

REVIEW

The impact of first Timing of antibiotics for community acquired pneumonia in emergency department

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Abstract

Background and objective: For patients with community-acquired pneumonia (CAP), reported associations between timing of the first dose of antibiotics and short-term mortality are inconsistent. To reduce the risks of antibiotic overuse in the emergency department, this summary of the relevant literature identified patients with CAP who benefit most from early antibiotic administration. **Methods:** A PubMed and Google Scholar search was performed for articles concerning the epidemiology, prognosis, diagnosis, and preliminary management of CAP. **Results:** Duplicate studies were eliminated and 370 citations were screened. Finally, 16 studies met the eligibility criteria. The review found that, in the presence of sepsis, antibiotics should not be delayed but administered as soon as possible. For patients with moderate-to-severe symptoms, antibiotics should be administered if a diagnosis of CAP is highly likely. For stable, non-critically ill patients with CAP, the timing of antibiotics remains unclear, but available evidence does not indicate strict requirements. For best quality of care, antibiotic timing whether rapid or delayed depends on the clinical situation. **Conclusions:** In suspected cases of pneumonia presenting in the emergency department, starting antibiotics early solely to conform to dogmatic guidelines within a rigid timeframe has led to unnecessary antibiotic treatment of uninfected patients, while the outcomes of patients with pneumonia have not improved. Since severity of illness is the key factor associated with poor outcomes in pneumonia, the timing of initial antibiotic treatment should be guided by the severity of symptoms.

Keywords

Pneumonia; Timing; Antibiotics; Outcome

1. Introduction

Community-acquired pneumonia (CAP) is often encountered in the emergency department (ED). CAP is a respiratory infection that is a leading cause of hospitalization, morbidity, and mortality [1–4]. Persons with CAP have, by definition, a syndrome of acute lung infection obtained through exposure outside the healthcare system [5]. The old and the very young are the most vulnerable to the effects of CAP, with an annual incidence of 9.2 to 33 per 1000 persons [2, 6]. Each year in the United States, CAP is responsible for approximately 600,000 hospital admissions, costing \$10.6 billion [7].

The effects of CAP can be very severe. In the United States and Canada, 5 to 7% of hospitalized patients suffer mortality, and for older immunocompromised patients or those with comorbidities, this rate is 28% [8]. Based on retrospective data, a short time to first antibiotic dose (TFAD) is thought to benefit patients with suspected CAP who present in the ED [9]. However, among studies, correlations between TFAD after ED arrival and short-term mortality have varied. For example, observational data suggested lower short-term mortality in

patients with moderate or severe pneumonia when antibiotic therapy was administered within 4 to 8 hours [7]. Other studies reported that mortality may not improve, and may even increase with short TFAD [10, 11]; the differences may be due to degree of CAP severity.

Given the risks of antibiotic overuse and misdiagnosis, and to prevent the misallocation of limited resources among time-sensitive patients, it is important to know the best indications for early antibiotics in all cases of suspected CAP [12]. TFAD should be guided by quality, optimal care. There may be a better standard for determining TFAD in CAP than average prognosis [10].

Herein, a literature review was conducted to determine the features of suspected CAP that may best indicate the timeframe for TFAD in patients presenting in the ED.

2. Methods

2.1 Search strategy and study selection

PubMed and Google Scholar were searched to identify English-language articles relevant to pneumonia, CAP,

management and emergency department. The following key words were used: “timing”, “duration”, “antibiotics”, “outcome”, and “epidemiology”.

Titles and abstracts were first screened and selected by consensus of the authors. The full texts of likely articles were accessed to determine final eligibility. The bibliographies of these were also perused for potentially relevant studies. The authors reviewed the articles further to identify those that were specifically relevant to the management of CAP in the ED.

The following exclusion criteria were applied: guidelines; pragmatic and explanatory clinical trials; letters; case reports; case series; exposure during pregnancy or lactation; children; drug adherence as outcome variables; and cost studies.

2.2 Data extraction and quality assessment

Data were extracted and transferred to standardized forms by one team member; the data were verified for accuracy by another team member. Discrepancies and questions were resolved through consensus. All team members participated in data extraction and review. Study quality was assessed in accordance with the GRACE (Good Research for Comparative Effectiveness) guidelines for rating the quality of studies. The GRACE checklist was applied by one team member and reviewed by another, with any conflict resolved by consensus. All team members participated in applying the GRACE checklist.

