Clinical Practice Guideline:
The Measurement of Time to Antibiotics for Admitted Patients with Community-Acquired Pneumonia (CAP) in the ED (3/1/09)

Reviewed and approved by the AAEM Clinical Practice Committee.

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1. Define the Issue and State the Question

A. Topic Area:

The measurement of time to antibiotics for admitted patients with community-acquired pneumonia (CAP) in the ED.

B. General Issue:

Unintended consequences of the implementation of a national guideline to assess antibiotic timing in CAP.

C. Specific Questions:

Executive Summary

Measurement of time to first antibiotic dose (TFAD) in the emergency department (ED) in community-acquired pneumonia (CAP) in public reporting has been controversial. The validity of the data supporting TFAD measurement is inconsistent. And more recently, several unintended consequences associated with TFAD measurement have been reported. The purpose of this review was to find & evaluate original research articles that report outcomes data in CAP patients before-and-after the use of TFAD measurement and how TFAD measurement may increase in antibiotic overuse in other patients with non-CAP conditions.

We performed several searches using Pubmed for which eight articles directly addressed our two study questions. 1.) “Is the measurement of time to first antibiotic dose (TFAD) in CAP associated with improvements in outcomes for

patients with CAP?" 2.) "Is the measurement of TFAD in CAP associated with antibiotic overuse or associated with ED-based interventions that may result in antibiotic overuse for patients with a non-CAP diagnosis?" Two independent reviewers assessed the studies with respect to evidence grade, quality, and whether the studies provided evidence to support, be neutral to, or oppose TFAD measurement in the ED.

There were no studies that provided clear, high-grade evidence (such as randomized trials) that either supported or opposed the implementation of TFAD. All studies were Grade C or D and of 'Adequate' quality. Two studies supported TFAD by showing improved outcomes (improved survival on one study & shorter hospital length of stay another) in CAP patients before-and-after the implementation of TFAD measurement (along with other interventions to improve CAP). One neutral article reported no difference in survival with improved TFAD timing. Five studies opposed TFAD measurement by demonstrating either increases in antibiotic overuse in non-CAP patients, or were surveys of emergency physicians that suggested that TFAD measurement would promote antibiotic misuse.

Given the inconsistent evidence demonstrating that implementation of efforts to improve TFAD in CAP improves outcomes and evidence that TFAD measurement is associated with antibiotic overuse and misuse, we have assigned a Class C indication (not acceptable/not appropriate) for TFAD measurement in the ED. The American Academy of Emergency Medicine (AAEM) recommends is that the measurement of TFAD in CAP in the ED should be discontinued as a quality measure.

2. Search

- Define separate strategy for each database / search process used in this review.
- Attach additional search strategies for other database / search process in this review.

SEARCH 1

A. Keywords used in search:

process of care and antibiotics and pneumonia

B. Database Searched / Process Performed (Ovid, BIOMEDNET, Pubmed, Cochrane, EMBASE, Textbook / Article Reference Review, etc):

_____**Pubmed**_____

C. Dates searched: **ALL** with # of references __**135**_____

D. Limits applied

limit _____humans_____ with # of references____**135**___

limit _____ with # of references_____

limit _____ with # of references_____

E. Final Search Result with # of references_____**135**_____

SEARCH 2

A. Keywords used in search: ____ **antibiotics and timing and pneumonia** _____

B. Database Searched / Process Performed (Ovid, BIOMEDNET, Pubmed, Cochrane, EMBASE, Textbook / Article Reference Review, etc):

_____**Pubmed**_____

C. Dates searched: From __**ALL**___ To _____ with # of references____**78**___

D. Limits applied

limit _____**humans**_____ with # of references___**78**____

limit _____ with # of references_____

limit _____ with # of references_____

E. Final Search Result with # of references_____**78**_____

SEARCH 3

A. Keywords used in search: ____ **antibiotics and hours and outcomes and pneumonia** _____

B. Database Searched / Process Performed (Ovid, BIOMEDNET, Pubmed, Cochrane, EMBASE, Textbook / Article Reference Review, etc):

_____**Pubmed**_____

C. Dates searched: From __**ALL**___ To _____ with # of references_____

D. Limits applied

limit _____humans_____ with # of references___**155**____

limit _____ with # of references_____

limit _____ with # of references_____

E. Final Search Result with # of references____**155**_____
antibiotics and emergency department and timing and pneumonia

SEARCH 4

A. Keywords used in search: **antibiotics and emergency department and timing and pneumonia**

B. Database Searched / Process Performed (Ovid, BIOMEDNET, Pubmed, Cochrane, EMBASE, Textbook / Article Reference Review, etc):
_____**Pubmed**_____

