Review

The Impact of First Timing of Antibiotics for Community Acquired Pneumonia in Emergency Department

Yiwu Zhou[1,2], Casey M. Clements[3], Man Li[4], Yanqi He[5]*, Rong Yao[1,2]*

[1] Department of Emergency Medicine, Emergency Medical Laboratory, West China Hospital, Sichuan University, Chengdu, Sichuan 610041, China; <u>456zyw@163.com</u> (YZ); <u>yaorong@wchscu.cn</u> (RY)

[2] Disaster Medical Center, Sichuan University, Chengdu 610041, Sichuan, Chengdu, Sichuan 610041, China

[3] Department of Emergency Medicine, Mayo Clinic, 200 First St SW, Rochester, MN, 55905, USA; <u>Clements.Casey@mayo.edu</u> (CC)

[4] Department of Information Technology, Mayo Clinic, 200 First St SW, Rochester, MN 55905, USA <u>Li.Man@mayo.edu</u> (ML)

[5] Department of Respiratory and Critical Care Medicine, West China Hospital, Sichuan University, Chengdu 610041, China; <u>heyq2004@126.com</u> (YH)

* Rong Yao: yaorong@wchscu.cn; Tel: 86018980601415

* Yanqi He: heyq2004@126.com; Tel: 86015390406812

Abstract: Background: The reported associations between time to first antibiotic dose after hospital arrival and short-term mortality have varied in prior studies of CAP. It is unclear the benefit of early antibiotics in all patients given the risks of antibiotic overuse and misdiagnosis; Methods: A PubMed and Google Scholar search was performed to identify articles detailing the epidemiology, prognosis, diagnosis, and preliminary management of CAP; Results: In sepsis, antibiotics should not be delayed, and should be administered as soon as possible after recognition. For moderate or severe CAP patients without sepsis, antibiotics should be administered as soon as the diagnosis of CAP is highly likely. For stable, non–critically ill patients with CAP, the timing of antibiotics is not as clear and available evidence does not recommend strict requirements. Antibiotic timing – both rapid and delayed could be used as indicators of quality care in differing clinical scenarios; Results: The dogma of starting antibiotics quickly, within a rigid timeframe of expectations and guidelines has not improved outcomes in pneumonia patients, and has led to an increase in antibiotic treatment in uninfected patients. Severity of illness is the key factor associated with poor outcomes and should more significantly guide the timing of antibiotic initiation.

Keywords: Pneumonia; Timing; Antibiotics; Outcome

1. Introduction

Community-acquired pneumonia is a commonly encountered respiratory infection in the emergency department that is a leading cause of hospitalization, morbidity, and mortality [1-4]. CAP is defined as a syndrome in which acute infection of the lungs develops in persons without recent health care exposure[5]. CAP particularly impacts the old or the very young, with an annual incidence of 9.2 to 33 per 1,000 persons[2, 6]. Each year in the United States, community-acquired pneumonia is responsible for approximately 600,000 hospital admissions and costs $10.6 billion[7]. CAP can be a severe infection and 5-7% of patients admitted with CAP die in the hospital in the United States and Canada. For older patients with comorbidities or immunocompromised the mortality reaches 28% in admitted patients[8].

A short time to first antibiotic dose (TFAD) has attracted attention as a popular and intuitive

target for CAP in the ED, although this is based on retrospective database studies[9]. The reported associations between TFAD after hospital arrival and short-term mortality have varied in prior studies of CAP, and TFAD after hospital arrival remains uncertain. Observational data suggest lower short-term mortality when antibiotic therapy is administered within four to eight hours of hospital arrival in patients with moderate or severe pneumonia[7]. This remains controversial however, and other studies have found that mortality may not improve, and may even increase with a short TFAD[10, 11], which may be caused by the urgent medical attention with severe CAP patients rather than a causal effect. It is unclear the benefit of early antibiotics in all patients given the risks of antibiotic overuse and misdiagnosis[12].

Attention to TFAD may also result in reduced attention to and investment in the needs of other time-sensitive patients in resource-limited settings like EDs. Previous efforts to require and report on TFAD in CAP were challenged for several reasons, including antibiotic abuse, overuse of antibiotics, misdiagnosis. So it has been proposed that TFAD in CAP should be used as a marker of quality, optimal care rather than predicting outcomes as it does with sepsis[10].

2. METHODS

A PubMed and Google Scholar search was performed to identify articles detailing the epidemiology, prognosis, diagnosis, and preliminary management of CAP. The following key words were used: community acquired pneumonia; timing; antibiotics; outcome. These results were narrowed to include English-language articles and, of those results, authors reviewed articles to identify those relevant to the emergency department (ED) management of CAP. Excluded studies include those that did not introduce the duration of initial antibiotic use.