3. Results

3.1 Study characteristics

The searches in PubMed and Google Scholar initially resulted in 370 potential studies (Fig. 1). Of these, 354 were excluded and 16 met the requirements for this study and were included in the analysis (Table 1).

3.2 Quality assessment

The evidence quality of the 16 studies was assessed by applying the GRACE 11-item checklist (Table 2). The checklist assesses data attributes and methods (items D1-6 and M1-5, respectively). Items were scored as sufficient or insufficient based on a qualitative judgment by the assessors.

3.3 Early administration of antibiotics for CAP

Four studies reported on TFAD administered within 4 hours: 2 retrospective, one prospective, and one systematic review (Table 1). Studies reported that early administration of antibiotics can improve the prognosis of CAP that is concomitant with sepsis [13–17]. The definitions of sepsis and septic shock were last updated in 2016, and a small number of SIRS (systemic inflammatory response syndrome) patients in earlier studies were excluded from the definition. Reports of the benefits of early TFAD motivated the international community to establish guidelines and quality benchmarks in sepsis care [18, 19].

In a large multicenter study of patients with sepsis in the ED, hourly delays in antibiotic administration were associated with

increased hospital mortality, even among those who received antibiotic therapy within 6 hours [20]. While some studies questioned this conclusion, most still support the administration of antibiotics quickly for patients with sepsis. However, where CAP is suspected but sepsis is absent, antibiotic treatment may be delayed because confirming a diagnosis of CAP and its severity requires time; most studies report a mean of approximately 3 hours to first antibiotic dose [21, 22]. A matched case-control, prospective study of 2 cohorts of patients in Europe showed that antibiotic therapy given within 3 hours was associated with improved survival of patients with severe pneumococcal CAP [23]. In addition, the mortality due to non-pneumococcal severe CAP was lower, associated with either early or combined antibiotic therapy. These findings are consistent with the conclusions from a previous study conducted with patients with pneumococcal severe CAP from the same database [23, 24].

3.4 Guidelines and a 4-hour standard

Six observational studies are inconsistent with the above conclusions; and suggest that the association between early antibiotics and short term-mortality diminishes or disappears in studies of higher methodological quality. Although quickening the TFAD in the ED for patients with confirmed CAP is a valuable clinical objective, evidence indicates that prioritizing a 4-hour timeframe before CAP confirmation is unreasonable [25, 26]. Yet, many subsequent studies adopted 4 hours as the cutoff for comparing outcomes.

A study of 13,771 older patients (≥ 65 y) reported that administering an antibiotic within 4 hours of ED arrival led to a 15% reduction in 30-day mortality [27]. Conversely, a large study by Rodrigo *et al.* [26] found that administering antibiotics within 4 hours did not benefit short-term mortality. Other smaller studies of adults of all ages found no significant association between the TFAD and short-term mortality [28–30]. Furthermore, a recent randomized controlled trial determined that a shorter TFAD was not associated with a favorable outcome, in patients hospitalized for moderate and severe CAP [31].

3.5 Administering antibiotics within 6 to 8 hours

Six articles in this review, all retrospective observational studies, concerned TFAD given within 6 to 8 hours. According to one study with a population of 1,170,022 elderly patients (≥ 65 y), after adjustments for demographics and comorbidities, administration of a first antibiotic within 6 hours of hospital arrival reduced 30-day mortality by 5% [32]. In general, 6 hours remains a widely held reasonable expectation [5, 33–37]. However, in a Brazilian cohort study by Bahlis *et al.* [38], initiation of antibiotic therapy occurred 10.4 ± 7.7 hours after patient arrival at the emergency room.

A retrospective study of 14,069 older patients (≥ 65 y) reported that, after adjusting for illness severity with the Pneumonia Severity Index (PSI), first antibiotics administered within 8 hours of hospital arrival was associated with a relative reduction of 15% mortality at 30 days (compared with > 8 h) [39]. Another retrospective cohort study of 2878 patients

TABLE 1. Studies evaluating TFAD for patients with CAP according to hour threshold.

