Diagnosis and Treatment of Adults with Community-Acquired Pneumonia

An Official Clinical Practice Guideline of the American Thoracic Society and Infectious Diseases Society of America

ONLINE SUPPLEMENT

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Methods

Panel composition

This guideline was developed by a multidisciplinary panel that consisted of 15 members including pulmonologists, infectious disease specialists, general internists, and two methodologists with expertise in evidence synthesis and the guideline development process (J.L.B. and A.C.L.). The panel was chaired by J.M. and G.W., representing the IDSA and ATS, respectively.

Conflict of interest declaration and management

Panel members disclosed all potential conflicts of interest according to ATS and IDSA policies. Declarations were reviewed by panel chairs, J.M. and G.W., along with staff of the ATS and IDSA conflict-of-interest committees and classified as: 1) no potential conflict; 2) the interest is irrelevant or insignificant; 3) manageable conflict of interest; or 4) disqualifying conflict of interest. Two guideline panel members ultimately recused themselves from participation in the process owing to conflicts of interest. Summary of the declarations of actual, potential or perceived conflicts of interest are provided at the end of this document. Methodologists were non-voting members of the panel, but when required they suggested the initial direction of the recommendation based on established criteria.

Meetings

An initial face-to-face meeting was held during the 2014 Infectious Disease Society of America Conference in Philadelphia, Pennsylvania, where the panel discussed the scope and objectives of the project and formulated the questions to be answered by the guideline. An additional face-to-face meeting was held at the 2016 ATS International Conference in San Francisco, California, at which the panel reviewed evidence summaries and made preliminary recommendations. Conference calls and email-correspondence were used to discuss refinement of PICO questions, analyze and grade evidence, and draft recommendations. Prior to the initial face-to-face meeting, J.L.B. presented the panel with an overview of the guideline development process as well as the GRADE approach to making recommendations. The sponsoring societies provided financial support for expenses resulting from face-to-face meetings and conference calls. The views and interests of the ATS and IDSA, as well as of any commercial entity that provided external funding for professional societies, had no influence on topics discussed and recommendations made.

Clinical questions and outcomes of interest

The scope and questions for the guideline were identified by the panel members, using the 2007 guideline document as a starting point. Potential outcomes of interest were generated by the panel members using an online survey developed by A.C.L., and then rated by each panel member. Ratings provided by panel members were used to categorize outcomes as critical or as important, but not critical. Examples of critical outcomes included: 30-day mortality, clinical failure as defined by persistence or progression or pneumonia, duration of antibiotic utilization, and hospital readmission. Consensus was achieved for all final outcomes. For questions where the original prioritization of outcomes was not felt to capture those outcomes that were both necessary and sufficient to adopt an intervention, the outcomes were re-prioritized accordingly.

Evidence review and development of clinical recommendations

With the exception of the question pertaining to healthcare-associated pneumonia, the methodologists conducted a pragmatic systematic review and performed evidence synthesis for all PICO questions and prepared the evidence summaries following the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach [1]. Due to the multi-faceted nature of the question addressing healthcare-associated pneumonia, it was challenging to

evaluate this topic using the PICO format. For this question, panel members, led by the chairs (J.M. and G.W.), performed a non-systematic literature review and made a recommendation based on the identified evidence and expert opinion. For each question addressed by the methodology group, search strategies were developed using medical subject heading keywords and text words and used the PubMed platform to search MEDLINE for relevant literature. Review of the literature began in 2015 and ended in 2017. During that time period existing search strategies were used to identify newly published literature on a monthly basis. A.C.L. completed title and abstract screening, followed by full review of all articles which were potentially relevant to the question of interest. Panel members were contacted to confirm completeness of the body of evidence and suggest additional articles that might have been missed in electronic searches. For articles selected as evidence for any given question, data abstraction was performed by A.C.L. using a pre-designed data abstraction form. Following completion of data abstraction, sub-groups of panel members assigned to each question were asked to review and provide feedback on abstracted data.

When appropriate, we performed meta-analysis using Cochrane Collaboration Review Manager Software (Version 5.3.5.31) to obtain estimates of effects on each outcome of interest. When meta-analysis was not appropriate we summarized the evidence in a narrative form. We prepared evidence summaries for each question following the GRADE approach [2, 3] using the GRADEpro Guideline Development Tool online application (www.gradepro.org). We assessed the quality of the evidence for each of the outcomes of interest following the GRADE approach [4], based on the following criteria: risk of bias in primary studies, precision, consistency, directness of the evidence, magnitude of effect, risk of publication bias, presence of dose-effect relationship, and an assessment of the effect of residual confounding. Quality of the evidence was categorized into 4 levels: high, moderate, low and very low. Evidence summaries were reviewed by panel members who provided feedback by electronic communication and during a face-to-face meeting. All comments were addressed, and evidence summaries were modified if necessary. The panel developed recommendations based on GRADE evidence summaries, when available, and final recommendations and their strengths were decided by consensus using an online survey. In certain cases, there was no evidence directly addressing the question posed by the panel. For these questions, no GRADE evidence table was generated. In these cases, and in those cases where the evidence was limited, literature that informed the recommendation was included in the summary of evidence within the guideline. We labeled recommendations as either “strong” or “conditional” according to the GRADE approach and in cases when strong recommendations were paired with low or very low quality evidence, we indicated the reasons for the discrepancy (e.g., significant risks of undertreating bacterial pathogens).

Manuscript preparation

Following finalization of recommendations, sub-groups of panel members drafted each section of the guideline document for their assigned question. The compiled manuscript was then reviewed by the entire panel, and feedback was provided by electronic communication until consensus on the final document was achieved. The final approved version was submitted to each co-sponsoring professional society for peer review.

