

Optimal Timing for Antibiotic Administration in Patients With Community-Acquired Pneumonia: A Rapid Review

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Rapid Review Methodology

Clinical questions are developed by the Division of Evidence Development and Standards at Health Quality Ontario in consultation with experts, end-users, and/or applicants in the topic area. A systematic literature search is then conducted to identify relevant systematic reviews (SRs), health technology assessments, and meta-analyses; if none are located, the search is expanded to include randomized controlled trials (RCTs), and guidelines. SRs are evaluated using a rating scale developed for this purpose. If the SR has evaluated the included primary studies using the GRADE Working Group criteria (<http://www.gradeworkinggroup.org/index.htm>), the results are reported and the rapid review process is complete. If the SR has not evaluated the primary studies using GRADE, the primary studies included in the SR are retrieved and a maximum of two outcomes are graded. If no well-conducted SRs are available, RCTs and/or guidelines are evaluated. Because rapid reviews are completed in very short timeframes, other publication types are not included. All rapid reviews are developed and finalized in consultation with experts.

About Health Quality Ontario

Health Quality Ontario is an arms-length agency of the Ontario government. It is a partner and leader in transforming Ontario's health care system so that it can deliver a better experience of care, better outcomes for Ontarians, and better value for money.

Health Quality Ontario strives to promote health care that is supported by the best available scientific evidence. Health Quality Ontario works with clinical experts, scientific collaborators, and field evaluation partners to develop and publish research that evaluates the effectiveness and cost-effectiveness of health technologies and services in Ontario.

Based on the research conducted by Health Quality Ontario and its partners, the Ontario Health Technology Advisory Committee (OHTAC)—a standing advisory subcommittee of the Health Quality Ontario Board—makes recommendations about the uptake, diffusion, distribution, or removal of health interventions to Ontario's Ministry of Health and Long-Term Care, clinicians, health system leaders, and policymakers.

Rapid reviews, evidence-based analyses and their corresponding OHTAC recommendations, and other associated reports are published on the Health Quality Ontario website. Visit <http://www.hqontario.ca> for more information.

About Health Quality Ontario Publications

To conduct its rapid reviews, Health Quality Ontario and/or its research partners reviews the available scientific literature, making every effort to consider all relevant national and international research; collaborates with partners across relevant government branches; consults with clinical and other external experts and developers of new health technologies; and solicits any necessary supplemental information.

In addition, Health Quality Ontario collects and analyzes information about how a health intervention fits within current practice and existing treatment alternatives. Details about the diffusion of the intervention into current health care practices in Ontario can add an important dimension to the review. Information concerning the health benefits, economic and human resources, and ethical, regulatory, social, and legal issues relating to the intervention may be included to assist in making timely and relevant decisions to optimize patient outcomes.

Disclaimer

This rapid review is the work of the Division of Evidence Development and Standards at Health Quality Ontario, and is developed from analysis, interpretation, and comparison of published scientific research. It also incorporates, when available, Ontario data and information provided by experts. As this is a rapid review, it may not reflect all the available scientific research and is not intended as an exhaustive analysis. Health Quality Ontario assumes no responsibility for omissions or incomplete analysis resulting from its rapid reviews. In addition, it is possible that other relevant scientific findings may have been reported since completion of the review. This report is current to the date of the literature search specified in the Research Methods section, as appropriate. This rapid review may be superseded by an updated publication on the same topic. Please check the Health Quality Ontario website for a list of all publications: <http://www.hqontario.ca/evidence/publications-and-ohtac-recommendations>.

Table of Contents

List of Abbreviations	5
Background	6
Objective of Analysis	6
Clinical Need and Target Population	6
Rapid Review	7
Research Question	7
Research Methods	7
Quality of Evidence	8
Results of Literature Search	9
Results for Outcomes of Interest	9
Conclusions	12
Appendices	13
Appendix 1: Literature Search Strategies	17
Appendix 2: Quality-Assessment Tables	19
References	21

List of Abbreviations

AMSTAR	Assessment of Multiple Systematic Reviews
CAP	Community-acquired pneumonia
CI	Confidence interval
HQO	Health Quality Ontario
LOS	Length of stay
MD	Mean difference
OR	Odds ratio
RCT	Randomized controlled trial
SR	Systematic review