	Design	Data	Sites, n	PTs, n	Age, y	Mortality	Risk (95% CI)	Quality *
Threshold evaluated within 1 h								
Phua et al., 2016 [24]	Syst. Rev.	1981-2016	NA	11,017	NA	INPT or 28-d	RR 0.39-0.90	Moderate
Threshold evaluated within 2 h								
Brett et al., 2017 [22]	Retrospective	2008-2016	1	406	61.8 (mean)	INPT	NR	Low
Threshold evaluated within 3 h								
Trad et al., 2017 [21]	Retrospective	2012-2013	1	312	71 (mean)	INPT 30-, 60-d	NR	Low
Gattarello et al., 2014 [2]	Prospective	2008-2013	29	160	58 (mean)	ICU	OR 0.82 (0.68-0.98)	Moderate
Threshold evaluated within 4 h								
Houck et al., 2004 [27]	Retrospective	1998-1999	3463	13 771	NA	30-d	OR 0.85 (0.76-0.95)	Low
Waterer et al., 2006 [29]	Prospective	1998-2001	1	451	58 (mean)	INPT	NR	Low
Yu et al., 2008 [25]	Syst. Rev.	1966-2006	NA	22 387	NA	30-d	OR 0.24-1.99	Low
Lee et al., 2011 [30]	Prospective	2001	32	2 076	74 (median)	30-d	OR 0.74 (0.48-1.13)	Low
Simonetti et al., 2012 [28]	Prospective	2001-2009	1	1 274	NA	30-d	OR 1.12 (0.38-3.33)	Low
Rodrigo et al., 2015 [26]	Prospective	2009-2013	2	371	76 (mean)	INPT 30-, 90-d	OR 1.62 (1.42-1.84)	Low
Threshold evaluated within 6 h								
Battleman et al., 2002 [34]	Retrospective	1998	7	609	67 (mean)	NA	NR	Low
Lee et al., 2014 [37]	Retrospective	2006-2010	4740	1 170 022	80 (mean)	30-d	OR 0.95 (0.93-0.98)	Low
Threshold evaluated within 8 h								
Meehan et al., 1997 [39]	Retrospective	1994-1995	3555	14 069	79 (mean)	30-d	OR 0.85 (0.75-0.96)	Low
Dedier et al., 2001 [35]	Retrospective	1997-1998	38	1 062	64 (median)	INPT	OR 1.69 (0.78-3.66)	Low
Arnold et al., 2007 [36]	Retrospective	2001-2006	39	2878	65 (mean)	INPT	OR 0.57 (0.44-0.74)	Low
Simonetti et al., 2012 [28]	Prospective	2001-2009	1	1 274	NA	30-d	OR 1.58 (0.64-3.88)	Low

INPT, inpatient; NA, not available; NR, not reported; OR, odds ratio; PT, patient; RR, risk ratio; Syst. Rev., systematic review. *Quality of the evidence was assessed using the GRACE guidelines.

found that administering antibiotic therapy within 8 hours of hospital arrival was associated with a relative reduction in hospital mortality of 43% [40].

Some studies have reported a wider time range for initial antibiotic dosing. A systematic review of 4 large observational studies concluded that administering antibiotics for CAP within 4 to 8 hours of hospital arrival reduced mortality 5% to 43%, even in non-ICU patients [7]. Administering antibiotics such as beta-lactam or macrolide or a fluoroquinolone within 4 to 8 hours of ED arrival led to lower adjusted short-term mortality. However, these studies were low-quality and observational only. For a stable, non-critical patient with CAP, the time from arrival at the ED to first dose of antibiotic is

determined managerially [7, 8]. Large scale, non-commercial, randomized controlled trials are needed to determine the optimal TFAD for treating CAP [5].

4. Discussion

4.1 Effect of timing of antibiotics on outcomes in CAP

Patients with bacterial pneumonia require treatment, but the timing of initial treatment remains controversial. With only inadequate evidence, we are forced to rely on current guidelines that recommend treating patients with antibiotics as soon as

TABLE 2. Checklist items of the GRACE and maximum assessment score for each.