C. Dates searched: From __ALL___ To _____ with # of references_____

D. Limits applied

limit _____humans_____ with # of references___**10**____

limit _____ with # of references_____

limit _____ with # of references_____

E. Final Search Result with # of references___**10**_____

SEARCH 5

A. Keywords used in search: **antibiotics and emergency department and time and pneumonia**

B. Database Searched / Process Performed (Ovid, BIOMEDNET, Pubmed, Cochrane, EMBASE, Textbook / Article Reference Review, etc):

_____**Pubmed**_____

C. Dates searched: From __ALL___ To _____ with # of references____**55**___

D. Limits applied

limit _____humans_____ with # of references___**55**____

limit _____ with # of references_____

limit _____ with # of references_____

E. Final Search Result with # of references_____**55**_____

Articles were determined to be included in this review if they directly addressed one of the two questions posed.

A total of 8 articles were included for the final review that directly addressed one of the two questions posed.

3. Final Evidence Database – Grade of Evidence Review

- For each reference from step 2, assign a grade of evidence using reference focus, design and methodology.
- Attach list of final evidence database with assigned grade of evidence

Grade A	Randomized clinical trials or meta-analyses (multiple clinical trials) or randomized clinical trials (smaller trials),directly addressing the review issue
Grade B	Randomized clinical trials or meta-analyses (multiple clinical trials) or randomized clinical trials (smaller trials), indirectly addressing the review issue
Grade C	Prospective, controlled, non-randomized, cohort studies
Grade D	Retrospective, non-randomized, cohort or case-control studies
Grade E	Case series, animal / model scientific investigations, theoretical analyses, or case reports
Grade F	Rational conjecture, extrapolations, unreferenced opinion in literature, or common practice

4. Final Evidence Database – Quality Ranking

- Critically assess each reference with regards design and methodology.
- Design Consideration – of the reference under review, consider the focus, model structure, presence of controls, etc.
- Methodology Consideration -- of the reference under review, consider the methodology.
- Attach list of final evidence database with assigned quality of evidence

Ranking	Design Consideration Present	Methodology Consideration Present	Both Considerations Present
Outstanding	Appropriate	Appropriate	Yes, both present
Good	Appropriate	Appropriate	No, either present
Adequate	Adequate with Possible Bias	Adequate	No, either present
Poor	Limited or Biased	Limited	No, either present
Unsatisfactory	Questionable / None	Questionable / None	No, either present

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5. Assign the Reference Support of the Question

- Separate the references into 3 categories: supportive, neutral, opposed.
- Construct 3 tables assigning the references to the appropriate location using both Grade of Evidence and Quality of Evidence.
- Use lead author name, journal abbreviation, and year of publication as reference.

Supportive Evidence

Quality / Grade	A	B	C	D	E	F
Outstanding						
Good						
Adequate			Meehan, Am J Med (2001) McGarvey, QRB (1993)			
Poor						
Unsatisfactory						

Neutral Evidence

Quality / Grade	A	B	C	D	E	F
Outstanding						
Good						
Adequate			Barlow, Thorax (2007)			
Poor						
Unsatisfactory						

Opposing Evidence

Quality / Grade	A	B	C	D	E	F
Outstanding						
Good						
Adequate				Welker, Arch Int Med (2008) Kanwar, Chest (2007) Drake, Qual Manag Health Care (2007)	Pines, Acad Emerg Med (2007) Nicks, Acad Emerg Med (2009)	
Poor						
Unsatisfactory						

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6. Recommendation

- Answer the clinical question, if possible.
- Assign a level of recommendation.
- Make a recommendation.

A. Recommendation:

There is inconsistent evidence that demonstrates that the implementation of efforts to improve TFAD in CAP improves outcomes, while there is evidence in a small number of studies that measurement of TFAD is associated with antibiotic overuse and misuse. The recommendation is that the measurement of TFAD in CAP in the ED should be discontinued as a quality measure.

B. Level of recommendation: Class C evidence (Not acceptable/not appropriate)

Level of Recommendation	Criteria for Level of Recommendation	Mandatory Evidence
Class A recommended with outstanding evidence	• Acceptable • Safe • Useful • Established / definitive	• Level A / B grade • Outstanding quality • Robust • All positive
Class B acceptable & appropriate with good evidence	• Acceptable • Safe • Useful • Not yet definitive	• Level A / B grade lacking • Adequate to Good quality • Most evidence positive • No evidence of harm
Class B 1	• Standard approach	• Higher grades of evidence • Consistently positive
Class B 2	• Optional or alternative approach	• Lower grades of evidence • Generally, but not consistently, positive
Class C not acceptable or not appropriate	• Unacceptable • Unsafe • Not useful	• No positive evidence • Evidence of harm
Class Indeterminate Unknown	• Minimal to no evidence	• Minimal to no evidence

7. List all conflicts of interest:

There may be an intellectual conflict of interest. JMP is an author of one the studies cited as evidence.