References

1. Guyatt G, Oxman AD, Akl EA, Kunz R, Vist G, Brozek J, Norris S, Falck-Ytter Y, Glasziou P, DeBeer H, Jaeschke R, Rind D, Meerpohl J, Dahm P, Schunemann HJ. GRADE guidelines: 1. Introduction-GRADE evidence profiles and summary of findings tables. J Clin Epidemiol. 2011;64(4):383-94. PubMed PMID: 21195583.
2. Guyatt GH, Oxman AD, Santesso N, Helfand M, Vist G, Kunz R, Brozek J, Norris S, Meerpohl J, Djulbegovic B, Alonso-Coello P, Post PN, Busse JW, Glasziou P, Christensen R, Schunemann HJ. GRADE guidelines: 12. Preparing summary of findings tables-binary outcomes. J Clin Epidemiol. 2013;66(2):158-72. PubMed PMID: 22609141.
3. Guyatt GH, Thorlund K, Oxman AD, Walter SD, Patrick D, Furukawa TA, Johnston BC, Karanicolas P, Akl EA, Vist G, Kunz R, Brozek J, Kupper LL, Martin SL, Meerpohl JJ, Alonso-Coello P, Christensen R, Schunemann HJ. GRADE guidelines: 13. Preparing summary of findings tables and evidence profiles-continuous outcomes. J Clin Epidemiol. 2013;66(2):173-83. PubMed PMID: 23116689.
4. Balshem H, Helfand M, Schunemann HJ, Oxman AD, Kunz R, Brozek J, Vist GE, Falck-Ytter Y, Meerpohl J, Norris S, Guyatt GH. GRADE guidelines: 3. Rating the quality of evidence. J Clin Epidemiol. 2011;64(4):401-6. PubMed PMID: 21208779.

Search Strategies and Literature Review Results by PICO

Should antimicrobial treatment be guided by results of sputum gram stain and culture rather than by empiric choice alone in patients hospitalized with CAP?

Should blood cultures versus no blood cultures be obtained in patients hospitalized with CAP?

Should spectrum of coverage be maintained, rather than de-escalation of coverage, for hospitalized patients with CAP and cultures that fail to reveal MDR pathogens at 48-72 hours?

	Query	Items found
#8	(#4 AND #7)	1407
#7	(#5 OR #6)	21534
#6	sputum culture*[tw]	2092
#5	blood culture*[tw]	19573
#4	(#1 OR #2 OR #3)	83866
#3	community acquired pneumonia[tw]	7188
#2	pneumonia[mh]	76881
#1	Infections, Community-Acquired[mh]	11021

The search strategy was designed to encompass the PICOs related to sputum or blood cultures as well as antibiotic management based on blood culture data. The search identified 1407 studies, and title/abstract screen left 58 studies for further review. For the sputum gram stain/culture PICO, 3 of these studies directly addressed our PICO. For the blood culture PICO, 4 had direct evidence. Subsequent to the original search, one new study that directly addressed the blood culture PICO was added (Costantini 2016). For the de-escalation question, 23 potentially relevant studies were identified. Twenty studies covered the utilization of sputum and/or blood cultures and described the relationship between culture results and changes in antibiotic therapy but did NOT provide information about clinical outcomes when treatment was altered (narrowed, broadened, or otherwise). One study covered clinical outcomes among non-responders, comparing empiric changes in antibiotic therapy to those based on culture data. Three studies had data about antibiotic changes relative to culture results AND some information about clinical outcomes; however, of these only 1 specifically addressed the concept of de-escalation. Of note, most of these studies focused on clinician behavior when cultures were POSITIVE as opposed to narrowing of antibiotics when cultures were NEGATIVE. Subsequent to the original search, three new studies that directly addressed the de-escalation PICO were added (Carugati 2015, Viasus 2016, Yamana 2016) along with one additional study (Khasawneh 2014) identified during review of Yamana 2016. For this PICO, we developed two evidence tables: one specific to studies where a pathogen had been identified (Cremers 2014, Khasawneh 2014, Carugati 2015, Viasus 2016, Yamana 2016) and one specific to the single study that reports on culture-negative patients (Yamana 2016).

Should rapid diagnostic testing (viral panels, urine antigen detection) versus no such testing be used in adults with suspected CAP?

	Query	Items found
#20	(#13 AND #19)	1207
#19	(#14 OR #15 OR #16 OR #17 OR #18)	1349068
#18	assay[tiab]	536377
#17	urine antigen[tiab]	141
#16	urin*[tw]	574730
#15	viral*[tiab]	280466
#14	binax*[tw]	239
#13	(#8 AND #12)	5259
#12	(#9 OR #10 OR #11)	3782872
#11	diagnos*[tiab]	1874315
#10	testing[tw]	473655
#9	test*[tiab]	2114563
#8	(#3 AND #7)	15079
#7	(#4 OR #5 OR #6)	1688452
#6	infecti*[tiab]	1216514
#5	lung[tiab]	466696
#4	pneumonia[tiab]	90235
#3	(#1 OR #2)	17579
#2	community-acquired[tiab]	14158
#1	Infections, Community-Acquired[mh]	10953

For this PICO there were 1207 studies in the original search, with 148 considered potentially relevant after title and abstract review. Of these, 79 addressed the characteristics of the different diagnostic tests (e.g. sensitivity and specificity), 34 addressed assay testing/development, and 18 were epidemiologic/other (related but not addressing our PICO question directly or indirectly). Of the remaining studies, 12 could be considered indirect evidence; either they discuss outcomes among patient who ALL underwent rapid diagnostic testing (thus no comparison group), who were managed according to multiple microbiologic tests (not just rapid diagnostic tests), or they include patients with lower respiratory tract infections (not just CAP). This left 5 studies that directly addressed our PICO, one an RCT and the others observational. Following review by panel members, 2 studies were moved to direct evidence and one was moved to an indirect folder (for a total of 6 direct studies). Following the initial search, the same search strategy produced one new study which was added to the database (Costantini 2016), for a final total of 7 studies. Evidence tables include all studies in one way or another (including those evaluating multiple microbiologic tests at once).

Should serum procalcitonin versus clinical judgment alone (without using a clinical prediction guide) be used in adults to guide initiation of treatment for CAP?