Checklist item	Total, n	% of total
Data attributes		
D1. Were treatment and/or important details of treatment exposure adequately recorded for the study purpose in the data source(s)?	13	81
D2. Were the primary outcomes adequately recorded for the study purpose?	15	94
D3. Was the primary clinical outcome(s) measured objectively rather than subjectly to clinical judgment?	15	94
D4. Were primary outcomes validated, adjudicated, or otherwise known to be valid in a similar population?	12	75
D5. Was the primary outcome(s) measured or identified in an equivalent manner for the treatment/intervention group and the comparison group?	12	75
D6. Were important covariates that may be known confounders or effect modifiers available and recorded?	9	56
Methods		
M1. Was the study (or analysis) population restricted to new initiators of treatment or those starting a new course of treatment?	8	50
M2. If one or more comparison groups were used, were they concurrent comparators? If not, did the authors justify the use of historical comparison groups?	7	44
M3. Were important confounding and effect-modifying variables taken into account in the design and/or analysis?	6	38
M4. Is the classification of exposed and unexposed person-time free of immortal time bias?	2	13
M5. Were any meaningful analyses conducted to test the key assumptions on which the primary results are based?	2	13

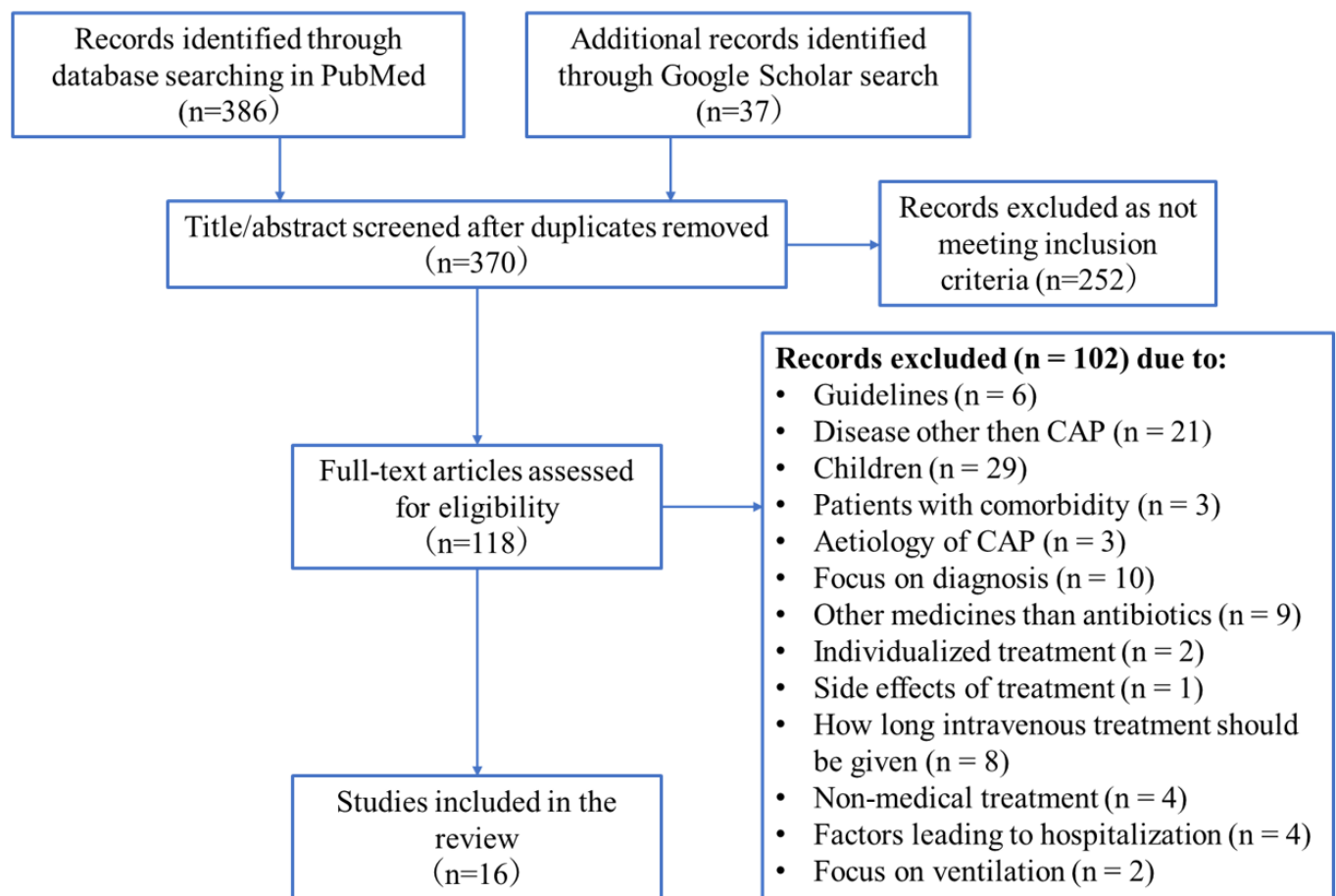


FIGURE 1. Flowchart of literature review and study selection.

the diagnosis of CAP is confirmed, ideally, before they leave the initial assessment area (ED or acute medical unit). The recommended TFAD of patients with CAP varies in different countries and regions.