Background

As legislated in Ontario's *Excellent Care for All Act*, Health Quality Ontario's mandate includes the provision of objective, evidence-informed advice about health care funding mechanisms, incentives, and opportunities to improve quality and efficiency in the health care system. As part of its Quality-Based Funding (QBF) initiative, Health Quality Ontario works with multidisciplinary expert panels (composed of leading clinicians, scientists, and administrators) to develop evidence-based practice recommendations and define episodes of care for selected disease areas or procedures. Health Quality Ontario's recommendations are intended to inform the Ministry of Health and Long-Term Care's Health System Funding Strategy.

For more information on Health Quality Ontario's Quality-Based Funding initiative, visit www.hqontario.ca.

Objective of Analysis

This aim of this rapid review is to determine the optimal timing for administering antibiotics to patients presenting with community-acquired pneumonia (CAP).

Clinical Need and Target Population

Community-acquired pneumonia (CAP) is a significant cause of hospitalization in Canada, with an estimated 60,000 hospitalizations a year and overall mortality rates up to 12% at 30 days post-admission. (1;2) Several studies reported that early initiation of antibiotic therapy decreases 30-day mortality and overall length of hospital stay (LOS) in patients with CAP. (1)

Many international guidelines recommend early initiation of antibiotic therapy for CAP, but the recommendations are limited by low to moderate quality evidence and/or expert opinion. Table 1 summarizes the guideline recommendations. The Canadian Infectious Disease Society and the Canadian Thoracic Society recommendations for management of CAP do not address time to antibiotic therapy. (3) Therefore, to inform Ontario health care professionals on best practices for treatment of CAP, it is essential to assess whether early initiation of antibiotic therapy improves patient outcomes.

Table 1. Guideline Recommendations for Early Administration of Antibiotics for Patients Hospitalized With Community-Acquired Pneumonia

BTS (GB) (4)	IDSA/ATS (US) (5)	ACEP (US) (6)	SWAB/NVALT (NL) (7)	SIGN (SCT) (8)	ERS/ESCMID (Europe) (9)
Within 4 hours	In the emergency department	As early as possible	Within 4 hours	Early	Early

Abbreviations: ACEP, American College of Emergency Physicians; ATS, American Thoracic Society; BTS, British Thoracic Society; CAP, community-acquired pneumonia; ERS, European Respiratory Society; ESCMID, European Society for Clinical Microbiology and Infection Diseases; GB, Great Britain; IDSA, Infectious Disease Society of America; NL, The Netherlands; NVALT, Dutch Association of Chest Physicians; SCT, Scotland; SIGN, Scottish Intercollegiate Guidelines Network; SWAB, Dutch Working Party on Antibiotic Policy; US, United States.

Rapid Review

Research Question

What is the optimal timing to administer antibiotics to patients presenting to the emergency department with community-acquired pneumonia?

Research Methods

Literature Search

A literature search was performed on May 10, 2013, using Ovid MEDLINE, Ovid MEDLINE In-Process and Other Non-Indexed Citations, Ovid Embase, EBSCO Cumulative Index to Nursing & Allied Health Literature (CINAHL), the Wiley Cochrane Library, and the Centre for Reviews and Dissemination database, for studies published from January 1, 2008, until May 10, 2013. Abstracts were reviewed by a single reviewer and, for those studies meeting the eligibility criteria, full-text articles were obtained. Reference lists were also examined for any additional relevant studies not identified through the search.

Inclusion Criteria

- English-language full reports
- published between January 1, 2008, and May 10, 2013
- health technology assessments, systematic reviews (SRs), and meta-analyses
- Hospitalized adult patients with CAP
- studies comparing < 4 hours with > 4 hours for antibiotic administration

Exclusion Criteria

- primary studies (randomized controlled trials [RCTs], observational studies, case series, etc.)
- children (patients < 18 years)
- outpatients with CAP
- patients with hospital-acquired and ventilator-acquired pneumonia
- studies where outcomes of interest cannot be extracted

Outcomes of Interest

- mortality
- length of stay (LOS) in hospital

Expert Panel

In April 2013, an Expert Advisory Panel on Episodes of Care for Pneumonia was struck. Members of the panel included physicians, nurses, allied health professionals and personnel from the Ministry of Health and Long-Term Care.