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8. Discussion

- Discuss the clinical question -- Address the issue
- Make a recommendation -- Succinctly discuss the rationale and evidence supporting the recommendation.

Background

The measurement of time to first antibiotic dose (TFAD) in the emergency department (ED) for community-acquired pneumonia (CAP) has been highly controversial.[1] The controversy has stemmed from concerns over the validity of the data and of the possible unintended consequences that might occur with deployment of TFAD measurement in public reporting.[2] A recent evidence review concluded that timely antibiotics should be encouraged, but the current evidence does not justify the inflated sense of priority that TFAD < 4 currently receives.[3] The data supporting the TFAD as a quality measure is based on two retrospective cohort studies of Medicare patients where an association between earlier antibiotics (within 4- or 8-hours of arrival) was associated with improved survival rates.[4,5] Proponents of the use of TFAD in quality reporting point to the robust methods demonstrating the association, while critics of the measure point to the possibility of unintended consequences, such as antibiotic overuse and misuse and misprioritization of patients.

Several research reports have been published detailing specific measures that hospitals have undertaken to ensure an early diagnosis and the effect on patient-oriented outcomes, such as mortality and length of stay.[6,7,8] However, subsequent reports have detailed increasing rates of misdiagnosis and antibiotic overuse for non-CAP conditions again references.[9,10,11,12,13]

The purpose of this review was to perform an assessment of original research papers that report the results of measure implementation to both patients with CAP (with regard to the provision of early antibiotics and outcomes) and other patients with non-pneumonia conditions similarly exposed to public reporting of TFAD for CAP.

In order to address this question, two specific questions were posed:

1) "Is the measurement of TFAD in CAP associated with improvements in outcomes for patients with CAP?

2) Is the measurement of TFAD in CAP associated with antibiotic overuse or associated with ED-based interventions that may result in antibiotic overuse for patients with a non-CAP diagnosis?"

We chose not to review the evidence behind the association (retrospective studies) which has been well-covered in a previous report.[3] Rather, the expressed intention of these questions was to perform a balanced assessment of improved in outcomes for patients with CAP versus increased rates of antibiotic overuse in formulating a final guideline recommendation on behalf of the American Academy of Emergency Medicine (AAEM).

Methods

To identify articles that addressed this question, we performed several searches in January 2009 using Pubmed (MEDLINE). We used several combinations of search terms with the following results:

Terms	Results
process of care antibiotics pneumonia	135
antibiotics timing pneumonia	78
antibiotics hours	155

outcomes pneumonia	
antibiotics emergency department timing pneumonia	10
antibiotics emergency department time pneumonia	55

Each search was limited to original articles (studies reporting data) and humans from 1990 to present. Two reviewers (JMP & JAI) assessed each article for inclusion such that the study question directly addressed the two specific review questions noted previously. For article that met inclusion criteria, the reference sections were searched for papers that could meet inclusion criteria. Included studies were assessed by two reviewers (JMP & PBH) and categorized as 'supporting evidence', 'neutral evidence' or 'opposing evidence'. A priori, supporting evidence was determined to be in favor of the measurement of TFAD. Each article was then assigned a Grade of Evidence from A (RCT or meta-analysis) to E (opinion) and a Quality Ranking (Outstanding to Unsatisfactory) based on design and methodological consideration. The categorization, quality, and grade of each study was assessed in isolation and where there were any disagreements, a third reviewer (JAI) was to act as a tie breaker.

Results

A total of eight original articles met inclusion criteria and were assessed by the reviewers. Two were categorized as 'supporting evidence', one as 'neutral evidence' and five as 'opposing evidence'. Blinded assessment by two reviewers found 100% agreement in the categorization of the eight articles, as well as the grades and quality rankings.

Supporting evidence

Two articles support the use of TFAD measurement; they provide evidence of an improvement in outcomes.