Any discussion of treatment times should consider disease severity. It is widely accepted and biologically plausible that administering antibiotics as early as possible to patients with CAP and sepsis or sepsis shock should improve their outcomes [41]. The Surviving Sepsis Campaign recommends administering antibiotics within the first hour of recognition of sepsis and septic shock. Yet for moderate or severe CAP without sepsis, TFAD is not definitive.

Early studies showed that early appropriate antimicrobial therapy could benefit the survival of patients with pneumonia [39, 42, 43]. Indeed, most observational data has suggested lower short-term mortality in patients with moderate or severe pneumonia, when TFAD is within 4 to 8 hours of hospital arrival. However, in a randomized controlled trial of patients hospitalized for moderate to severe CAP, a shorter TFAD was not associated with a favorable outcome [31]. This prospective study also raised concerns about the early administration of antibiotics to patients with CAP. The 2007 revised guideline of the Infectious Disease Society of America/American Thoracic Society changed the initial 4-hour time mandate (PN-5b) to 6 hours (PN-5c) [44]. According to a systematic review published in 2016, the evidence supporting a 6-hour or 8-hour mandate is no stronger than for the initial 4-hour mandate [7].

For patients with mild disease, there is no clear evidence to guide TFAD. Antibiotics are administered within 8 hours of hospital arrival for most patients with CAP. Of course, for some patients treatment is delayed due to unclear diagnosis or other reasons. Patients with mild CAP typically have been sick for several days prior to their visit, and timing may be influenced by factors that are not related to the course of the infection. Therefore, rushing to antibiotics quickly may not be imperative, and diagnosis could be more reliably confirmed by adequate testing.

4.2 Factors affecting antibiotic timing

Chest computed tomography (CT) imaging will increase the diagnosis rate of pneumonia, with sensitivity that approaches 100% [45, 46]. A chest CT image is often warranted in patients with respiratory symptoms and signs of sepsis or shock, but showing a negative chest radiograph. The time to complete and interpret the chest radiograph and CT image greatly influences the time of first antibiotic administration, and can vary greatly in different practice environments, based on available resources. Lung ultrasound is highly sensitive and specific for the diagnosis of pneumonia in adults [47–49], with good discrimination even in patients with acute dyspnea. Lung ultrasound can be performed in fewer than 13 minutes in the ED, which is much less than the time required for a chest X-ray or CT scan. There is currently no quality metric offered by the CMS (Centers for Medicare & Medicaid Services) for specifying TFAD, but within 4 to 8 hours of hospital arrival is widely accepted [33] as ideal for a stable patient without critical illness. Patients with CAP who exhibit signs of sepsis should be given antibiotics as soon as possible; preferably

within 1 hour [41]. On the other hand, compared with sepsis the urgency to treat is less for patients with moderate or severe CAP, and lesser still for patients with mild disease.

Often, the time at which patients with CAP present in the ED depends on reasons other than the disease course stage. Since the timing of antibiotic initiation depends on disease severity, it is reasonable that emergency physicians should routinely adhere to a structured approach or clinical decision rule to stratify the risk of patients with CAP. Several guidelines and recommendations exist for the purpose, including the PSI, and CURB-65 (based on scores for confusion, blood urea nitrogen, respiratory rate, blood pressure, and age 65 and older). In addition, several national and international societies have offered guidelines that prognose the course of illness and help guide patient management [50].

Both the PSI and CURB-65 help identify patients who may be treated safely as outpatients [51]. However, few studies have applied these rules to guide the TFAD in the ED, and clinicians invariably base such treatment decisions on the severity of the patient's condition, i.e., those with a more severe infection are administered antibiotics more quickly. Serum inflammatory markers (such as procalcitonin and C-reactive proteins (CRP)) have been proposed as adjuncts or alternatives to clinical severity scores, which may affect the TFAD in CAP [52]. However, it remains unclear if serum inflammatory markers are useful in the ED. CRP may reflect clinical stability, but its kinetics lag behind clinical presentation, which makes it an unreliable indicator for CAP severity [53]. In addition, CRP is not sensitive and does not rule out a complicated course of illness. This limits its usefulness for guiding early treatment. We do not recommend using CRP to determine the start of antibiotics [54].