	Query	Items found
#10	(#8 AND #9)	239
#9	procalcitonin*[tw]	3356
#8	(#3 AND #7)	15079
#7	(#4 OR #5 OR #6)	1688452
#6	infecti*[tiab]	1216514
#5	lung[tiab]	466696
#4	pneumonia[tiab]	90235
#3	(#1 OR #2)	17579
#2	community-acquired[tiab]	14158
#1	Infections, Community-Acquired[mh]	10953

We identified 239 studies in the original search, with 66 considered potentially relevant after title and abstract review. Of these, 43 were concerned with procalcitonin as a predictor of etiology, severity, or prognostication, and 5 addressed procalcitonin in the context of sepsis. There were 8 studies that provided indirect evidence (i.e. they addressed procalcitonin use in respiratory infections, some focused on COPD or VAP while others focused on lower respiratory tract infections, but did not provide separate data for CAP in the manuscript), and 1 study that addressed cost using a decision-tree analysis. This left 9 studies with direct evidence related to CAP (8 RCTs; 1 observational).

Should serum procalcitonin versus clinical judgment alone (without using clinical prediction guide) be used in adults to guide duration of treatment for CAP?

Pertinent studies were captured in the search strategy for the previous PICO about procalcitonin as it was broad, essentially looking for anything related to pneumonia or lung infection and procalcitonin. Of the studies from that search there were 8 studies, all of which overlapped with the Diagnosis-related procalcitonin question. Given the number of randomized trials, the observational data was not included in the evidence table which addresses the procalcitonin questions in both the Diagnosis and Management categories. The final evidence table for this PICO is a combination of Diagnosis and Management PICOs, as included studies address the initiation of antibiotics and modification of therapy simultaneously.

Should clinical prediction rules versus clinical judgment alone be used to determine treatment location for adults with CAP?

Should a clinical prediction rule for prognosis be used in addition to clinical judgment versus clinical judgment alone to determine inpatient general medical versus higher levels of inpatient treatment intensity (intensive care unit, step-down, or telemetry unit) for adults with CAP?

#15	(#4 AND #9 AND #14)	3032
#14	(#10 OR #11 OR #12 OR #13)	1829590
#13	index[tiab]	536082
#12	rule[tiab]	61775
#11	score[tiab]	346219
#10	predict*[tiab]	1090189
#9	(#5 OR #6 OR #7 OR #8)	1182645
#8	ambulatory[tiab]	64393
#7	outpatient[tiab]	94292
#6	home[tiab]	163943
#5	hospital*[tiab]	947686
#4	(#1 OR #2 OR #3)	85528
#3	community acquired pneumonia[tw]	7216
#2	pneumonia[mh]	78529
#1	Infections, Community-Acquired[mh]	11073

After title/abstract screen of 3032 studies there were 109 studies for further review. After further review of those articles, we identified 15 studies that seemed to provide direct or indirect evidence about this question (of the original 104, those not included focused on developing rules, using them to stratify severity or to determine retrospectively if admissions were appropriate or inappropriate, or they were purely descriptive). Of these, 7 were retained for inclusion in the evidence tables. We designed two different evidence tables: one with observational data and another which included randomized trials. For the second question, an additional search was conducted including the terms intensive care OR critical care OR ICU. This search did not identify any literature detailing patient outcomes when comparing the use of a clinical prediction rule to clinical judgement alone to determine general medical versus intensive care unit treatment location in adults with CAP.

Should a macrolide versus respiratory fluoroquinolone be used for treatment of CAP in adults in the outpatient setting?

Should a macrolide versus β-lactam be used for treatment of CAP in adults in the outpatient setting?

Should a macrolide versus doxycycline be used for treatment of CAP in adults in the outpatient setting?

Should a β-lactam versus respiratory fluoroquinolone be used for treatment of CAP in adults in the outpatient setting?

	Query*	Items found
#37	(#26 AND #36)	3569
#36	(#34 NOT #35)	3022652
#35	(animals [mh] NOT humans [mh])	3979126
#34	(#27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33)	3510179
#33	groups[tiab]	1461144
#32	trial[tiab]	384521
#31	randomly[tiab]	228763
#30	drug therapy[sh]	1732418
#29	randomized[tiab]	337949
#28	controlled clinical trial[pt]	88467
#27	randomized controlled trial[pt]	382837
#26	(#9 AND #12 AND #25)	4950
#25	(#13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24)	642415
#24	(doxycyclin* OR tetracyclin*)	48781
#23	(co-trimoxazole OR trimethoprim*)	19172
#22	clavulan*[tiab]	6608
#21	(quinolone* OR fluoroquinolon* OR ciprofloxacin* OR gemifloxacin* OR levofloxacin*)	46135
#20	(beta-lactam* OR penicillin* OR amoxicillin* OR amoxycillin* OR ampicillin* OR cloxacillin* OR dicloxacillin* OR carbenicillin* OR cephalosporin* OR ceftibuten* OR cefuroxim* OR cefpodoxim*)	141998
#19	(macrolide* OR makrolide* OR azithromycin* OR clarithromycin* OR erythromycin* OR roxithromycin* OR telithromycin* OR clindamycin*)	53866
#18	Tetracyclines[mh]	40782
#17	Quinolones[mh]	36952
#16	beta-lactams[mh]	109162
#15	Macrolides[mh]	88028
#14	antibiotic*[tw]	276074
#13	Anti-Bacterial Agents[mh]	274122
#12	(#10 OR #11)	119094
#11	pneumonia[tiab]	84386
#10	pneumonia[mh]	74831
#9	(#3 OR #4 OR #5 OR #6 OR #7 OR #8)	187444
#8	(outpatient*[tw] OR out-patient*[tw])	141149
#7	ambulate*[tw]	1410
#6	ambulatory care[mh]	45696
#5	outpatients[mh]	9282
#4	outpatient[tiab]	87715
#3	(#1 OR #2)	16747
#2	community-acquired[tiab]	13443

#1	Infections, Community-Acquired[mh]	10537

*Used search to update recent systematic review, restricting search to 02/01/2014 – Time of Initial Search (04/22/2014) - 137 studies resulted, none of which addressed these PICO questions.