The McGarvey article reported data from a before-after study where TFAD less than four hours was part of a multi-faceted intervention to improve pneumonia care.[6] Other aspects of the intervention included obtaining routine sputum cultures, blood cultures, and to encourage pulmonary and infectious disease consultation if the patient did not improve within 48 hours. The pneumonia clinical pathway was introduced in January 1990 and in the 18-months following the intervention, there were increases in the proportion of patients with prompt antibiotics (TFAD < 4 hours) from 42% to 87%. There was also reduction in the in-hospital mortality in its 3 acute care hospitals in 860 pneumonia cases from 10.2% to 6.8% and average length of stay decreased from 10.4 to 9.1 days. When the authors stratified by risk (High- v. Low-risk), they observed that the majority of the improvements in mortality were observed in Low-risk cases (8.0% mortality [pre] v. 1.5% mortality [post]). There was no significant difference in the High-risk group (14.1% mortality [pre] v. 15.6% mortality [post]). This study did not assess any data on patients admitted for non-CAP illnesses. Consensus review by our group assigned a Grade C and a quality ranking of 'Adequate' to this work.

The Meehan article reported data from a statewide quality initiative in Connecticut to improve process-of-care performance and decrease length of stay in patients admitted with CAP.[7] This study reported data from the implementation of a pneumonia pathway that involved a multi-faceted intervention that included early antibiotic use, blood culture collection, and oxygenation assessments. Data were reported from 31 hospitals. The baseline period was January 1995 to March 2006 and the intervention period was January to June 1997. Only patients 65 and older were included. A total of 1,242 patients were studied in the control period and 1,146 in the follow-up period. The follow-up period had fewer high risk patients (pneumonia-specific risk index of 5 [highest risk]), 25.4% [pre] v. 13.4% [post]. TFAD within 8 hours of arrival increased from 83.4% to 88.8%, adjusted risk ratio 1.21 (95% CI 1.10-1.32). Thirty-day mortality improved from 15.3% to

11.3%, however, after risk adjustment, there was no significant improvement in survival, risk ratio 0.96 (95% CI 0.78-1.18). Survival was only one important endpoint. The length of stay (LOS) improved from 7.0 to 5.0 days (<0.001). Consensus review by our group assigned this a Grade of C and a quality ranking of 'Adequate'.

Neutral evidence

The one neutral study was a controlled before-and-after trial performed in the UK by Barlow et al.[8] In this study, the authors performed an intervention aimed at improving TFAD of an appropriate antibiotic to less than four hours. This involved an intervention site and a control site where the intervention was not implemented. The intervention period was 2002-3 and the control period was 2001-2. A total of 11,987 admissions were studied at the control site and 7,012 at the control site. The intervention site experienced an increase in the proportion receiving appropriate antibiotics within 4 hours from 33% to 56% and the control site from 32% to 36%. Despite a higher proportion of patients receiving antibiotics within 4 hours, there were no differences in survival or mortality in either the intervention or the control site. The consensus review assigned a Grade C and quality ranking of 'Adequate' to this study.

Opposing evidence

Five studies were included that documented either adverse outcomes (increased rates of misdiagnosis) or detailed interventions that may result in the inappropriate prioritization of patients for the purpose of meeting quality measures.

A study by Pines et al. sought to determine operational changes in academic EDs to ensure early antibiotic administration by surveying medical directors from the 135 academic ED training programs.[9] The response rate was 70% and the survey was administered in 2006. The major findings were that 51% automate chest x-ray ordering from triage, 41% prioritize patients with suspected pneumonia over other patients, and 37% have policies where antibiotics are given prior to chest x-ray results. It was interpreted that these wasteful or unnecessary medical decisions do not benefit patients. Consensus review assigned this Grade E evidence and a Quality ranking as 'Adequate."

A separate investigation by Welker et al. sought to study the accuracy of CAP diagnosis in two periods in one hospital: 1) when the core measure for TFAD was < 8 hours (November 2003 to April 2004), and 2) when TFAD was reduced to 4 hours (November 2004 to April 2005).[10] In 548 total patients, they found that those in group 2 were 39% less likely to meet predefined criteria for CAP compared to group 1 patients at admission, odds ratio 0.61 (95% CI 0.42-0.86). And at hospital discharge, 53.9% in group 2 met the predefined criteria for CAP compared to 62.0% in group 1. They found that TFAD was similar in both groups (<3 hours). It was interpreted that instituting TFAD < 4 leads to increased number of suboptimal CAP diagnoses. The consensus review assigned this Grade D evidence and 'Adequate' quality.

