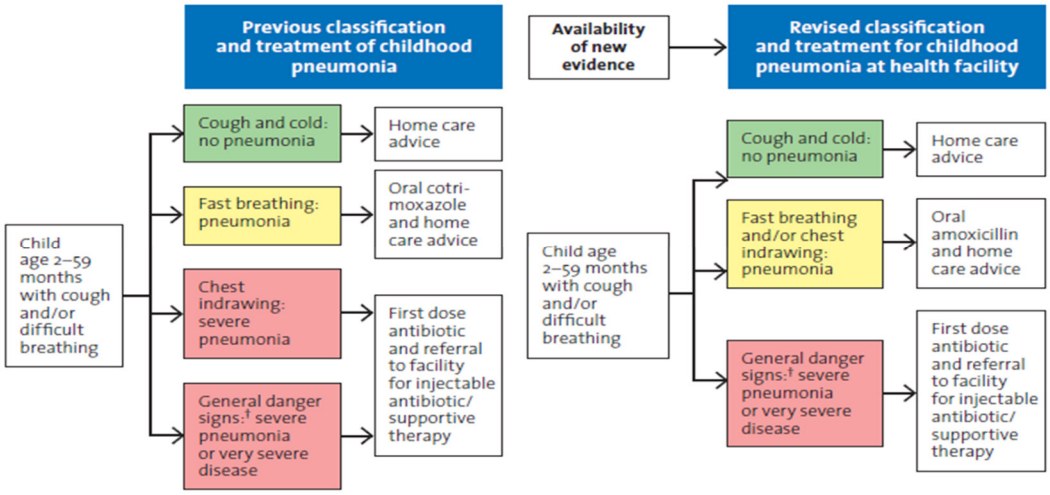
Effective management of pneumonia cases formed thecornerstone of this strategy. Simple signs were identified to classify varying severities of pneumoniain settings with little or no access to diagnostic technology; the classifications determinedthe appropriate case management actions [16]. The original guidelines issued by WHO classified the respiratory symptoms of children 2 to 59 months of age into four categories. Children with cough and cold who did not have signs of pneumonia were classified as "no pneumonia", and their caregivers were advised on appropriate home care with fast breathing were classified as having"pneumonia" and were given an oral antibiotic (at that time oral cotrimoxazole) to take at home for five days.

Children who had chest indrawing with or without fast breathing were classified as having"severe pneumonia" and were referred to the closest higher-level health facility for treatment with injectable penicillin.Children who had any general danger signs were classified as having "very severe disease". These children received a first dose of oral antibiotic and were then urgently referred to a higher-level health facility for further evaluation and treatment with parenteral antibiotics [17-18]. These pneumonia classification and management guidelines had been developed based on evidence generated in the 1970s and early 1980s, and were incorporated into the original version of Integrated Management of Childhood Illness (IMCI). These World Health Organization (WHO) recommen-dations for case management of pneumonia in children aged 2–59 months have been credited with contributing to substantial reductions inmortality [19].

Data shows that the majority of childhood pneumonia deaths are due to severe pneumonia [20]. Management of these severe pneumonia cases requires early identification, prompt referral and the availability of good-quality higher-level care. However, in many low-resource settings, referral is difficult and often does not take place [21-25]. In 2014 WHO undertook a major revision of the treatment recommendations for childhood pneumonia published in its evidence summaries generated from several large multi centre trials with study population of over >3000 children from developing countries.

According to these revised recommendations, children with lower chest wall in-drawing are now to be treated with outpatient oral amoxicillin (at least 40mg/kg/dose twice daily for five days) replacing inpatient benzylpenicillin. The WHO panel utilizing the GRADE methodology [26]. [Grading of Recommendations, Assessment, Development and Evaluation process] was moderately confident in these effect estimates and provided a strong recommendation in favor of this policy shift [27].

Comparison of previous and revised classification and treatment of childhood pneumonia at health facility



† Not able to drink, persistent vomiting, convulsions, lethargic or unconscious, stridor in a calm child or severe malnutrition.

Materials and Methods

Type of study: This is a prospective observational comparative study.

Place of study: This study was conducted in the department of pediatrics, MGM hospital, Kakatiya Medical College, Warangal. This study was approved by the institutional ethical committee.

Duration of study: The study was conducted from December 2015 to November 2017.

