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Monotherapy Versus Combination Therapy for Adults Hospitalized for Community-Acquired Pneumonia: A Rapid Review

Health Quality Ontario

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Evidence Development and Standards Branch at Health Quality Ontario

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Conflict of Interest Statement

All reports prepared by the Division of Evidence Development and Standards at Health Quality Ontario are impartial. There are no competing interests or conflicts of interest to declare.

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, health technology assessments, and meta-analyses; if none are located, the search is expanded to include randomized controlled trials (RCTs), and guidelines. Systematic reviews are evaluated using a rating scale developed for this purpose. If the systematic review 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 systematic review has not evaluated the primary studies using GRADE, the primary studies included in the systematic review are retrieved and a maximum of two outcomes are graded. If no well-conducted systematic reviews 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 policy makers.

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.

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List of Abbreviations

CAP	Community-acquired pneumonia
CI	Confidence interval
HQO	Health Quality Ontario
ICU	Intensive care unit
RCT	Randomized controlled trial

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

The objective of this rapid review is to assess the effectiveness of monotherapy versus combination therapy in adults hospitalized with community-acquired pneumonia (CAP).

Clinical Need and Target Population

There are several drug therapies used to manage community-acquired pneumonia. These drugs can be used alone (monotherapy) or in combination. The major drug classes most often cited in the literature for treating CAP include: macrolides, quinolones, beta-lactamases and cephalosporins. Over-prescribing or inappropriate use of some of these drugs can lead to antimicrobial resistance. Treatment preference will vary regionally depending on the common strains of pneumonia in particular areas.

Guidelines

Internationally, guidelines on the diagnosis and management of CAP have varying recommendations for first line treatment. (Table 1) For instance, the American (1) and British guidelines (2) recommend the use of a macrolide in the treatment of hospitalized patients with mild or moderate CAP, while the Dutch guidelines (3) recommended monotherapy with a beta-lactam as initial treatment for patients admitted to the hospital (non-ICU) with CAP. The Dutch guidelines also specifically state that tetracyclines (e.g., doxycycline) and macrolides should not be used due to increasing antibiotic resistance.

Table 1: Guideline Recommendations for Antibiotic Coverage for Atypical Pathogens in Patients Hospitalized With Community-Acquire Pneumonia (CAP)

Guideline	Patients in ICU	Patients in Ward (not ICU)
American College of Emergency Physicians (2009) (6)	Not reported	Not reported
Anti-infective Guidelines for Community-Acquired Infections in Ontario (2013) (5)	Not reported	Not reported
British Thoracic Society (2009) (2)	***Combination therapy:*** Beta-lactam and macrolide	***Combination therapy:*** Moderate severity: Beta-lactam and macrolide or ***Monotherapy:*** Low severity: Beta-lactam
Canadian Infectious Disease Society/Canadian Thoracic Society (2000) (4)	***Combination therapy:*** Respiratory fluoroquinolone and beta-lactam	***Monotherapy:*** Respiratory fluoroquinolone
European Respiratory Society (8)	***Combination therapy:*** Macrolide + cephalosporin	***Combination therapy:*** Macrolide + cephalosporin or beta-lactam
Infectious Disease Society of America/American Thoracic Society (2007) (1)	***Combination therapy:*** Beta-lactam and macrolide	***Monotherapy:*** Respiratory fluoroquinolone or ***Combination therapy:*** Beta-lactam and macrolide[a]
Scottish Intercollegiate Guidelines Network (2002) (7)	Not reported	Not reported
South African Guidelines (9)	***Combination therapy:*** Beta-lactam + cephalosporin + macrolide	***Monotherapy or combination therapy:*** Beta-lactam with or without cephalosporin (fluoroquinolone if atypical pathogen suspected)
SWAB/NVALT Dutch Guidelines (2011)	***Combination therapy:*** Quinolone with or without beta-lactam or macrolide + cephalosporin	***Monotherapy:*** Beta-lactam
Swedish Society of Infectious Diseases (2012)	***Combination therapy:*** Macrolide + fluoroquinolone + cephalosporin	***Monotherapy or combination therapy:*** Beta-lactam with or without cephalosporin

Abbreviations: CAP, community-acquired pneumonia; ICU, intensive care unit.