This includes literature review for new studies since publication of the Pakhale systematic review, review of all studies included/excluded from the systematic review, and inclusion of studies excluded from the review as approved by committee chairs. Full review and data extraction led to exclusion of three studies: Kinasewitz (only inpatients per communication from author), Udupa (poor quality, compares multiple different antibiotics with an extremely small sample size, low priority outcome), and Vacarezza (mostly inpatients, unclear outcome data). In the end, we had 16 studies (one study includes two studies within one paper); none for the fourth question above and several for questions that we did not originally ask but were later felt to be important by the panel (Cephalosporin vs Penicillin, Ketolide vs Macrolide, Ketolide vs Quinolone, Non-fluorinated Quinolone vs Fluorinated Quinolone, Macrolide versus B-lactam + Macrolide).

Should the combination of a β-lactam and macrolide versus quinolone alone be used in adults hospitalized with CAP?

Should the combination of a β-lactam and macrolide versus macrolide alone be used in adults hospitalized with CAP?

Should the combination of a β-lactam and macrolide versus β-lactam alone be used in adults hospitalized with CAP?

	Query	Items found
#36	((#25 AND #35))	4604
#35	((#33 NOT #34))	3580040
#34	((animals [mh] NOT humans [mh]))	4009169
#33	((#26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32))	4166335
#32	groups[tiab]	1490425
#31	trial[tiab]	393984
#30	randomly[tiab]	234030
#29	drug therapy[sh]	1755768
#28	randomized[tiab]	346563
#27	controlled clinical trial[pt]	88920
#26	randomized controlled trial[pt]	388731
#25	((#8 AND #11 AND #24))	6492
#24	#12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23	650723
#23	((doxycyclin* OR tetracyclin*))	49278
#22	((co-trimoxazole OR trimethoprim*))	19382
#21	clavulan*[tiab]	6700
#20	((quinolone* OR fluoroquinolon* OR ciprofloxacin* OR gemifloxacin* OR levofloxacin*))	46963
#19	((beta-lactam* OR penicillin* OR amoxicillin* OR amoxycillin* OR ampicillin* OR cloxacillin* OR dicloxacillin* OR carbenicillin* OR cephalosporin* OR ceftibuten* OR cefuroxim* OR cefpodoxim*))	144368
#18	((macrolide* OR makrolide* OR azithromycin* OR clarithromycin* OR erythromycin* OR roxithromycin* OR telithromycin* OR clindamycin*))	54518
#17	Tetracyclines[mh]	41012
#16	Quinolones[mh]	37382
#15	beta-lactams[mh]	109824
#14	Macrolides[mh]	88975
#13	antibiotic*[tw]	280406
#12	Anti-Bacterial Agents[mh]	277867
#11	((#9 OR #10))	120759
#10	pneumonia[tiab]	85795
#9	pneumonia[mh]	75657
#8	((#3 OR #4 OR #5 OR #6 OR #7))	282656
#7	hospitali*[tw]	213684
#6	inpatient*[tw]	77496
#5	inpatients[mh]	13779
#4	inpatient[tiab]	48878
#3	((#1 OR #2))	17071
#2	community-acquired[tiab]	13717
#1	Infections, Community-Acquired[mh]	10725

Search strategy identified 4604 studies. Title and abstract review was completed, with 149 potentially relevant studies for full review. Total included in data extraction = 11; total of 7 studies for the first question, 2 studies for the second question, and 1 study for the third question – one study is a cluster-randomized controlled trial that covers more than one PICO. Regarding the cluster randomized trial, we contacted the study authors requesting adjusted RD/RR for BLM vs FQ comparison and they were able to provide the OR. For the BLM vs BL comparison, we used the RD reported in Postma as a narrative outcome in the evidence table (combining the 90-day mortality outcomes from Garin and Postma was not advised from a statistical standpoint). For the BLM vs FQ comparison, we reported the OR and 95% CIs provided by the study authors (another narrative outcome in the evidence table).

Should antibiotic regimens with additional anaerobic coverage versus standard regimens be used for CAP patients with risk factors for aspiration?

	Query	Items found
#12	(#4 AND #7 AND #11)	1155
#11	(#8 or #9 or #10)	374921
#10	Pneumonia, Aspiration/therapy[MeSH Terms]	2161
#9	Anti-Bacterial Agents[mh]	299242
#8	antibiotics[tiab]	157069
#7	(#5 or #6)	67635
#6	aspiration[tiab]	65293
#5	Pneumonia, Aspiration[mh]	5413
#4	(#1 or #2 or #3)	100850
#3	pneumonia[tiab]	91922
#2	community-acquired[tiab]	14449
#1	Infections, Community-Acquired[mh]	11160

Search strategy identified 1155 studies. After title/abstract screening we had 24 studies for further review. After full review, we had 11 studies that might provide evidence for our PICO. These were further reviewed with panel members, but none of these directly addressed our PICO. Thus, the aforementioned studies did not undergo data extraction and no evidence table was generated.

Should corticosteroids versus no corticosteroids be used in adults hospitalized with CAP?

There were FIVE recent (2015) systematic reviews on this topic, one of which was a Cochrane review. In the Cochrane review, they identified > 3000 studies and included 13 randomized controlled trials in their final assessment. A review by Wan et al included 9 of the 13 studies in the Cochrane review. A review by Marti et al included 14 studies, 12 of those in the Cochrane review and two additional studies (these address severe infections, not CAP, so were not included). A review by Chen et al included 7 studies, 6 of which were in the Cochrane review and 1 was not (determined to be a secondary analysis of one of the included randomized trials). A review by Horita et al included 10 studies, all of which were in the Cochrane review. A broad search for "pneumonia" and "corticosteroid" from May 2015 to April 2017 did not reveal any new randomized trials relative to this PICO.