Inclusion criteria: Children from 6 months to 59 months old who are diagnosed as having severepneumonia as defined by WHO: cough for less than two weeks, rapid breathing (defined as a respiratory rate of more than 50breaths /min in children above 2 months to 12 months old, and more than 40 breaths/min in children 12 to 59 months old), Inter costal/sub costal retractions during breathing.

Exclusion criteria: Presence of any of the following WHO defined danger signs of very severe pneumonia, Laryngeal stridor, somnolence, lethargy, difficulty in drinking liquids or breast feeding, convulsions, more than three episodes of vomiting per hour, children with co-morbidities such as congenital heartdiseases, HIV/AIDS, tuberculosis, Children with available documented evidence of injectable or oral antibiotic treatment for more than 24 hours before enrollment, children of caregivers who have not given consent to allow the subjects to participate in the study, children with severe acute malnutrition.

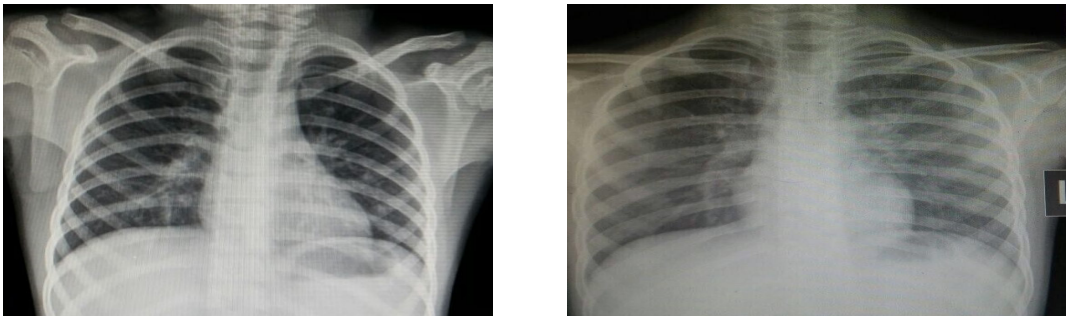
Methodology: A total of 268 patients were recruited for the study as per the inclusion and exclusion criteria. Informed consent was taken from the caregivers of the pediatric patients. The data was collected in a specially designed case record form (enclosed), which contained patient information like name, IP number, age in months, sex and details of physical signs of WHO defined severe pneumonia (i.e tachypnea, chest in-drawing), drug data, duration of treatment, details of any progression to WHO defined very severe pneumonia (danger signs of WHO defined very severe pneumonia are enlisted in the proforma).

Data from relevant investigations like chest X-ray, complete blood picture, blood culture was entered in the case record form. Eligible children were allotted to either “oral group” or “parenteral group”. Children on oral amoxicillin at the WHO-recommended dose of 40–45 mg/kg 8thhourly (group 1) and children on intravenous ampicillin at 100mg/kg 6th hourly plus amikacin at 15mg/kg 12th hourly, are formed group 2.

Patients remained in close clinical observation and daily changes in respiratory rates and progression or regression of the chest retractions were recorded. Observation or clinical monitoring time was minimum 5 days or till discharge.

Study participants were monitored for signs of clinical deterioration or appearance of any “Danger signs” of WHO defined very severe pneumonia, which resulted in prompt revision of treatment and considered as treatment failure. Follow-up data on inpatient treatment failure continued until discharge from hospital or day 5 post enrollments.

Statistical methods: Appropriate statistical tests were applied using software SPSS version 21, percentages, pvalues (chi square test) were calculated and results analyzed.



Chest x ray of a child with Chest x ray of an infant with severe pneumonia severe pneumonia

Results

Table-1: Demographic distribution of total study population.

Age (months)	Male	Female	Total	Percentage
6 to 12	24	21	45	16.8%
13 to 24	40	39	79	29.5%
25 to 36	35	23	58	21.6%
37 to 48	22	21	43	16%
49 to 59	16	27	43	16%
	137	**131**	**268**	**100%**

A total of 268 children have been enrolled in the present study. Among them, majority (n=79 ; 29.5%) of the children are between 13-24 months.

Table-2: Demographic distribution of children with severe pneumonia treated with oral amoxicillin and injection ampicillin and amikacin.