Rapid Review

Research Question

Is combination antimicrobial therapy more effective than monotherapy in patients with severe pneumonia, in terms of mortality and treatment failure?

Research Methods

Literature Search

A literature search was performed on May 23, 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 23, 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 23, 2013
- health technology assessments, systematic reviews and meta-analyses, randomized controlled trials
- hospitalized adults with community-acquired pneumonia (CAP) or nursing home-acquired pneumonia
- no specific pathogens identified in study population
- comparing monotherapy (with any drug) to combination therapy (with any combination of drugs)

Exclusion Criteria

- observational studies, case series, case reports, editorials, non-peer reviewed literature, conference abstracts
- children
- outpatients with CAP
- patients with hospital-acquired pneumonia

Outcomes of Interest

- overall mortality
- treatment failure

Expert Panel

In April 2013, Health Quality Ontario struck an Expert Advisory Panel on Evidence-Based Episode of Care for Pneumonias Presenting to Hospitals. Members included physicians, nurses, allied health professionals, and personnel from the Ministry of Health and Long-Term Care.

The role of the expert panel was to contextualize the evidence produced by Health Quality Ontario 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 panel members.

Quality of Evidence

The quality of the body of evidence for each outcome was examined according to the GRADE Working Group criteria. (10) The overall quality was determined to be very low, low, moderate, or high using a step-wise, structural methodology.

Study design was the first consideration; the starting assumption was that randomized controlled trials 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 main factors that may raise the quality of evidence were considered: large magnitude of effect, dose response gradient, and accounting for all residual confounding factors. (10) For more detailed information, please refer to the latest series of GRADE articles. (10)

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 may 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 Rapid Review

The database search yielded 1,792 citations published between January 1, 2008, and May 23, 2013 (with duplicates removed). Articles were excluded based on information in the title and abstract. The full texts of potentially relevant articles were obtained for further assessment.

No systematic reviews or meta-analyses were identified that specifically compared monotherapy to combination therapy in patients with CAP. However, several systematic reviews included RCTs comparing monotherapy to combination therapy. (11-13) Thus, 8 RCTs from the systematic reviews were analyzed. Where possible, the data were extracted from the systematic review; otherwise the original publication was retrieved. In addition, the literature search found 1 other RCT that met the inclusion criteria. (14)

The 9 RCTS tested several different combinations and comparisons of antibiotic therapy. Table 2 lists the characteristics of the studies. All of the studies reported treatment failure as an outcome. Only 3 studies reported mortality.

Table 2. Characteristics of RCTs Included in the Rapid Review

Study	Number of patients	Monotherapy	Combination therapy	Outcomes
Hatipoglu et al, 2010[a] (11)	66	Cephalosporin	Cephalosporin + macrolide	Treatment failure
Kalbermatter et al, 2000[a] (11)	84	Quinolone	Cephalosporin + beta-lactam	Treatment failure Mortality[b]
Lee et al, 2012 (14)	40	Quinolone	Macrolide + cephalosporin	Treatment failure
Lode et al, 1995[a] (11)	808	Beta-lactam	Quinolone + macrolide	Treatment failure Mortality
Portier et al, 2005 (15)	349	Quinolone	Beta-lactam + macrolide	Treatment failure
Rizzato et al, 1997[a] (11)	225	Cephalosporin	Quinolone + teicoplanin	Treatment failure Mortality
Torres et al, 2008 (16)	733	Quinolone	Quinolone + cephalosporin	Treatment failure
Torres et al, 2003 (17)	564	Quinolone	Beta-lactam + macrolide	Treatment failure
Xu et al, 2006 (18)	40	Quinolone	Macrolide + cephalosporin	Treatment failure

Abbreviation: RCT, randomized controlled trial.
[a] Data from these studies were extracted from the Cochrane Systematic Review by Eliakim-Raz et al. (11)
[b] No deaths occurred in either treatment arm.