Kanwar et al. reported similar findings in a before-after study (pre and post-guideline implementation) and studied two periods: January to June 2003 and January to June 2005.[11] In 518 patients, he found that 28.5% of patients had an admission diagnosis of CAP without radiographic abnormalities after guideline implementation, compared to 20.6% before (p=0.04). In addition, the proportion with a final diagnosis of pneumonia was 58.9% in 2005, while it was 75.9% in 2003. While a greater proportion had received antibiotics within four hours of arrival after the guideline implementation (66% v. 54%, p<0.001), there was no difference in mortality rates. It was interpreted that instituting TFAD < 4 leads to increased number of suboptimal CAP diagnoses and or increased inappropriate antibiotic use. The consensus review assigned a Grade D to this evidence and 'Adequate' quality.

Drake et al. performed an ecological study in hospitals in the Premier clients that participated in the Hospital Quality Incentive Demonstration (HQID) pay-for-performance project, run by the Centers for Medicare & Medicaid Services (CMS).[12] They identified 3 APR-DRGs for antibiotic non-responsive diseases similar to pneumonia (heart failure, asthma, and chronic obstructive pulmonary disease) and found positive correlations with performance on antibiotic timing in pneumonia and antibiotic use for these non-antibiotic responsive conditions. They concluded that

increased success in meeting the TFAD < 4 hours in pneumonia was associated with an increase in antibiotic use for these conditions. The consensus review assigned a Grade D to this evidence and 'Adequate' quality.

A recent study by Nicks et al. was a 5-ED survey from North Carolina, where 121 emergency physicians filled out a questionnaire regarding their understanding of the core measures (81% response rate).[13] The authors found that 55% of respondents reported prescribing antibiotics to patients they did not believe had pneumonia to comply with Centers for Medicare & Medicaid Services guidelines and 42% reported that they had done this > 3 times per month. Consensus review assigned a Grade E to this with a quality ranking of 'Adequate'.

Discussion

A review of these studies in combination yields several observations. First, the evidence supporting the implementation of TFAD < 4 hours is clouded because it involves no randomized trials. In addition, the studies that demonstrate a beneficial clinical impact do not isolate TFAD as a single intervention and are rather a part of a multi-faceted intervention.[6,7] There appears to be inconsistent evidence as to whether it has a beneficial effect on mortality or hospital length of stay.[6,7,8] In addition, the one trial that did demonstrate a mortality difference was from almost 20 years ago.[6] These studies did not assess the impact on patients with non-CAP diagnoses.

Similarly, there is no strong evidence that implementing measures to ensure TFAD < 4 hours is associated with direct patient harm such as increased mortality rates or prolonged hospital length of stay. However, there are three studies that demonstrate an increasing rate of antibiotic use in patients with non-CAP diagnosis and a reduction in the accuracy of the assignment of CAP in the ED.[10,11,12] Antibiotic overuse can potentially harm patients because it can lead to increased antibiotic resistance and may delay a definitive diagnosis if CAP is assigned prematurely in the ED. The two survey studies corroborate the effects of TFAD measurement.[9,13] One demonstrates institutional policies in 1/3 of academic EDs in the U.S. that promote the use of antibiotics prior to chest x-ray diagnosis reference.[9] The same study demonstrated that more than 1/3 of hospitals had policies where pneumonia patients were prioritized over other patients outside of normal triage. While this may benefit those with cough illness or other symptoms of pneumonia, this may result in inappropriate prioritization of resources at triage (which is typically performed based on acuity). Similarly, in a 5-hospital study reported more that more than half of the physicians reported administering antibiotics to patients without pneumonia in order to meet guidelines.[13]

To cast further doubt on measuring TFAD in CAP, a recent study of patients receiving antibiotics within 6 hours produced results that conflicted with previous studies demonstrating an association between early antibiotics and improved mortality.[14] This suggests that the association observed in the large, retrospective Medicare trials may be more a remnant of unmeasured confounding factors such as the presence of atypical presentations that lengthen time to diagnosis, and also may be associated with worse survival in of themselves.[15,16]

In the absence of convincing data that suggests that the measurement of TFAD has a positive effect on patients with pneumonia and with an increasing number of reports suggesting that the measurement of TFAD is associated with antibiotic overuse, it is difficult to support the continued measurement of TFAD in the ED as a quality measure. The 2007 American Thoracic Society/Infectious Disease Society of America guidelines have withdrawn their support for TFAD measurement in favor of the recommendation to give antibiotics in the ED once a diagnosis of pneumonia is established.[17]

Given the results of this review, the AAEM has assigned a Class C recommendation (not acceptable or not appropriate) to the measurement of TFAD in the ED. While there is no direct evidence of harmful outcomes (such as death), the AAEM cannot support a quality measure with conflicting evidence. The implementation improves outcomes in some studies, but in a series of studies it is clear that the measure itself is leading to antibiotic overuse.

References:

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