3. Results

A total of 16 studies that meet the requirements were included in the analysis (Table 1).

Table 1. Description of Studies Evaluating Time to Initiate Antibiotic Therapy for Patients Hospitalized With Community-Acquired Pneumonia

Source	Study design	Patient of data collection	NO. of Study Sites	NO. of Patients	Ages	Mortality definition	Evidence quality[a]
Threshold Evaluated within 1 h							
Jason et al[29], 2016	Systematic review	1981-2016	Data not available	11,017	Data not available	In-hospital or 28-day	Moderate
Threshold Evaluated within 2 h							
Brett A. et al[27], 2017	Retrospective	2008-2016	1	406	61.8 (mean)	In-hospital	Low
Threshold Evaluated within 3 h							
Trad MA et al[26], 2017	Retrospective	2012-2013	1	312	71 (mean)	In-hospital 30-day 60-day	Low
Gattarello et al[28], 2014	Prospective	2008-2013	29	160	58 (mean)	ICU	Moderate
Threshold Evaluated within 4 h							

Houck et al[32], 2004	Retrospective	1998-1999	3463	13 771	Data not available	30-day	Low
Waterer et al[34], 2006	Prospective	1998-2001	1	451	58 (mean)	In-hospital	Low
Kenneth et al[30], 2008	Systematic review	1966-2006	Data not available	22 387	Data not available	30-day	Low
Lee et al[35], 2011	Prospective	2001	32	2 076	74 (median)	30-day	Low
Simonetti et al[33], 2012	Prospective	2001-2009	1	1 274	Data not available	30-day	Low
Chamira et al[31], 2015	Prospective	2009-2013	2	371	76 (mean)	In-hospital 30-day 90-day	Low
Threshold Evaluated within 6h							
Battleman et al[39], 2002	Retrospective	1998	7	609	67 (mean)	Data not available	Low
Lee et al[42], 2014	Retrospective	2006-2010	4740	1 170 022	80 (mean)	30-day	Low
Threshold Evaluated within 8h							
Meehan et al[14], 1997	Retrospective	1994-1995	3555	14 069	79 (mean)	30-day	Low
Dedier et al[40], 2001	Retrospective	1997-1998	38	1 062	64 (median)	In-hospital	Low
Arnold et al[41], 2007	Retrospective	2001-2006	39	2878	65 (mean)	In-hospital	Low
Simonetti et al[33], 2012	Prospective	2001-2009	1	1 274	Data not available	30-day	Low

[a] According to the levels of recommendation, evaluation, development and evaluation system, the two authors of this study classified them as high, medium, low or very low respectively.

4. Discussion

The impact of timing of antibiotics on outcomes in CAP

Clearly, patients with bacterial pneumonia warrant treatment. However, the timing of that treatment remains controversial and we are forced to rely on current guidelines based on relatively poor evidence. Guidelines recommend treating patients with antibiotics as soon as the diagnosis of CAP is confirmed. Ideally, these should be given before they leave the initial assessment area (emergency department or acute medical unit). It should be noted that TFAD of CAP patients varies in different countries and regions. In addition, any discussion on treatment times must take into account disease severity. Antibiotics should be administered within the first hour of recognition of CAP with sepsis. But TFAD is controversial for moderate or severe CAP without sepsis. Early studies demonstrated some survival benefit in pneumonia patients related to early appropriate antimicrobial therapy[13-15]. Indeed, most observational data suggest lower short-term mortality

when TFAD within four to eight hours of hospital arrival in patients with moderate or severe pneumonia. But in a randomized controlled trial of patients hospitalized for moderate-severe CAP, a shorter time to TFAD was not associated with a favorable outcome[16]. This prospective study has also raised concerns about the early administration of antibiotics in CAP patients. In patients with more mild disease, there is not clear evidence to guide TFAD.

Early administration of antibiotics for CAP

It is widely accepted and biologically plausible that administering antibiotics as early as possible to CAP patients with sepsis or sepsis shock should improve their outcomes[17]. The Surviving Sepsis Campaign recommends administering antibiotics within the first hour of recognition of sepsis and septic shock. Indeed, early studies have shown that this can improve the prognosis of CAP with sepsis[18-22]. Early TFAD has motivated international guidelines and quality benchmarks in sepsis care[23, 24]. In a large multicenter study of patients with sepsis in the emergency department, hourly delays in antibiotic administration were associated with increased hospital mortality rate even among patients who received antibiotics therapy within 6 hours[25]. Although some studies had questioned this point view, most studies still support the administering antibiotics quickly for sepsis patients.