A series of meta-analyses were performed to assess differences in mortality or treatment failure between the monotherapy and combination therapy arms in the studies identified. Table 3 outlines the results of these analyses. With the exception of the comparison of cephalosporin versus quinolone and teicoplanin (shown in italics), none of the meta-analyses found a significant difference between monotherapy and combination therapy. The GRADE quality of evidence ranged from very low to moderate across the comparisons.

Table 3. Results from the Meta-Analyses Comparing Monotherapy to Combination Therapy

Monotherapy	Combination Therapy	Number of RCTs (Patients, n)	Risk Ratio (95% CI)	GRADE
Overall mortality				
Beta-lactam	Quinolone + macrolide	1 (808)	0.43 (0.15, 1.23)	Moderate
Cephalosporin	Quinolone + teicoplanin	1 (225)	0.67 (0.21, 2.17)	Very low
Treatment failure				
Quinolone	Beta-lactam + macrolide	2 (823)	0.83 (0.58, 1.20)	Moderate
Quinolone	Beta-lactam + cephalosporin	1 (84)	0.50 (0.06, 4.27)	Very low
Quinolone	Macrolide + cephalosporin	2 (80)	0.78 (0.13, 4.51)	Low
Quinolone	Quinolone + cephalosporin	1 (733)	1.26 (0.93, 1.72)	Moderate
Quinolone	Combination therapy	6 (1,468)	1.12 (0.82, 1.53)	Moderate
Beta-lactam	Quinolone + macrolide	1 (808)	1.07 (0.86, 1.34)	Moderate
Cephalosporin	*Quinolone + teicoplanin*	*1 (225)*	*3.83 (1.74, 8.40)*	*Very low*
Cephalosporin	Cephalosporin + macrolide	1 (66)	0.81 (0.30, 2.14)	Very low
Cephalosporin	Combination therapy	2 (291)	2.26 (0.74, 6.89)	Low

Abbreviations: CI, confidence interval; n, number; RCT, randomized controlled trial.

Limitations

Due to the limitations of the rapid review process, this review did not conduct a thorough analysis of all of the individual included studies, and it did not consider the severity of community-acquired pneumonia. In addition, this review grouped classes of drug therapies and also grouped several generations of each drug, which may not be appropriate. Further analysis through a more comprehensive literature search (searching more than the last 5 years and including more databases) may identify differences between these treatments. This research question may be ideally suited for a network meta-analysis where multiple therapies can be compared directly and indirectly.

Conclusions

Based on the results of this rapid review, there does not appear to be a significant difference in mortality or treatment failure in hospitalized patients receiving monotherapy versus combination therapy for community-acquired pneumonia. A broader evidence-based analysis of the literature may alter these results.

Acknowledgements

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

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Appendices

Appendix 1: Literature Search Strategies

Search date: May 23, 2013
Databases searched: OVID MEDLINE, MEDLINE In-Process and Other Non-Indexed Citations, EMBASE; All EBM Reviews
Limits: 2008-current; English
Filters: HTA-MA-SR-RCT-Guidelines