All 13 studies from the Cochrane review were retrieved and pragmatic data extraction was undertaken. Two inconsistencies were identified: 1) different numbers for ICU admission in Appendix Table 4 and Appendix Figure 5. Authors may have entered data from the Torres study by mistake. Review of the Meijvis paper suggested the numbers in Appendix Table 4 were correct so used those; and 2) in the Snijders paper, the number of adverse events, total sample, and noted percentage did not correspond. Thus, this information was not included in our analysis. Finally, for the outcomes in the Cochrane review where they converted median (IQR) to mean (SD), we used their calculated numbers for mean (SD).

Should empiric antiviral therapy versus no antiviral therapy be used in adults with CAP during influenza season?

Should antiviral therapy versus no antiviral therapy by used in adults with CAP who test positive for influenza?

(((community acquired pneumon*[tiab]) OR (pneumonia[mh]) OR (pneumonia[tiab])) AND ((amantadine*[tiab] OR rimantadine*[tiab] OR oseltamivir*[tiab] OR zanamivir*[tiab]) OR (antiviral agents[mh]) OR (antiviral*[tiab]) OR (neuraminidase[tiab] AND inhibit*[tiab]))) AND (influenza[mh] OR influenza*[tiab] OR flu[tiab])	**923**

For these two questions we searched for literature addressing antiviral therapy in patients with CAP. The search strategy covered both questions, with 923 studies identified. After initial title/abstract screening as well as a cross-reference search using existing systematic reviews of antiviral treatment, we had 182 studies for further review. Of those, 5 studies contained data that directly addressed our second PICO question. All of these studies assessed antiviral treatment in patients with confirmed influenza, thus no direct evidence was available for the first of these two questions (two studies, Dominguez 2009 and Estenssoro 2009, included individuals with probable or suspected influenza, but in the analysis combined those individuals with patients who had confirmed influenza).

Should antibiotics versus no antibiotics be used in adults with CAP who test positive for influenza?

((community acquired pneumon*[tiab]) OR (pneumonia[mh]) OR (pneumonia[tiab])) AND ((antibiotic*[tiab]) OR (Anti-Bacterial Agents[mh])) AND ((influenza[mh]) OR (influenza[tiab]) OR (flu[tiab]))	**663**

Search strategy developed, 663 studies identified. After initial title/abstract screening, 70 studies underwent further review. Of those, none contained data that directly addressed the comparison outlined in our PICO question, thus no data was extracted and no evidence table generated.

Should testing for influenza versus no such testing be used in adults with suspected CAP during influenza season?

((community acquired pneumon*[tiab]) OR (pneumonia[mh]) OR (pneumonia[tiab])) AND ((assay[tiab]) OR (rapid influenza*[tiab]) OR (PCR*[tiab]) OR (swab*[tiab])) AND ((influenza[mh]) OR (influenza*[tiab]) OR (flu[tiab]))	**783**

Search strategy developed, 783 studies identified. After initial title/abstract screening, we had 25 studies for further review. Of those, 1 study contained descriptive information about patients who were tested versus those who were not but did not assess outcomes based on the testing approach. Thus, no data was extracted and no evidence table generated. Of note, this topic was also addressed in the PICO question covering rapid diagnostic testing.

Should ≤ 7 days versus > 7 days of antibiotic therapy be used for adults hospitalized with CAP?

	Query	Items found
#16	(#7 AND #14) Filters: Publication date from 2011/01/01 to 2015/12/31	1076
#15	(#7 AND #14)	3141
#14	(#8 OR #9 OR #10 OR #11 OR #12 OR #13)	3667186
#13	day*[tiab]	1551024
#12	course*[tiab]	498482
#11	long*[tiab]	1410906
#10	short*[tiab]	873018
#9	long-course[tw]	1072
#8	short-course[tw]	6222
#7	(#3 AND #6)	10076
#6	(#4 OR #5)	413236
#5	respiratory*[tiab]	341803
#4	pneumonia[tiab]	90866
#3	((#1 OR #2))	17706
#2	community-acquired[tiab]	14263
#1	Infections, Community-Acquired[mh]	11021

**Added in RCT component with 498 results
groups[tiab]
trial[tiab]
randomly[tiab]
drug therapy[sh]
randomized[tiab]
controlled clinical trial[pt]
randomized controlled trial[pt]

Three systematic reviews addressed this question, the most recent of which was from 2013. We reviewed these studies and then performed a search from 2011-2015, identifying an additional 498 potential studies. After title/abstract screening there were 22 studies for further review. Of these, 4 compared dissimilar antibiotics, leaving 18 studies for full review: 4 were conducted in outpatients only; 6 included a mix of inpatients and outpatients, and 1 study was not clear about the patient population. This left 7 studies that assessed duration of antibiotic therapy, comparing similar antibiotics in adults hospitalized with CAP. Subsequent to the original search, one new study that directly addressed this PICO was added (Uranga 2016).

Should follow-up imaging with chest X-ray versus no follow-up imaging be done in all patients with CAP (both outpatients and inpatients)?

	Query	Items found
#12	(#4 AND #7 AND #11)	1385
#11	(#8 OR #9 OR #10)	2884695
#10	follow*[tiab]	2636630
#9	convalesc*[tiab]	10290
#8	recovery*[tiab]	337392
#7	(#5 OR #6)	1029294
#6	radiograph*[tiab}	770452
#5	radiography[mh]	672804
#4	(#1 OR #2 OR #3)	85574
#3	community acquired pneumonia[tw]	7220
#2	pneumonia[mh]	78574
#1	Infections, Community-Acquired[mh]	11086

After title/abstract screen of 1385 studies, there were 14 studies that seemed promising for this PICO. After full review, these studies were found to either address the epidemiology of CAP at follow-up or examine the incidence of malignancy in patients who all had CXRs or other imaging after CAP (no comparison group without CXR follow-up). Thus, no study directly addressed our PICO and no evidence table was generated.