The role of the Expert Advisory Panel on Episodes of Care for Pneumonia was to contextualize the evidence produced by Health Quality Ontario (HQP) and provide advice on the appropriate clinical

pathway for a patient with pneumonia in the Ontario health care setting. However, the statements, conclusions and views expressed in this report do not necessarily represent the views of Expert Advisory Panel members.

Quality of Evidence

The Assessment of Multiple Systematic Reviews (AMSTAR) tool was used to assess the quality of the final selection of the SR. (10) Details on the outcomes of interest were abstracted from the selected review, and primary studies were referenced as needed.

The quality of the body of evidence for each outcome was examined according to the GRADE Working Group criteria. (11) The overall quality was determined to be very low, low, moderate, or high using a step-wise, structural method.

Study design was the first consideration; the starting assumption was that RCTs are high quality, whereas observational studies are low quality. Five additional factors—risk of bias, inconsistency, indirectness, imprecision, and publication bias—were then taken into account. Limitations in these areas resulted in downgrading the quality of evidence. Finally, 3 factors that could raise the quality of evidence were considered: large magnitude of effect, dose-response gradient, and accounting for all residual factors. (11) For more detailed information, please refer to the latest series of GRADE articles. (11)

As stated by the GRADE Working Group, the final quality score can be interpreted using the following definitions:

High	Very confident that the true effect lies close to the estimate of the effect;
Moderate	Moderately confident in the effect estimate—the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different;
Low	Confidence in the effect estimate is limited—the true effect could be substantially different from the estimate of the effect;
Very Low	Very little confidence in the effect estimate—the true effect is likely to be substantially different from the estimate of effect.

Results of Literature Search

The database search yielded 589 citations published between January 1, 2008, and May 10, 2013 (with duplicates removed). Articles were excluded on the basis of information in the title and abstract. The full texts of potentially relevant articles were obtained for further assessment.

Two SRs met the inclusion criteria. (12;13) Both report on the outcome of mortality, but neither report on LOS. AMSTAR was used to review both SRs (Appendix 2, Table A1); the 2009 Pines et al (13) review received an AMSTAR rating of 3 while the 2008 Yu et al (12) review received an AMSTAR rating of 7. The mortality results from both SRs were included for the current analysis because the Pines et al review captures literature not reported by Yu et al.

The SRs by Yu et al and Pines et al are summarized in Table 2.

Table 2. Summary of Systematic Reviews Included in This Rapid Review

Author, Year	Review Type	Search Dates	Inclusion Criteria	No. of Studies	AMSTAR Score
Yu et al, 2008 (12)	SR	To August 2006	Retrospective and prospective observational studies English-language only Patients aged ≥ 18 years with moderate CAP	7	7
Pines et al, 2009 (13)	SR	To January 2009	Adult patients with community-acquired pneumonia	2	3

Abbreviations: AMSTAR, Assessment of Multiple Systematic Reviews; CAP, community-acquired pneumonia; SR, systematic review

Results for Outcomes of Interest

Both SRs by Yu et al (12) and Pines et al (13) report on mortality, but neither report on LOS as an outcome. However, primary studies from the SR by Yu et al (12) do report on LOS; these studies were therefore retrieved and analyzed. Since neither SR provides the GRADE level of evidence, all primary studies were retrieved and the GRADE for both outcomes was separately assessed.

Mortality

Both reviews identified no difference in mortality in patients to whom antibiotics were administered within 4 hours versus later than 4 hours. (12;13) The review by Yu et al (12) summarized outcome data into a forest plot, but did not provide a summary estimate of the impact on mortality of administering antibiotics within 4 hours compared to later than 4 hours. (12) Since both SRs capture similar literature, but Pines et al (13) captures a few additional studies, effect estimates from the individual studies' in both SRs were meta-analyzed (see Figure 1).