Age (months)	Oral amoxicillin	Injection ampicillin plus amikacin
	Total (percentage)	Total (percentage)
6 to12	24 (17.9%)	21 (15.67%)
13 to 24	40 (29.8%)	39 (29.10%)
25 to 36	27(20.1%)	31 (23.13%
37 to 48	25(18.6%)	18 (13.43%
49 to 59	18(13.4%)	25 (18.65%)
Total	**134(100%)**	**134 (100%)**

A total of 134 children were included in the amoxicillin group. Of them 29.8% (n=40) are in the age group between13 months to 24 months. A total of 134 children were included in the Inj. ampicillin plus Inj. amikacin group. Majority of them fall between the age group of 13 to 24 months (29.10%).

Table-3: Comparative table of treatment outcome in oral amoxicillin group versus Inj.Ampicillin plus Amikacin group.

Treatment group	Treatment outcome				P value
	Success		Failure		
	Number	%	Number	%	
Oral amoxicillin	117	87.31%	17	12.6%	
Inj. Ampicillin plus amikacin	119	88.8%	15	11.1%	= 0.7063

Treatment Failure rate in oral amoxicillin group is 12.6% and in Inj. ampicillin plus Amikacin group is 11.1%. The difference in treatment outcome in the two treatment groups is not statistically significant.

Table-4: Age wise distribution treatment failure in oral amoxicillin group, injection ampicillin plus amikacin group.

Age (months)	Oral amoxicillin		Injection ampicillin plus amikacin	
	Total no. of cases	No. of failure cases (percentage)	Total no. of cases	No. of failure cases (percentage)
6 to 12	24	6 (25%)	21	6 (28.5%)
13 to 24	40	6 (15%)	39	3 (7.6%)
25 to 36	27	3 (11.1%)	31	3 (9.6%)
37 to 48	25	1 (4%)	18	2 (11.1%)
49 to 59	18	1 (5.5%)	25	1 (4%)
Total	**134**	**17 (12.68%)**	**134**	**15 (11.1%)**

A total of 17 out of 134 children in oral amoxicillin group have progressed to treatment failure which amounts to a failure rate of 12.68%. Failure rate is highest among 6 to 12 months age group, in which 6 out of 24 children have progressed to treatment failure, corresponding to a treatment failure of 25%. A total of 15 out of 134 children in Inj. ampicillin plus Inj.amikacin group have progressed to treatment failure, which corresponds to a treatment failure of 11.1% Failure rate is highest among 6 to 12 months age group, in which 6 out of 21 children have progressed to treatment failure, corresponding to a treatment failure of 28.5%.

Table-5: Cause of treatment failure in oral amoxicillin group, and in injection ampicillin plus amikacin group.

Cause	Amoxicillin group	Injection ampicillin plus amikacin group
	Number(percentage)	Number(percentage)
Persistence of signs of severe pneumonia	3 (17.6%)	1 (6.6%)
Progression to very severe pneumonia	9 (52.9%)	7 (46.6%
Change of diagnosis or antibiotics	4 (23.5%)	6 (40%)
Lost to follow-up or withdrawal of consent	1 (5.8%)	1 (6.6%)
Total	**17 (100%)**	**15 (100%)**

More than half (9/17) of the children who progressed cumulatively to treatment failure in the amoxicillin group have developed at least one of the signs of WHO defined very severe pneumonia. Change of treatment by the clinician in the absence ofany of the trial-specified criteria for treatment failure was observed in 4 children. Persistence of signs of WHO defined severe pneumonia was observed in 3 children. 1 child was lost to follow up during the study. More than half (7/15) of the children who progressed cumulatively to treatment failure in the inj ampicillin plus amikacin group have developed at least one of the signs of WHO defined very severe pneumonia.

Table-6: Comparative table of treatment failure rate among children between 6-12 months in oral and parenteral group.

Children between 6-12 months	Treatment failure rate	
Oral Amoxicillin group	25%	p= 0.94
Inj.Ampicillin plus Amikacin group	28.5%	

As treatment failure rate is highest in the children between 6–12 monthsin both “oral amoxicillin” and “parenteral ampicillin plus amikacin” groups, a comparison table was drawn to find any statistically significant difference exists in the treatment failure rates in both the groups.

In children between 6-12 months, the treatment failure rate in oral group is 25% and in parenteral group it is 28.5% and the treatment failure rate is statistically similar in both the groups (p=0.94%).

Table-7: A comparative table showing the number of cases in oral and parenteral groups which have progressed to very severe pneumonia.