Confirming the diagnosis and severity of CAP takes some time, and in the absence of sepsis antibiotic treatment may be delayed. In most studies the mean time to first antibiotic dose in CAP patients is approximately 3 hours[26, 27]. A matched case-control, prospective study of two cohorts of patients in Europe demonstrated early antibiotic administering within 3 h was associated with improved survival in severe pneumococcal CAP[28]. The mortality due to non-pneumococcal severe CAP decreased between the two cohorts, and early antibiotic administration as well as the use of combined antibiotic therapy were associated with lower hospital mortality. These findings are consistent with the conclusions from a previous study carried out in patients with pneumococcal severe CAP from the same database[28, 29].

Guidelines and a four hours standard

In 2004, the Joint Commission on Accreditation of Hospital Organizations (JCAHO) mandated the time to first antibiotics for patients with a "working diagnosis" of pneumonia to be within 4 hours of ED arrival. The 2009 and 2015 British Thoracic Society (BTS) Guideline for CAP states that the objective for any service should be to confirm a diagnosis of pneumonia with chest radiography and first antibiotic be administered for the majority of patients with CAP within 4 h of presentation to hospital. However, the evidence in support of this comes from observational studies that are inconsistent and that suggest the association between early antibiotics administering and short term-mortality diminishes or disappears in studies of higher methodological quality. Although the time to first antibiotics administered in the ED with confirmed CAP is a valuable clinical objective, an inflated sense of priority of the 4-hour time frame or antibiotic administration before confirmation of the CAP diagnosis is unreasonable by the clinical evidence[30, 31]. Since these guidelines have been released, there have been many studies which adopt 4-hour time as the cut-off time to compare outcomes. A subsequent study of 13,771 older patients (≥65 years) that used a similar design and severity adjustment method also reported that antibiotic administering within 4 hours or less of ED arrival was associated with 15% reduction in 30-day mortality[32]. Conversely, a

large study by Rodrigo et. al., showed that administering antibiotics within 4 hours did not translate into a benefit in short-term mortality[31]. Other smallest studies found no significant associations between the time to first antibiotic administering and short-term mortality in adults of all ages[33-35]. Recently a randomized controlled trial was reported that found in patients hospitalized for moderate and severe CAP, a shorter time to first antibiotic administration was not associated with a favorable outcome[16].

Administering antibiotics within six to eight hours

In September 2007, The Joint Commission specification manual was revised to recommend TAFD for CAP to be within 6 hours. Citing the Infectious Disease Society of America/American Thoracic Society guideline revision in 2007, the manual replaces the initial 4-hour time mandate (PN-5b) with a 6-hour mandate (PN-5c)[36]. However, a systematic review indicates that the evidence supporting a 6-hour or 8-hour mandate is no stronger than that in favor of the initial 4-hour mandate[7]. A recent retrospective study of 1,170,022 elderly patients ((≥65years) demonstrated that administration of a first antibiotic within 6 hours of hospital arrival resulted in a 5% relative reduction in 30-day mortality, adjusting for the patient's demographic characteristics and comorbidity[37]. In 2012, JCAHO again altered their recommendation to focus on antibiotic selection within the first 24 hours of hospitalization and has veered away from recommending TFAD. Six hours remains a widely held expectation in general[5, 38-42].

Antibiotics are administered within 8 hours of hospital arrival for most CAP patients. Of course, for some patients the treatment will be delayed due to unclear diagnosis or other reasons. A cohort study by Laura Fuchs Bahlis reported the mean time from patient arrival at the emergency room to initiation of antibiotic therapy was 10.4 ± 7.7 hour in a (which country/kind of ED)[43]. A retrospective study of 14,069 older patients (≥65 years) reported that first antibiotics were administered within 8 hours (vs >8 hours) of hospital arrival was associated with a relative reduction of 15% mortality at 30 days, adjusting for illness severity with the pneumonia severity index[14]. Another retrospective cohort study of 2,878 patients proved that administering antibiotic within 8 hours of hospital arrival was also associated with a relative reduction in hospital mortality of 43%[44]. Of course, some recent studies have not specified a specific point in first antibiotics time, but rather proposed a relatively loose time period. A recent systematic review of four large observational studies concluded that administering antibiotics for CAP within 4-8 hours of hospital arrival resulted in a relative 5-43% reduction in mortality, even in non-ICU patients[7]. Administering antibiotics such as beta-lactam and macrolide, or a fluoroquinolone within 4–8 h of ED arrival was associated with lower adjusted short-term mortality, but the conclusion only comes from low-quality, observational studies. Large scale, non-commercial, randomized controled trials are needed to determine the optimal time to first antibiotic administering for CAP[5].