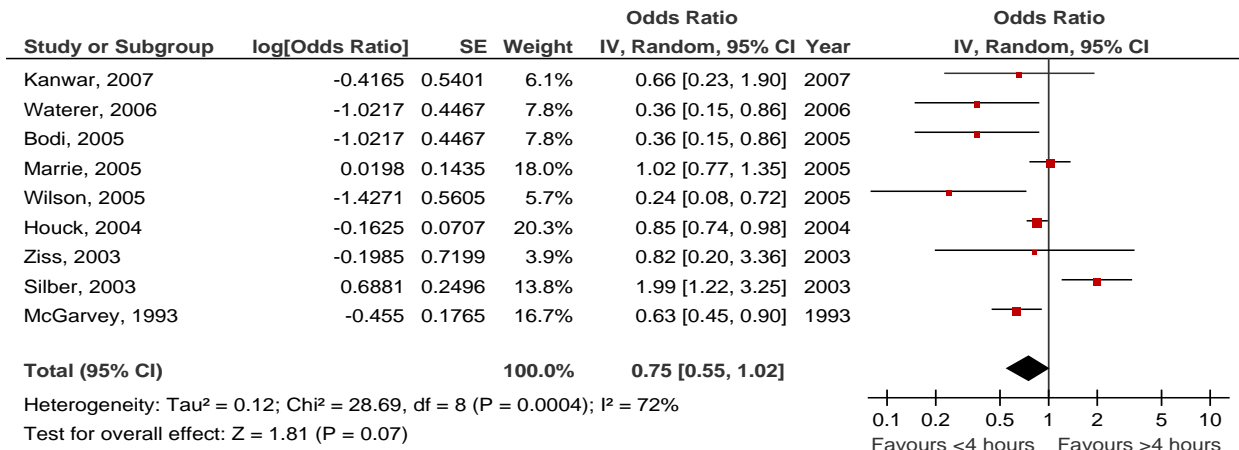


Figure 1: Effect on Mortality of Antibiotic Administration Within 4 Hours of Admission Versus After 4 hours of Admission

Although the random effects model takes heterogeneity into account, the meta-analysis in Figure 1 still shows considerable heterogeneity ($I^2 = 72\%$, $P < 0.05$). Sensitivity analysis showed the heterogeneity to be largely attributed to the study type, that is, whether or not the primary study uses severity controls (see Figure 2).

The random effects model of odds ratio (OR) comparison of administering antibiotics within 4 hours versus later than 4 hours identified no significant difference in mortality (OR, 0.75; 95% confidence interval [CI], 0.55–1.02).