Author(s):
Date:
Question: Sputum gram stain and culture compared to no sputum gram stain and culture in adults hospitalized with CAP
Setting:
Bibliography: Sato 2002; Signori 2008; Uematsu 2014

Quality assessment							Impact	Quality	Importance
Nº of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**			
Mortality (follow up: in-hospital)									
2	observational studies	not serious	serious [a]	not serious	serious [b,c]	none	In one observational study (Signori 2008), there were 19 deaths (32.7% mortality) among 58 patients without expectoration, 26 deaths (20.9% mortality) among 124 patients with expectoration but from whom sputum was not collected and 6 deaths (6.5% mortality) among the 92 patients whose sputum was collected. Risk of death was 3.7 times greater in the group with expectoration but from whom sputum samples were not collected (OR = 3.78; 95% CI: 1.40-10.23). Another observational study (Uematsu 2014), found no difference in risk of death among those having sputum tests, compared to those who did not have sputum tests (OR 1.06; 95% CI 0.98-1.15).	⊕◯◯◯ VERY LOW	CRITICAL
Hospital length of stay									
2	observational studies	not serious	not serious	not serious	serious [b,c]	none [d]	In one observational study (Sato 2002), 33 patients who had sputum testing had an average hospital LOS of 9.67 days (3.81), compared to 11.75 days (4.5) among the 32 patients who did not have testing. Another observational study (Uematsu 2014), found performance of sputum tests was not associated probability for discharge (HR: 0.98; 95% CI 0.97–1.00).	⊕◯◯◯ VERY LOW	CRITICAL
Duration of IV antibiotic use									
1	observational studies	not serious	not serious	not serious	serious [b]	none	In one observational study (Sato 2002), duration of IV antibiotic therapy was 6.73 days (2.63), on average, among those who had sputum testing, compared to 7.91 days (3.83) among those who did not have sputum testing.	⊕◯◯◯ VERY LOW	CRITICAL

CI: Confidence interval

a. Unexplained heterogeneity of results
b. CI does not exclude an appreciable increase or reduction in the absolute risk
c. Few events
d. Sato 2002 does not account for confounding in analysis

References

Author(s):
Date:
Question: Blood cultures compared to no blood cultures in adults hospitalized with CAP
Setting:
Bibliography: Meehan 1997; Dedier 2001; Benenson 2007; Uematsu 2014; Costantini 2016

Certainty assessment							Impact	Certainty	Importance
Nº of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**			
30-day mortality									
3	observational studies	not serious	not serious	serious [a]	serious [b]	none	Meehan 1997: Blood culture collection within 24 hrs of hospital arrival was associated with lower 30-day mortality in analyses adjusted for patient risk status and performance of other processes of care (OR, 0.90; 95% CI, 0.81-1.0). Blood culture collection before antibiotic administration was not associated with significantly higher or lower 30-day mortality. Uematsu 2014: Found a lower risk of death among those having blood cultures on the first day of hospitalization (OR 0.78; 95% CI 0.71-0.85). Costantini 2016: There was a lower risk of death among those having blood cultures (OR 0.600; 95% CI 0.328-1.097).	⊕◯◯◯ VERY LOW	CRITICAL
In-hospital mortality									
3	observational studies	serious [c]	not serious	serious [d]	serious [b]	none	Dedier 2001: Patients who had blood cultures performed within 24 hours of arrival were compared with all others (included patients who achieved the process marker beyond 24 hours and those who did not achieve the process marker at all). In-hospital death - adjusted OR 0.86 (0.36-2.07). Benenson 2007: 4.7% of patients with blood cultures obtained in the ED versus 6.6% of patients without blood cultures in the ED died in the hospital. Uematsu 2014: Found a lower risk of death among those having blood cultures on the first day of hospitalization (OR 0.78; 95% CI 0.71-85). Costantini 2016: There was a lower risk of death of among those having blood cultures (OR 0.677; 95% CI 0.377-1.213).	⊕◯◯◯ VERY LOW	CRITICAL
Duration of antibiotic therapy									
1	observational studies	not serious	not serious	serious [e]	not serious	none	Costantini 2016: Performance of blood cultures was associated with a longer duration of antibiotic therapy (2.73 days; 95 % CI 1.42–4.04 days).	⊕◯◯◯ VERY LOW	CRITICAL
Hospital length of stay									
4	observational studies	serious [c]	not serious	serious [d]	serious [b]	none	Dedier 2001: Patients who had blood cultures performed within 24 hours of arrival were compared with all others (includes patients who achieved the process marker beyond 24 hours and those who did not achieve the process marker at all) LOS longer than median - adjusted OR 1.04 (0.72-1.50). Benenson 2007: Patients with blood cultures obtained in the ED had an average LOS of 5.3 days (3.4) compared to a LOS of 5 days (4.3) for those who did not. Uematsu 2014: Performance of blood cultures was associated with HR 1.00 for discharge (0.98–1.02). Costantini 2016: Performance of blood cultures was associated with a longer length of stay (2.63 days; 95 % CI 1.26–4.00 days).	⊕◯◯◯ VERY LOW	IMPORTANT

CI: Confidence interval

Explanations

a. In Meehan 1997 and Costantini 2016, patients admitted from a skilled nursing facility, intermediate care facility, or nursing home were included in the study population. These patients have a different risk profile compared to individuals admitted from the community.
b. CI does not exclude an appreciable increase or reduction in the absolute risk.
c. Benenson 2007 included patients admitted from the community as well as patients admitted from a nursing home environment; there is no adjustment made for this or any other factor for the comparison of those with and without blood cultures.
d. In Benenson 2007 and Costantini 2016, patients admitted admitted from a nursing home environment were included in the study population. These patients have a different risk profile compared to individuals admitted from the community.
e. In Costantini 2016, patients admitted admitted from a nursing home environment were included in the study population. These patients have a different risk profile compared to individuals admitted from the community.