Administering antibiotics for stable CAP patients

The time from ED visit of a stable, non-critical patient with CAP to the administering of first antibiotics dose is a managerially determined characteristic[7, 8]. Patients with this type of 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 biological time scale of the infection. So rushing to antibioitics quickly may not be as critical, and diagnosis could be more reliably confirmed by adequate testing.

Factors affecting antibiotic timing

Chest CT imaging enhances the diagnosis rate of pneumonia, with sensitivity that approaches 100%[45, 46]. Chest CT image is often warranted in patients with respiratory symptoms and signs of sepsis or shock, but negative chest radiograph.   The time to complete the chest radiograph and CT image greatly influences the time of first antibiotic administration. The time to image acquisition and interpretation can vary greatly in different practice environments based on available resources. Lung ultrasound had a high sensitivity and specificity for the diagnosis of pneumonia in adults[47-49]. It has good discrimination even in patients with acute dyspnea. Lung ultrasound can be performed in less than 13 minutes in ED and substantially shorter than the timeframe required for a CXR or chest CT scan.

There is no longer a time for Medicare & Medicaid Services (CMS) quality metric regarding to first antibiotics administering, but a widely accepted target is within four to eight hours of hospital arrival[38]. This recommendation is largely based on the ideal of a stable patient without critical illness. CAP patients who exhibit signs of sepsis should been administered antibiotics as soon as possible and recent guidelines have recommended giving them within 1 hour[17]. Moderate to severe has to have a lower threshold for administration than mild disease.

Often, the timing of ED presentation for CAP patients is influenced by factors having little to do with the biological time scale of the infection itself. Since the timing of antibiotic initiations is variable based on disease severity, it is reasonable that emergency physicians routinely use a structured approach or clinical decision rule to risk stratify patients with CAP before starting antibiotics. Several guidelines and recommendations exist for risk stratification of CAP including: pneumonia severity index (PSI), CURB-65, and several national and international societies' guidelines have been proposed to prognose CAP patients' course of illness and have been proposed to help guide disposition of the patient[50]. Bot PSI and CURB-65 use vital signs and lab data to calculate a score that correlates with clinical outcomes. PSI is more specific with five classifications and requires several lab measurements. CURB-65 on the other hand only requires five data points and is simple to use. Both PSI and CURB65 aim to help identify patients that may be safely treatable as an outpatient[51]. IDSA in cooperation with the American Thoracic Society (ATS), published criteria in 2007 that also aim to help identify level of care determination for inpatients, and provide separate recommendations for outpatients including comorbidities. The British Thoracic Society (BTS) guidelines use the CURB 65 score in conjunction with clinical judgment. A Dutch guideline is a mixture of IDSA/ATS and BTS guidelines, as it is recommended to use any of the three classification systems (PSI, CURB 65, or pragmatic classification) rather than special recommendations. However, few studies have used these rules to guide the time to first antibiotics administering in ED. In fact, clinicians always determine the time of first antibiotic administering based on the severity of the patient's condition. Those who have a more severe infection should be administered antibiotics more quickly.

Serum inflammatory markers (such as procalcitonin, c-reactive proteins, etc.) are being proposed as adjuncts or alternatives to clinical severity scores, which may affect TFAD in CAP[52]. It remains unclear if serum inflammatory markers are useful in the ED. CRP may play a role in determining clinical stability, but its kinetics lag behind clinical presentation which makes it an unreliable indicator for CAP severity at ED presentation[53]. In addition, CRP is not sensitive and

does not rule out a complicated course of illness, limiting its use in guiding early treatment. We do not recommend using CRP within the decision start antibiotics[54]. Early studies using procalcitonin (PCT) to help direct antibiotic use in CAP were promising [55]. The thinking was that PCT could help separate out viral pneumonia, COPD exacerbation, and pulmonary edema from bacterial pneumonia that requires antibiotics if the diagnosis of CAP was unclear in patients without critical illness. These early studies found that using PCT to guide antibiotic treatment, helped reduce treatment duration, cost and adverse effects and helped in making decisions to step down to oral antibiotics[56-58]. However, the ProACT trial, a multicenter randomized trial to evaluate the use of PCT in guiding antibiotic initiation did not find PCT adequately effective. This may be because other acute illness conditions, including heart failure can lead to increases in PCT[59]. Additionally, antibiotic administration in admitted patients is associated with decreasing PCT levels even in the absence of likely bacterial infection (e.g. bronchitis, COPD exacerbation). Other biomarkers, such as IL-6 and pro-adrenomedullin may have prognostic value but these tests have not been studied extensively in many clinical settings and remain rare and expensive. Elevated blood urea nitrogen (BUN) and glucose, as well as low levels of sodium, while not biomarkers in the traditional sense, are associated with worse outcomes and therefore more severe disease. These are incorporated into several of the risk stratification scoring systems and should not be ignored in the clinical evaluation of CAP patients. Currently however, these are rarely used to guide the initiation of antibiotics in ED[12].