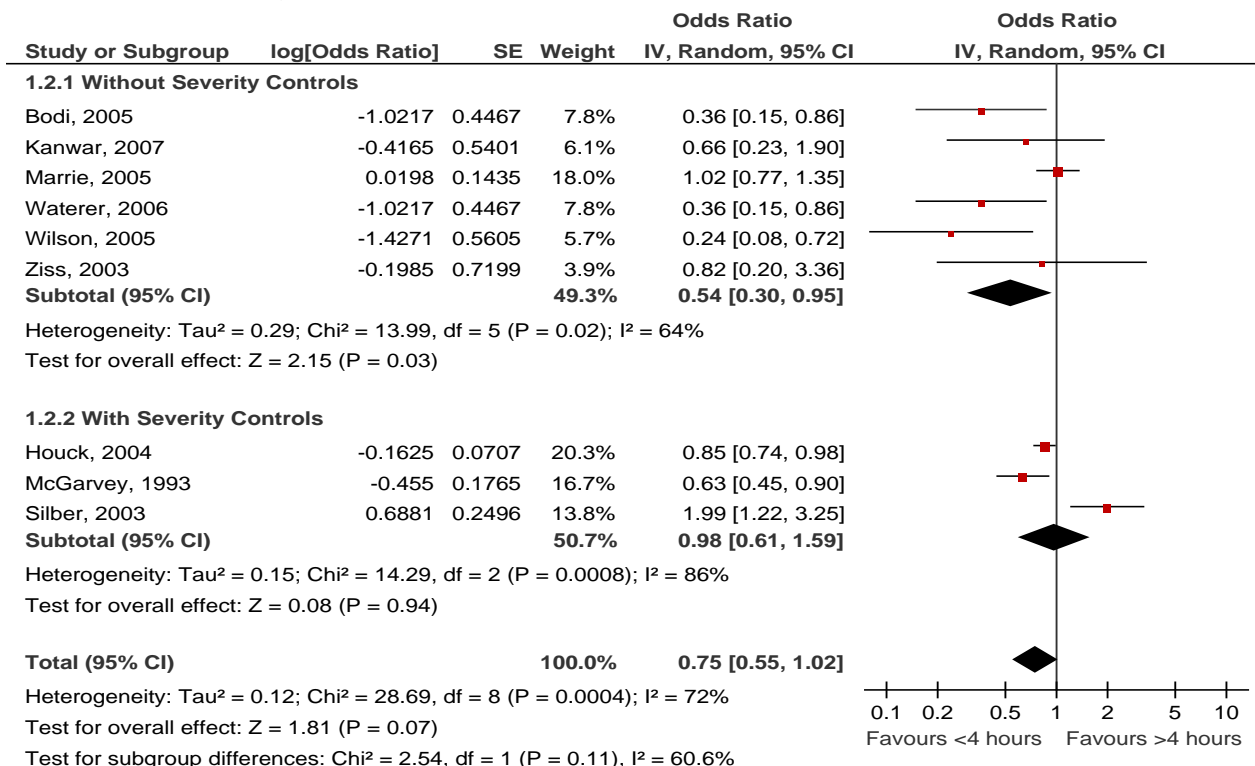


Figure 2: Sensitivity Analysis for Antibiotic Administration Within 4 hours of Admission Versus After 4 hours of Admission on Mortality

Quality Assessment

The quality assessment was conducted based on details published in both SRs. (12;13) Given the nature of the topic, none of the studies were RCTs and risk of bias was identified in a number of areas were identified. In addition, a number of studies do not isolate the timing of antibiotic administration as a single intervention, thereby clouding the results of the outcome. As a result, the effect estimate for the outcome of mortality is based on very low quality of evidence (Appendix 2, Table A2 and Table A3).

Length of Stay

Neither SR reports on LOS as an outcome. (12;13) The review by Yu et al (12), however, identifies 3 primary studies that report on LOS, but the authors do not evaluate the outcome. These primary studies were therefore pulled and the outcome was assessed.

A meta-analysis conducted on the primary studies comparing effects of administering antibiotics within the first 4 hours of admission versus after the first 4 hours identified no statistically significant mean difference (MD) on LOS between the two study groups (MD, -0.32; 95% CI, -0.93 to 0.30).

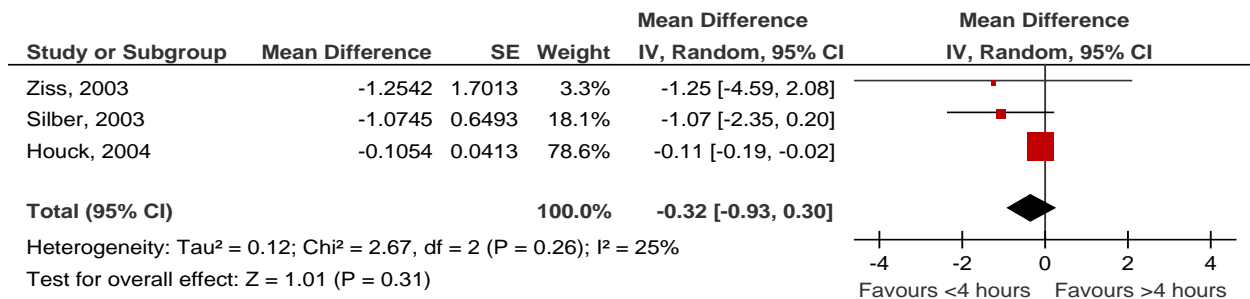


Figure 3: Effect on Length of Stay of Antibiotic Administration Within 4 hours of Admission Versus After 4 Hours of Admission

Quality Assessment

The quality assessment was conducted based on details in the Yu et al review. (12) No RCTs were identified, and therefore the outcome of LOS was assessed entirely on prospective and retrospective observational studies. In addition, a number of sources of risk of bias were identified and many studies did not isolate timing of antibiotic administration as a single intervention. As a result of these limitations, the GRADE for this outcome was assessed as very low (Appendix 1, Table A2 and Table A3).