Early studies using procalcitonin to help direct the application of antibiotic in CAP were promising [55]. These early studies found that using procalcitonin to guide antibiotic treatment was associated with reduced treatment duration, cost, and adverse effects, and helped indicate conversion to oral antibiotics [56–58]. However, the ProACT (Procalcitonin Antibiotic Consensus Trial), a multicenter randomized trial to evaluate the use of procalcitonin in guiding antibiotic initiation, did not find procalcitonin adequately effective. This may be because other acute illness conditions, including heart failure, can lead to increases in procalcitonin [59]. Other biomarkers, such as IL-6 and pro-adrenomedullin, are rarely used to guide the initiation of antibiotics in the ED [12].

Overcrowding in the ED affects almost all aspects of care delivery, including the rush to diagnosis or its delay, and ordering and initiation of antibiotics [60]. Without systemic changes, this situation may worsen as ED presentations increase worldwide. Delivering the highest quality of care may be unsustainable [61, 62]. Presentations and admissions due to CAP are common and are not exempt from this trend [26]. Indeed, available evidence shows that overcrowding is associated with delays and poor outcomes in adults with CAP [63].

4.3 Disadvantages of early antibiotic therapy for CAP

A retrospective study of adult patients with CAP found that decreasing the TFAD from 8 to 4 hours, as recommended by the CMS, reduced the diagnostic accuracy of ED physicians, but the actual TFAD did not shorten significantly [64]. In another study, the attempt to increase the number of patients with a TFAD of < 4 hours led to a 17% increase in the number of patients who received antibiotics unnecessarily [65]. Observational studies also find that implementation of a TFAD < 4 hours for CAP did not improve all-cause mortality, but was associated with an increase in unnecessary antibiotic treatment [11]. A retrospective study reported that pressure to comply with the 4-h TFAD in the ED, i.e., in accordance with a better-safe-than-sorry approach, led to overtreatment of adults with intravenous antibiotics, regardless of CAP severity [66].

This is problematic, since the effects of unnecessary antibiotic treatment-e.g., *Clostridium difficile* infection, drug reactions, allergies, dehydration in the setting of diarrhea, and antibiotic resistance-are difficult to measure. Adverse outcomes may go unrecognized; and a risk/benefit decision is made difficult by the possibility of underappreciated harm. Imposing rigor in deciding to start antibiotics for CAP that is less than severe is of great concern in this setting, and is being addressed by national multidisciplinary goals such as that of the Department of Health Antimicrobial Resistance Strategy of the United Kingdom [28].

Our assessment is that TFAD, with the appropriate antibiotic, should be earliest for cases of sepsis, regardless of the source of infection. Next earliest is for patients with likely CAP concomitant with severe features or comorbidities. However, a strict TFAD timeframe for CAP of low severity has limited value, and rigorous adherence has had detrimental effects.

5. Conclusions

The dogma of starting antibiotics quickly, within a rigid expected timeframe, has not improved the outcomes of pneumonia patients, but has led to an increase in antibiotic treatment of uninfected patients. Severity of illness is the key factor associated with poor outcomes, and should be the most significant guide for timing antibiotic initiation. Contrary to the recommendations of many organizations, we suggest that best quality care demands that rapid or delayed administration should depend on the clinical situation. Rather than an inflexible set TFAD for all patients with suspected CAP presenting in the ED, the decision to treat rapidly should rest on clinical assessment, risk stratification, clarity of imaging studies, ancillary data such as lab testing, and patient factors and comorbidities.

AUTHOR CONTRIBUTIONS

Conception and design: Yiwu Zhou and Yao Rong. Collection and assembly of data: Yiwu Zhou, Yanqi He. Data analyzes and interpretation: Yiwu Zhou and Yanqi He. Manuscript preparation: Yiwu Zhou. Manuscript proofing: all authors.

Final approval of the manuscript: all authors.

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CONFLICT OF INTEREST

The authors have no conflict of interest to declare.

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