ED overcrowding affects almost all aspects of care delivery in an ED, including antibiotic initiation, and should not be ignored as a major contributor to delaying or rushing in diagnosis, ordering, and administration of antibiotics[60]. This may only get worse without systemic changes since data suggest that recent growth in ED presentations worldwide may be unsustainable while trying to deliver the highest quality of care[61, 62]. CAP presentaitons and admissions are common and are not exempt from this trend[31]. Indeed, available evidence shows that overcrowding is associated with delays and poor outcomes in adults with CAP[63]. Overcrowding could also affect aggressive ED providers to have a lower threshold to initiate treatment of pneumonia, even without confirmation of the diagnosis, since overcrowding prevents attention to detail given competing clinical responsibilities. However, studies are lacking and would be difficult to conduct given the adverse effects of inappropriate antibiotic treatment are long term and can affect populations as well as individuals.

Disadvantages of early antibiotic therapy for CAP

A retrospective study of adult CAP patients showed that the CMS guideline reduction in the expected time to first antibiotic administration from 8 to 4 hours was associated with a reduction in diagnostic accuracy by ED physicians, while failing to significantly reduce the actual TFAD given to CAP patients[64]. In another study, in order to achieve an increase in the number of patients with time to first antibiotic administering <4 h, an additional 17% of patients were unnecessarily administered antibiotics[65]. Observational studies also find that implementation of the < 4 hours expection for antibiotics in CAP did not improve all-cause mortality but was associated with an increase in unnecessary antibiotic treatment[11]. A retrospective study reported that the pressure to comply with the 4 h antibiotics administering principle in ED and a 'better safe than sorry' approach tended to "overtreat" adults with intravenous antibiotics regardless of CAP severity[66].

This is problematic since the effect of unnecessary antibiotic treatment, such as Clostridium Difficile infection, drug reactions and allergies, physiologic detriment such as dehydration in the setting of diarrhea, and antibiotic resistance are difficult to measure leading to an underappreciation of the incidence of adverse outcomes. This makes a risk/benefit decision difficult since the harm is likely underappreciated. Improving our rigor in deciding to start antibiotics for low severity CAP is increasingly important in this setting and is consistent with national multidisciplinary goals such as the UK's Department of Health Antimicrobial Resistance Strategy[33]. In this as well, our assessment is that attention should be directed to starting early appropriate antibiotic treatment first in sepsis, regardless of the source of infection, then for patients with likely CAP with severe features or comorbidities, and that guidelines focusing on low severity CAP are of limited value and past experiences have shown detrimental effects to implementing such rigorous expectations.

5. Conclusions

he dogma of starting antibiotics quickly, within a rigid timeframe of expectations and guidelines has not improved outcomes in pneumonia patients, and has led to an increase in antibiotic treatment in uninfected patients. Severity of illness is the key factor associated with poor outcomes and should more significantly guide the timing of antibiotic initiation. Unlike many organizations' guidelines and recommendations, we suggest a change in thinking around antibiosis for pneumonia where rapid administration and delayed prescribing can both be thought of as quality care within differing clinical situations. This could be operationalized around systems that focus on clinical assessment, risk stratification, clarity of imaging studies, and incorporation of ancillary data such as lab testing and patient factors/comorbidities in order to guide the rapidity of treatment.

Author Contributions:

Conceptualization, Yiwu Zhou and Casey M. Clements; methodology, Yanqi He; software, Man Li; validation, Yiwu Zhou, Casey M. Clements and Rong Yao; formal analysis, Yanqi He; investigation, Man Li; data curation, Yiwu Zhou; writing—original draft preparation, Yiwu Zhou and Casey; writing—review and editing, Casey M. Clements; visualization, X.X.; supervision, Yanqi He; project administration, Rong Yao; funding acquisition, Rong Yao. All authors have read and agreed to the published version of the manuscript.

Conflicts of Interest:

The authors have no conflict of interest to declare.

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