#	Searches	Results
1	exp Pneumonia/	248084
2	(pneumoni* or peripneumoni* or pleuropneumoni* or lobitis or ((pulmon* or lung*) adj inflammation*)).ti,ab.	292575
3	or/1-2	404696
4	exp Anti-Bacterial Agents/ use mesz,acp,cctr,coch,clcmr,dare,clhta,cleed or exp antibiotic agent/ use emez	1411484
5	exp Quinolones/ use mesz,acp,cctr,coch,clcmr,dare,clhta,cleed or exp quinolone derivative/ use emez	143021
6	exp Macrolides/ use mesz,acp,cctr,coch,clcmr,dare,clhta,cleed or exp macrolide/ use emez	209332
7	exp Tetracyclines/ use mesz,acp,cctr,coch,clcmr,dare,clhta,cleed or exp tetracycline derivative/ use emez	154926
8	exp Chloramphenicol/	65592
9	exp Streptogramins/ use mesz,acp,cctr,coch,clcmr,dare,clhta,cleed or exp streptogramin derivative/ use emez	1898
10	exp Ketolides/ use mesz,acp,cctr,coch,clcmr,dare,clhta,cleed or exp ketolide/ use emez	3885
11	(((anti?bacterial or anti?mycobacterial or bacteriocidal) adj agent) or antibiotic* or bacteriocide* or quinolon* or fluoroquinolon* or macrolid* or doxycyclin* or t etracyclin* or chloramphenicol* or streptogramin* or ketolid* or erythromycin* or roxithromycin* or azithromycin* or clarithro mycin* or ciprofloxacin* or ofloxacin* or levofloxacin* or trovaflox acin* or moxifloxacin* or grepafloxacin* or tigecyclin* or minocyclin* or pristinamycin* or quinupristin* or telithromycin*).ti,ab.	634694
12	or/4-11	1705779
13	3 and 12	111562
14	exp Drug Therapy, Combination/ use mesz,acp,cctr,coch,clcmr,dare,clhta,cleed	280028
15	exp drug combination/ use emez	177229
16	(polytherapy or multiple or combination* or combine* or dual).ti,ab.	4009707
17	cb.fs.	600835
18	or/14-17	4660006
19	13 and 18	30787
20	(Meta Analysis or Controlled Clinical Trial or Randomized Controlled Trial).pt.	870712
21	Meta-Analysis/ use mesz,acp,cctr,coch,clcmr,dare,clhta,cleed or exp Technology Assessment, Biomedical/ use mesz,acp,cctr,coch,clcmr,dare,clhta,cleed	49796
22	Meta Analysis/ use emez or Biomedical Technology Assessment/ use emez	82386
23	(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 or ((health technolog* or biomedical technolog*) adj2 assess*)).ti,ab.	355131
24	exp Random Allocation/ use mesz,acp,cctr,coch,clcmr,dare,clhta,cleed or exp Double-Blind Method/ use mesz,acp,cctr,coch,clcmr,dare,clhta,cleed or exp Control Groups/ use mesz,acp,cctr,coch,clcmr,dare,clhta,cleed or exp Placebos/ use mesz,acp,cctr,coch,clcmr,dare,clhta,cleed	331829
25	Randomized Controlled Trial/ use emez or exp Randomization/ use emez or exp RANDOM SAMPLE/ use emez or Double Blind Procedure/ use emez or exp Triple Blind Procedure/ use emez or exp Control Group/ use emez or exp PLACEBO/ use emez	614394
26	(random* or RCT or placebo* or sham* or (control* adj2 clinical trial*)).ti,ab.	2097510
27	exp Standard of Care/ use mesz,acp,cctr,coch,clcmr,dare,clhta,cleed or exp Guideline/ use mesz,acp,cctr,coch,clcmr,dare,clhta,cleed or exp Guidelines as Topic/ use mesz,acp,cctr,coch,clcmr,dare,clhta,cleed	130255
28	exp Practice Guideline/ use emez or exp Professional Standard/ use emez	546862
29	(guideline* or guidance or consensus statement* or standard or standards).ti.	234998
30	or/20-29	3651296
31	19 and 30	6025
32	limit 31 to (english language and yr="2008 -Current") [Limit not valid in CDSR,ACP Journal Club,DARE,CCTR,CLCMR; records were retained]	2025
33	limit 32 to english language [Limit not valid in CDSR,ACP Journal Club,DARE,CCTR,CLCMR; records were retained]	2025
34	limit 33 to yr="2008 -Current" [Limit not valid in DARE; records were retained]	2025
35	remove duplicates from 34	1792

Appendix 2: GRADE Tables

Table A1: GRADE Evidence Profile for Comparison of Monotherapy and Combination Therapy