Conclusions

On the basis of two SRs evaluating the optimal timing for antibiotic administration for patients presenting with signs of CAP, the following conclusions were reached:

- Very low quality evidence indicates that there is no significant difference in mortality for patients who received antibiotics within the first 4 hours of admission compared to those receiving antibiotics after 4 hours of admission.
- Very low quality evidence shows no significant difference in terms of LOS for patients who received antibiotics within the first 4 hours of admission compared to those receiving antibiotics after 4 hours of admission.

Acknowledgments

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HQO's Expert Advisory Panel on Evidence-Based Episodes of Care for Pneumonias Presenting to Hospitals

Panel Members	Affiliation(s)	Appointment(s)
Co-Chairs		
Dr Andrew Morris	Mount Sinai Hospital University Health Network University of Toronto	Medical Director, MSH-UHN Antimicrobial Stewardship Program Associate Professor, Division of Infectious Diseases
Dr Howard Ovens	Mount Sinai Hospital University of Toronto	Director, Schwartz-Reisman Emergency Centre Associate Professor, Department of Family and Community Medicine
Respirologist		
Dr Meyer Balter	University of Toronto Mount Sinai Hospital	Professor of Medicine Director, Asthma and COPD Education Clinic
Dr Gerard Cox	St. Joseph's Healthcare Hamilton McMaster University	Head of the Division of Respirology
Dr David Fishbein	Humber River Hospital	Chief of the Department of Medicine, Division of Respirology
Dr Kevin Sanders	North York General Hospital Sunnybrook Health Sciences	Respirologist, Intensive Care Unit, Critical Care Response Team
Intensivist		
Dr Christine Bradley	Hamilton General Hospital McMaster University	Associate Clinical Professor
Dr Niall Ferguson	Mount Sinai Hospital University of Toronto	Director of Critical Care
Dr Cindy Hamielec	McMaster University Hamilton General Hospital	Associate Clinical Professor Past National Chair at Canadian Intensive Care Foundation
Dr Michael Miletin	William Osler Health Centre	Director of Critical Care
Dr John Muscedere	Kingston General Hospital Queen's University	Research Director, Clinical Care Program
Dr Mark Soth	McMaster University St. Joseph's Healthcare Hamilton	Associate Professor Chief, Department of Critical Care

Panel Members	Affiliation(s)	Appointment(s)
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Dr Jeff Powis	Toronto East General Hospital University of Toronto	Director of Antimicrobial Stewardship Program
Dr Dan Ricciuto	Lakeridge Health	Physician Lead, IPAC and Antimicrobial Stewardship
Infectious Disease Specialist/Medical Microbiologist		
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Medical Microbiologist		
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Emergency Medicine Specialist		
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Dr John Jordan	Byron Family Medical Centre Western University	Professor of Family Medicine
Dr Frank Martino	William Osler Health Centre McMaster University Ontario College of Family Physicians	Lead Physician President, OCFP
Hospitalist		
Dr Robert Maloney	Sault Area Hospital	Chief Hospitalist
Dr Cary Shafir	Guelph General Hospital	Chief Hospitalist
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Geriatrician		
Dr Anthony Kerigan	Hamilton Health Sciences	Geriatrician
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Physiotherapist		
Cathy Relf	Trillium Health Partners – Mississauga Hospital	Physiotherapist
Intensive Care Physiotherapist		
Tania Larsen	London Health Sciences	Intensive Care Physiotherapist

Decision Support and Case Costing Specialist

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Southlake Regional Health Centre

Decision Support and Case Costing
Specialist

Appendices

Appendix 1: Literature Search Strategies

Search date: May 10, 2013

Databases searched: OVID MEDLINE, MEDLINE In-Process and Other Non-Indexed Citations, EMBASE; Cochrane Library; CRD

Q: What is the optimal timing to administer antibiotics in patients presenting to the emergency department with signs of community acquired pneumonia (CAP)?