Group	Percentage of treatment failure cases which have progressed to very severe pneumonia	
Oral amoxicillin	52.9% (n=9)	p = 0.79
Inj.ampicillin+amikacin	46.6% (n=7)	

In the oral amoxicillin group 52.9% (n=9) of treatment failure cases have progressed to very severe pneumonia, where as in the parenteral Inj. Ampicillin plus Amikacin group 46.6% (n=7) cases have progressed to very severe pneumonia. There is no statistically significant difference between them (p=0.79%) i.e. chances for progression to severe pneumonia is equal in children treated with oral amoxicillin or Inj. Ampicillin plus Amikacin.

Discussion

In the study conducted by Ambroseet al [28], 527 children between 6 to 59 months with WHO defined severe pneumonia were recruited, of them 263 received oral amoxicillin and 264 received Inj.penicillin. Haziret al [29] recruited, 2037 Children aged3–59 monthswith WHOdefinedsevere pneumonia. Out of them 1025 received oral amoxicillin and 1012 received parenteral ampicillin. Atkinson, Lakhanpaulet al [30] recruited 246 children with WHO defined severe pneumonia in PIVOT Trial in which 126 children received oral amoxicillin, while the rest of120 children received Inj.penicillin. The APPIS study conducted by Addoyoboet al [31] recruited 1702 children and were randomly allocated to receive either oral amoxicillin (n=857) or parenteral penicillin (n=845).

In the present study a total of 268 children between 6 months to 59 months have been recruited for study. Of the total children, 134 received oral amoxicillin and 134 received intra venous ampicillin plus amikacin. Our study population is comparable to the pivot trial conducted by Atkinson, lakhanpaul et al [30]. The study populations in the studies conducted by ambrose et al, hazir et al and Addoyobo et al, are comparatively large because they are multi centric trials, where as our study population is confined to a single centre [28,29,31].

In the study conducted by Ambrose et al, males were 57.1% and females were 42.8%. In Hazir et al NO SHOTS study, males were 60.4% and females were 39.5%. In the present study males were 51.1% and females were 48.8%, indicating a slight male preponderance in our study [29].

The results of the current study are consistent with other large multi centre trials. Treatment failure rates in the different studies have varied from 7.5% to 19% in the oral amoxicillin group and from 8.6% to 19% in the Inj.penicillin group.

This variation in the failure rates can be attributed to the wide variation in the study population, study setting (low and middle income countries like Ghana, Vietnam, Bangladesh in Addo-yobo APPIS study, Kenya in Ambrose et al study and high incomeplaces like London in PIVOT study by Atkinson et al), day of measurement of primary outcome (48 hrs in Addoyobo APPIS study, 5th day in Ambrose et al study [28], 7th day in Atkinson et al PIVOT study) and the drug used in the parenteral group (benzyl penicillin in study by Ambrose et al, APPIS study and ampicillin in Hazir et al NO SHOTS study) etc [29].

In the open-label, multicenter, randomized controlled non-inferiority trial conducted by Ambroseagweyu et al, treatment failure by day 5 post enrollment was 11.4% and11.0% in the amoxicillin and benzyl penicillin groups respectively [28]. In the randomized, open-label equivalency trial at seven study sites in Pakistan by Hazir et al, there were 87 (8·6%) treatment failuresin the hospitalized group and 77 (7·5%) in the ambulatory group (risk difference 1·1%; 95% CI –1·3 to 3·5) by day 6.

The multicenter, randomized, open-label equivalency study undertaken at tertiary-care centers in eight developing countries in Africa, Asia, and South America by Addo yobo et al, treatment failure was 19% in each group (161 patients in penicillin arm; 167 patients in amoxicillin arm; risk difference –0·4%; 95% CI –4·2 to 3·3) at 48 hr [31]. In the Present study, treatment failure in oral Amoxicillin group is 12.6% and in the Inj. Ampicillin+Amikacin group is 11.1% by day 5. The treatment failure rates of the present study are comparable to those in the study conducted by Ambrose et al.

Causes for treatment failure in oral amoxicillin group- In the study by Ambrose et al, progression to very severe pneumonia is the most common cause of treatment failure in the amoxicillin group, accounting for 62% of the total treatment failures. In the present study also progression to very severe pneumonia is the most common cause of treatment failure in the amoxicillin group, accounting for 52.9% of all the treatment failures. In the study by Ambrose et al, change of diagnosis/ antibiotic by the treating physician is the second most common cause of treatment failure in the amoxicillin group, accounting for 27.5% of all the treatment failures [28].