No. of Studies (Design)	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Upgrade Considerations	Quality
Outcome: Mortality (beta-lactam vs quinolone + macrolide)							
1 (RCT)	No serious limitations	Serious limitations (-1)[a]	No serious limitations	No serious limitations	Undetected	None	⊕⊕⊕ Moderate
Outcome: Mortality (cephalosporin vs quinolone + teicoplanin)							
1 (RCT)	Serious limitations (-1)b	Serious limitations (-1)a	No serious limitations	Serious limitations (-1)c	Undetected	None	⊕ Very low
Outcome: Treatment failure (quinolone vs beta-lactam +macrolide)							
2 (RCTs)	Serious limitations (-1)[b]	No serious limitations	No serious limitations	No serious limitations	Undetected	None	⊕⊕⊕ Moderate
Outcome: Treatment Failure (quinolone vs beta-lactam + cephalosporin)							
1 (RCT)	Serious limitations (-1)[b]	Serious limitations (-1)[a]	No serious limitations	Serious limitations (-1)[c]	Undetected	None	⊕ Very low
Outcome: Treatment Failure (quinolone vs macrolide + cephalosporin)							
2 (RCTs)	No serious limitations	Serious limitations (-1)[d]	No serious limitations	Serious limitations (-1)[c]	Undetected	None	⊕⊕ Low
Outcome: Treatment Failure (quinolone vs quinolone + cephalosporin)							
1 (RCT)	No serious limitations	Serious limitations (-1)[a]	No serious limitations	No serious limitations	Undetected	None	⊕⊕⊕ Moderate
Outcome: Treatment Failure (quinolone vs combination therapy)							
6 (RCTs)	Serious limitations (-1)[b]	No serious limitations	No serious limitations	No serious limitations	Undetected	None	⊕⊕⊕ Moderate
Outcome: Treatment Failure (beta-lactam vs quinolone + macrolide)							
1 (RCT)	No serious limitations	Serious limitations (-1)[a]	No serious limitations	No serious limitations	Undetected	None	⊕⊕⊕ Moderate
Outcome: Treatment Failure (cephalosporin vs quinolone + teicoplanin)							
1 (RCT)	Serious limitations (-1)[b]	Serious limitations (-1)[a]	No serious limitations	Serious limitations (-1)[c]	Undetected	None	⊕ Very low
Outcome: Treatment Failure (cephalosporin vs cephalosporin + macrolide)							
1 (RCT)	Serious limitations (-1)[b]	Serious limitations (-1)[a]	No serious limitations	Serious limitations (-1)[c]	Undetected	None	⊕ Very low
Outcome: Treatment Failure (cephalosporin vs combination therapy)							
2 (RCTs)	Serious limitations (-1)[b]	No serious limitations	No serious limitations	Serious limitations (-1)[c]	Undetected	None	⊕⊕ Low

Abbreviation: RCT, randomized controlled trial.

[a] Only 1 study—not possible to assess consistency.

[b] See "Risk of Bias" Table A2.

[c] Wide confidence intervals.

[d] Inconsistency in results of the 2 studies.

Table A2: Risk of Bias Among Randomized Controlled Trials for the Comparison of Monotherapy and Combination Therapy

Author, Year	Allocation Concealment	Blinding	Complete Accounting of Patients and Outcome Events	Selective Reporting Bias	Other Limitations
Hatipoglu et al, 2010[a] (11)	Limitations[b]	Limitations[b]	Limitations[c]	Limitations[b]	No limitations
Kalbermatter et al, 2000[a] (11)	Limitations[b]	Limitations[d]	No limitations	No limitations	No limitations
Lee et al, 2012 (14)	No limitations	Limitations[b]	No limitations	No limitations	No limitations
Lode et al, 1995[a] (11)	Limitations[b]	No limitations	No limitations	No limitations	No limitations
Portier et al, 2005 (15)	Limitations[b]	Limitations[b]	No limitations	No limitations	No limitations
Rizzato et al, 1997[a] (11)	Limitations[b]	Limitations[d]	Limitations[e]	No limitations	No limitations
Torres et al, 2008 (16)	No limitations	Limitations[b]	No limitations	No limitations	No limitations
Torres et al, 2003 (17)	No limitations	Limitations[b]	No limitations	No limitations	No limitations
Xu et al, 2006 (18)	Limitations[b]	Limitations[b]	No limitations	No limitations	No limitations

[a] Data from these studies were extracted from the Cochrane Systematic Review by Eliakim-Raz et al. (11)
[b] Not reported.
[c] Satisfactory data provided for treatment failure, unclear data for mortality.
[d] Open trial, no blinding stated.
[e] Unsatisfactory data provided for mortality and treatment failure.

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