Limits: 2008-current; English

Filters: Meta-analyses, systematic reviews, health technology assessments, guidelines

Database: Embase 1980 to 2013 Week 18, Ovid MEDLINE(R) 1946 to May Week 1 2013, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations May 09, 2013

Search Strategy:

#	Searches	Results
1	exp Pneumonia/	245279
2	(pneumoni* or peripneumoni* or pleuropneumoni* or lobitis or ((pulmon* or lung*) adj inflammation*)).ti,ab.	286976
3	or/1-2	398237
4	exp Anti-Bacterial Agents/ use mesz	508332
5	exp antibiotic agent/ use emez	882116
6	((anti?bacterial or anti?mycobacterial or bacteriocidal) adj agent) or antibiotic* or bacteriocide*).ti,ab.	480056
7	or/4-6	1572824
8	3 and 7	104774
9	exp Time Factors/ use mesz or exp early diagnosis/ use mesz	980173
10	exp early intervention/ use emez or exp dose time effect relation/ use emez or "time to first antibiotic dose"/ use emez	38463
11	(time* or timing or delay* or earl* or hour* or dose-response or TFAD or 4?h or 8?h or (first adj2 dose)).ti,ab.	8045034
12	or/9-11	8633988
13	8 and 12	25853
14	Meta Analysis.pt.	40231
15	Meta-Analysis/ use mesz or exp Technology Assessment, Biomedical/ use mesz	49071
16	Meta Analysis/ use emez or Biomedical Technology Assessment/ use emez	82034
17	(meta analy* or metaanaly* or pooled analysis or (systematic* adj2 review*) or published studies or published literature or medline or embase or data synthesis or data extraction or cochrane).ti,ab.	317193
18	((health technolog* or biomedical technolog*) adj2 assess*).ti,ab.	4093
19	exp Standard of Care/ use mesz or exp Guideline/ use mesz or exp Guidelines as Topic/ use mesz	128854
20	exp Practice Guideline/ use emez or exp Professional Standard/ use emez	544943
21	(guideline* or guidance or consensus statement* or standard or standards).ti.	227369
22	or/14-21	1154126
23	13 and 22	1697
24	limit 23 to english language	1533
25	limit 24 to yr="2008 -Current"	670
26	remove duplicates from 25	583

EBM Reviews - Cochrane Database of Systematic Reviews 2005 to March 2013, EBM Reviews - ACP Journal Club 1991 to April 2013, EBM Reviews - Database of Abstracts of Reviews of Effects 2nd Quarter 2013, EBM Reviews - Cochrane Central Register of Controlled Trials March 2013, EBM Reviews - Cochrane Methodology Register 3rd Quarter 2012, EBM Reviews - Health Technology Assessment 2nd Quarter 2013, EBM Reviews - NHS Economic Evaluation Database 2nd Quarter 2013

#	Searches	Results
1	exp Pneumonia/	2150
2	(pneumoni* or peripneumoni* or pleuropneumoni* or lobitis or ((pulmon* or lung*) adj inflammation*)).ti,ab.	4868
3	or/1-2	5447
4	exp Anti-Bacterial Agents/ use acp,cctr,coch,clcmr,dare,clhta,cleed	18290
5	((anti?bacterial or anti?mycobacterial or bacteriocidal) adj agent) or antibiotic* or bacteriocide*).ti,ab.	11757
6	or/4-5	24091
7	3 and 6	2077

8	exp Time Factors/ use acp,cctr,coch,clcmr,dare,clhta,cleed	44394
9	exp early diagnosis/ use acp,cctr,coch,clcmr,dare,clhta,cleed	440
10	(time* or timing or delay* or earl* or hour* or dose-response or TFAD or 4?h or 8?h or (first adj2 dose)).ti,ab.	202251
11	or/8-10	224014
12	7 and 11	854
13	Meta Analysis.pt.	464
14	Meta-Analysis/ use acp,cctr,coch,clcmr,dare,clhta,cleed	21
15	exp Technology Assessment, Biomedical/ use acp,cctr,coch,clcmr,dare,clhta,cleed	438
16	(meta analy* or metaanaly* or pooled analysis or (systematic* adj2 review*) or published studies or published literature or medline or embase or data synthesis or data extraction or cochrane).ti,ab.	32939
17	((health technolog* or biomedical technolog*) adj2 assess*).ti,ab.	608
18	exp Standard of Care/ use acp,cctr,coch,clcmr,dare,clhta,cleed	29
19	exp Guidelines as Topic/ use acp,cctr,coch,clcmr,dare,clhta,cleed	1047
20	(guideline* or guidance or consensus statement* or standard or standards).ti.	6944
21	or/13-20	41050
22	12 and 21	30
23	limit 22 to yr="2008 -Current" [Limit not valid in DARE; records were retained]	6
24	remove duplicates from 23	6