In the present study also, Change of diagnosis/ antibiotic by the treating physician is the second most common cause of treatment failure in the amoxicillin group, accounting for 23.5% of all the treatment failures. In the study by Ambrose et al, persistence of severe pneumonia is the thirdmost common cause of treatment failure in the amoxicillin group, accounting for 6% of all the treatment failures [28]. In the present study alsopersistence of severe pneumonia is the third most common cause of treatment failure in the amoxicillin group, accounting for 17.6% of all the treatment failures. In the study by Ambrose et al, withdrawal of consent/lost to follow up is the fourth most common cause of treatment failure in the

amoxicillin group, accounting for 3.4% of all the treatment failures [28]. In the present study also, withdrawal of consent/lost to follow up is the fourth most common cause of treatment failure in the amoxicillin group, accounting for 5.8% of all the treatment failures. In the oral amoxicillin group, theorder of the common causes for treatment failure i.e. from the most common cause to the least common cause, remained same in both the studies, albeit a difference in the failure percentages which could be due to difference in the study sample size.

C**auses for treatment failure in parenteral antibiotic group-** In the study by Ambrose et al, persistence of severe pneumonia is the most common cause of treatment failure in the benzyl penicillin group, accounting for 50% of the total treatment failures [28]. In the present study also persistence of severe pneumonia is the most common cause of treatment failure in the Inj. Ampicillin plus Amikacin group, accounting for 46.6% of all the treatment failures. In the study by Ambrose et al, change of diagnosis/ antibiotic by the treating physician is the second most common cause of treatment failure in the benzyl penicillin group, accounting for 39.6% of all the treatment failures. In the present study also, change of diagnosis/ antibiotic by the treating physician is the second most common cause of treatment failure in the Inj. Ampicillin plus amikacin group, accounting for 40% of all the treatment failures. In the study by Ambrose et al, progression to very severe pneumonia is the third most common cause of treatment failure in the Benzyl penicillin group, accounting for 6% of all the treatment failures. In the present study also persistence of severe pneumonia is the third most common cause of treatment failure in the Inj. Ampicillin plus amikacin group, accounting for 17.6% of all the treatment failures.

In the study by Ambrose et al, withdrawal of consent/lost to followup is the fourth most common cause of treatment failure in the benzyl penicillin group, accounting for 3.3% of all the treatment failures. In the present study also, withdrawal of consent/lost to followup is the fourth most common cause of treatment failure in the Inj.Ampicillin plus amikacingroup, accounting for 6.6% of all the treatment failures.In the parenteral antibiotic group, the order ofcommon causes for treatment failure i.e from the most common cause to the least common cause, remained same in both the studies, albeit a difference in the failure percentages which could be due to difference in the study sample size. In the present study children in the age group of 6 to 12 months have been observed to have higher treatment failure rates than children in other age groups. Similarly, children between 6 to 12 months were observed to have higher rate of treatment failures by Hazir et al in NO SHOTS study [29]. In the current study, progression to very severe pneumonia and change of diagnosis/antibiotic by the treating clinician are the major causes for treatment failure in both the treatment groups in children between 6months to 12 months.

Conclusion

The results of the present study are consistent with findings of other large multicenter studies that informed a recent evidence-driven review of the treatment guidelines for WHO defined severe pneumonia, recommending outpatient oral amoxicillin. In the present study it has been observed that there is no statistically significant difference in the failure rate in oral amoxicillin group and Inj. Ampicillin plus Inj. Amikacin group, suggesting similar outcome for severe pneumonia treated with oral amoxicillin and Inj. Ampicillin plus amikacin.

Relevance of the present study- Severe pneumonia is one of the leading causes for admission in the already overburdened tertiary care government hospitals. With the publication of "Revised WHO classification and treatment of childhood pneumonia at health facilities-evidence summaries 2014", decision concerning the choice of oral amoxiclav as an alternative to the injectable penicillin has come under scrutiny.

As the present study found that oral amoxiclav is equivalent to injectable penicillin in the treatment of severe pneumonia, ithelped us in concluding thatthe Revised WHO guidelines hold good for the local population of Warangal and its neighbouring districts. With the implementation of the new revised guidelines access to antibiotic treatment closer to home is increased and the need for referrals to higher level facilities is decreased

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Contributions- Dr. Vasudev and Dr. Vamsi Krishna contributed to the concept, design of the study, data acquisition and drafting the manuscript. Dr. Vijay Kumar contributed to data analysis, and data interpretation. All authors approved the final manuscript.

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