Author(s):
Date:
Question: PCR for viral and atypical pathogens compared to no PCR for viral and atypical pathogens in adults with suspected CAP
Setting:
Bibliography: Oosterheert 2005

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**PCR for viral and atypical pathogens**	**no PCR for viral and atypical pathogens**	**Relative (95% CI)**	**Absolute (95% CI)**		
Mortality (follow up: 28 days)												
1	randomised trials	not serious	not serious	serious [a]	not serious	none	3/55 (5.5%)	3/52 (5.8%)	not pooled	see comment	⊕⊕⊕◯ MODERATE	CRITICAL
Duration of antibiotic use (follow up: 28 days)												
1	randomised trials	not serious	not serious	serious [a]	not serious	none	The duration of antimicrobial treatment was comparable in both study groups, with median durations of 10 days (range, 1–46 days) in the intervention group and 9 days (range, 1–31 days) in the control group.				⊕⊕⊕◯ MODERATE	CRITICAL
Hospital length of stay (follow up: 28 days)												
1	randomised trials	not serious	not serious	serious [a]	not serious	none	The use of real-time PCR had no effect on the duration of hospital stay, with a median length of stay of 8.0 days (range, 1–24 days) in the intervention group and 8.0 days (range, 1–19 days) in the control group.				⊕⊕⊕◯ MODERATE	IMPORTANT

CI: Confidence interval

a. Conducted to evaluate the feasibility and clinical and economic impact of the use of rapid TaqMan PCR for detection of respiratory viruses and atypical pathogens in patients hospitalized on general wards with LRTI. Of those enrolled, 51% had CAP.

References

Author(s):
Date:
Question: Pneumococcal UAT compared to no pneumococcal UAT in adults with suspected CAP
Setting:
Bibliography: Piso 2012

Quality assessment							Impact	Quality	Importance
Nº of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**			
No change in antibiotic therapy									
1	observational studies	serious [1]	not serious	not serious	not serious	none	In the group with PnAG testing, 51 of 139 (37%) had no change in antibiotic therapy, compared to 67 ot 147 (46%) in the no PnAG group. In 22 of 139 patients in the tested group, PnAG was positive. In 8 of these 22 patients streptococcus was additionally confirmed by blood culture positivity, and in 3 of 22 patients S. pneumoniae were also identified in sputum. In the remaining 11/22 patients, PnAG was the only confirmatory diagnosis for pneumococcal pneumonia. In five patients, antibiotic treatment was not streamlined despite the availability of the results.	⊕◯◯◯ VERY LOW	
Narrowing antibiotic therapy									
1	observational studies	serious [1]	not serious	not serious	not serious	none	In the group with PnAG testing, 66 of 139 (47%) had narrowing of antibiotic therapy, compared to 73 ot 147 (50%) in the no PnAG group.	⊕◯◯◯ VERY LOW	

CI: Confidence interval

1. Authors mention extending the univariate model to a multivariable logistic regression analysis where they adjusted for the severity of pneumonia (pneumonia severity index, PSI), age, gender and need for intensive care unit (ICU) care. They go on to suggest that results were not significant after adjustment but do not seem to present multivariable analysis results.

Author(s):
Date:
Question: Viral PCR compared to no viral PCR in adults with suspected CAP
Setting:
Bibliography: Afzal 2013

Quality assessment							Impact	Quality	Importance
Nº of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**			
Antibiotic use									
1	observational studies	not serious	not serious	not serious	serious [1]	none	In Afzal 2013, patients (n = 30) in whom PCR identified a respiratory virus were stratified into those whose PCPs were notified of the result, and those whose PCPs were not notified. In patients whose PCPs were not notified of a positive viral PCR, the median number of antibiotics, duration, and intensity were 3, 12, and 13, respectively, similar to those results in patients with bacterial pneumonia (P>0.9 for all 3 comparisons).	⊕◯◯◯ VERY LOW	CRITICAL
Duration of antibiotic use									
1	observational studies	not serious	not serious	not serious	serious [1]	none	In Afzal 2013, 11 patients whose PCPs were informed that a respiratory virus had been identified received less antibiotic therapy; the median duration of antibiotics was 7 days, and the median antibiotic-days was 9, less than in patients with bacterial pneumonia (13 and 16.5 days) and also less than in patients with a positive viral PCR whose physicians were not notified of the results.	⊕◯◯◯ VERY LOW	CRITICAL

CI: Confidence interval; **MD:** Mean difference

1. Few events.

Author(s):
Date:
Question: Urine antigen testing compared to no urine antigen testing in adults with suspected CAP
Setting:
Bibliography: Uematsu 2014; Constantini 2016

Quality assessment							Impact	Quality	Importance
Nº of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**			
In-hospital mortality									
2	observational studies	not serious	not serious	not serious	not serious	none	In Uematsu 2014, the authors provide OR (95% CI) for a multivariable logistic regression model. For urine antigen tests, the was a lower risk of death among those having the test (OR 0.75; 95% CI 0.69-0.82). In Constantini 2016, adjusted regression analyses showed that mortality was negatively associated with performance of urinary antigen tests for S. pneumoniae and L. pneumophila. Performance of urinary antigen test was associated with 42.7 % lower odds of in-hospital mortality (95 % CI 21.5–85.0 %).	⊕⊕◯◯ LOW	
30-day mortality									
1	observational studies	not serious	not serious	not serious	not serious	none	In Constantini 2016, adjusted regression analyses showed that mortality was negatively associated with performance of urinary antigen tests for S. pneumoniae and L. pneumophila. Performance of urinary antigen test was associated with 31.4% lower odds of 30-day mortality (95 % CI 17.0–68.5 %) compared to subjects who were not tested for urinary antigens, while holding all other predictors constant.	⊕⊕◯◯ LOW	
Hospital length of stay									
2	observational studies	not serious	not serious	not serious	not serious	none	In Uematsu 2014, performance of urine antigen tests was statistically associated with an increased HR for discharge (HR: 1.07; 95% CI 1.05–1.10). In Constantini 2016, no significant association between UAT and LOS was identified in regression analysis.	⊕⊕◯◯ LOW	
Duration of antibiotic therapy									
1	observational studies	not serious	not serious	not serious	not serious	none	In Constantini 2016, no significant association between UAT and duration of antibiotic therapy was identified in regression analysis.	⊕⊕◯◯ LOW	