Appendix 2: Quality-Assessment Tables

Table A1: AMSTAR Score of Systematic Reviews^a

Author, Year	AMSTAR score ^a	1) Provided Study Design	2) Duplicate Study Selection	3) Broad Literature Search	4) Considered Status of Publication	5) Listed Excluded Studies	6) Provided Characteristics of Studies	7) Assessed Scientific Quality	8) Considered Quality in Report	9) Methods to Combine Appropriate	10) Assessed Publication Bias	11) Stated Conflict of Interest
Yu et al, 2008 (12)	7	✓		✓	✓		✓	✓	✓	✓		
Pines et al, 2009 (13)	3	✓	✓	✓								

Abbreviations: AMSTAR, Assessment of Multiple Systematic Reviews

^aDetails of AMSTAR method are described in Shea et al (10)

Table A2: Risk of Bias for All Studies included in the Yu et al (12) and Pines et al (13) Systematic Reviews of Optimal Timing to Administer Antibiotics

Source Author, Year	Allocation Concealment	Blinding	Complete Accounting of Patients and Outcome Events	Selective Reporting Bias	Other Limitations
Kanwar et al, 2007 (14)	Very serious limitations ^a	Very serious limitations ^a	No serious limitations	No serious limitations	Serious limitations ^b
Waterer et al, 2006 (15)	Very serious limitations ^a	Very serious limitations ^a	No serious limitations	No serious limitations	Serious limitations ^b
Bodi et al, 2005 (16)	Very serious limitations ^a	Very serious limitations ^a	No serious limitations	No serious limitations	Serious limitations ^b
Marrie et al, 2005 (17)	Very serious limitations ^a	Very serious limitations ^a	No serious limitations	No serious limitations	Serious limitations ^b
Wilson et al, 2005 (18)	Very serious limitations ^a	Very serious limitations ^a	No serious limitations	No serious limitations	Serious limitations ^b
Houck et al, 2004 (19)	Very serious limitations ^a	Very serious limitations ^a	No serious limitations	No serious limitations	No serious limitations
Silber et al, 2003 (20)	Very serious limitations ^a	Very serious limitations ^a	No serious limitations	No serious limitations	No serious limitations
Ziss et al, 2003 (21)	Very serious limitations ^a	Very serious limitations ^a	No serious limitations	No serious limitations	Serious limitations ^b
McGarvey et al, 1993 (22)	Very serious limitations ^a	Very serious limitations ^a	No serious limitations	No serious limitations	No serious limitations

^aAll studies are observational studies, and therefore there is no adequate sequence generation, blinding, or allocation concealment for any.

^bNo severity controls were used in any study, except for McGarvey et al (22), Houck et al (19), and Silber et al (20).

Table A3: GRADE Evidence Profile for Optimal Timing of Antibiotic Administration in Patients with Community-Acquired Pneumonia

No. of Studies (Design)	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Upgrade Considerations	Quality
Mortality							
9 (Observational)	Very serious limitations (-2) ^a	No serious limitations	Serious limitations ^{b,c}	No serious limitations	Undetected	None	⊕Very Low
Length of Hospital Stay							
3 (Observational)	Very serious limitations (-2) ^a	No serious limitations	Serious limitations ^b	No serious limitations	Undetected	None	⊕Very Low

Abbreviation: ICU, intensive care unit.

^aAll studies are observational, leading to no allocation concealment, blinding, or adequate sequence generation

^b Indirectness in interventions; not all interventions isolate timing of antibiotic administration as the primary intervention.

^cMeasures of mortality range from 30-day mortality, inpatient mortality, ICU mortality, and undefined mortality.

References

- (1) Anstett D, Smallfield A, Vlahaki D, Milne WK. Door-to-antibiotic time for pneumonia in a rural emergency department. *CJEM*. 2010;12(3):207-11.
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