CI: Confidence interval

References

Author(s):
Date:
Question: Pathogen-directed treatment based on urine antigen testing compared to empirical treatment in adults with suspected CAP
Setting:
Bibliography: van der Eerden 2005; Falguera 2010

Quality assessment							Impact	Quality	Importance
Nº of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**			
Clinical failure									
2	randomised trials	not serious	not serious	serious [a]	not serious	none	No significant difference in clinical failure observed in either study.	⊕⊕⊕◯ MODERATE	CRITICAL
Mortality									
2	randomised trials	not serious	not serious	serious [a]	not serious	none	No significant difference in mortality observed in either study.	⊕⊕⊕◯ MODERATE	CRITICAL
Duration of antibiotic use									
2	randomised trials	not serious	not serious	serious [a]	not serious	none	No significant difference in duration of antibiotic use observed in either study.	⊕⊕⊕◯ MODERATE	CRITICAL
Any adverse event									
2	randomised trials	not serious	not serious	serious [a]	not serious	none	In van der Eerden 2005, more adverse events were encountered in the empirical broad spectrum antibiotic treatment group than in the pathogen directed treatment group (77 patients (60%) vs 23 patients (17%), 95% CI 20.5 to 20.3). In Falguera 2010, no difference in adverse events was observed between the two treatment groups.	⊕⊕⊕◯ MODERATE	CRITICAL
Hospital length of stay									
2	randomised trials	not serious	not serious	serious [a]	not serious	none	No significant difference in hospital length of stay observed in either study.	⊕⊕⊕◯ MODERATE	CRITICAL
ICU admission									
2	randomised trials	not serious	not serious	serious [a]	not serious	none	No significant difference in ICU admission observed in either study.	⊕⊕⊕◯ MODERATE	IMPORTANT

CI: Confidence interval

a. In addition to UAT, multiple microbiological tests were performed during the initial assessment of patients, including blood cultures and sputum cultures; it is unclear how these tests affected clinical behavior, in comparison to urinary antigen testing alone.

References

Author(s):
Date:
Question: Clinical judgment compared to serum procalcitonin in adults to guide initiation/modification of treatment for CAP
Setting:
Bibliography: Christ-Crain 2004; Christ-Crain 2006; Briel 2008; Kristoffersen 2009; Long 2009; Schuetz 2009; Bouadma 2010; Long 2011

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**clinical judgment**	**serum procalcitonin**	**Relative (95% CI)**	**Absolute (95% CI)**		
Clinical failure												
3	randomised trials	not serious	not serious	not serious	serious [a]	none	42/296 (14.2%)	40/295 (13.6%)	**RR 1.05** (0.70 to 1.57)	**7 more per 1,000** (from 41 fewer to 77 more)	⊕⊕⊕◯ MODERATE	CRITICAL
Antibiotic use												
5 [b]	randomised trials	not serious	not serious	not serious	serious [a]	none	803/833 (96.4%)	720/829 (86.9%)	**RR 1.13** (1.03 to 1.23)	**113 more per 1,000** (from 26 more to 200 more)	⊕⊕⊕◯ MODERATE	CRITICAL
Mortality												
4	randomised trials	not serious	not serious	not serious	serious [a]	none	47/787 (6.0%)	44/777 (5.7%)	**RR 1.07** (0.72 to 1.58)	**4 more per 1,000** (from 16 fewer to 33 more)	⊕⊕⊕◯ MODERATE	CRITICAL
Duration of antibiotic use												
4	randomised trials	not serious	not serious	not serious	not serious	none	824	793	-	MD **4.15 higher** (2.12 higher to 6.18 higher)	⊕⊕⊕⊕ HIGH	CRITICAL
Adverse effect rate from antibiotics												
1	randomised trials	not serious	not serious	not serious	serious [a]	none	154/465 (33.1%)	108/460 (23.5%)	**RR 1.41** (1.14 to 1.74)	**96 more per 1,000** (from 33 more to 174 more)	⊕⊕⊕◯ MODERATE	CRITICAL
Hospitalization												

1	randomised trials	not serious	not serious	not serious	serious [a]	none	146/151 (96.7%)	146/151 (96.7%)	**RR 1.00** (0.96 to 1.04)	**0 fewer per 1,000** (from 39 fewer to 39 more)	⊕⊕⊕◯ MODERATE	CRITICAL
Hospital length of stay												
3	randomised trials	not serious	not serious	not serious	serious [a]	none	723	714	-	MD **0.29 higher** (0.34 lower to 0.91 higher)	⊕⊕⊕◯ MODERATE	CRITICAL
Cost of antibiotics												
1	randomised trials	not serious	not serious	not serious	not serious	none	151	151	-	MD **90 higher** (71.92 higher to 108.08 higher)	⊕⊕⊕⊕ HIGH	IMPORTANT
Clinical and radiographic recurrence												
1	randomised trials	not serious	not serious	not serious	serious [a,c]	none	4/151 (2.6%)	4/151 (2.6%)	**RR 1.00** (0.25 to 3.93)	**0 fewer per 1,000** (from 20 fewer to 78 more)	⊕⊕⊕◯ MODERATE	IMPORTANT
ICU admission												
2	randomised trials	not serious	not serious	not serious	serious [a,c]	none	26/258 (10.1%)	27/254 (10.6%)	**RR 0.96** (0.58 to 1.60)	**4 fewer per 1,000** (from 45 fewer to 64 more)	⊕⊕⊕◯ MODERATE	IMPORTANT

CI: Confidence interval; **RR:** Risk ratio; **MD:** Mean difference

Explanations

a. CI does not exclude appreciable harm or benefit
b. An additional study, a cluster RCT (Christ-Crain 2004), also assessed standard antimicrobial therapy compared to procalcitonin-guided antimicrobial treatment among patients with suspected LRTI. For patients with CAP, 45/45 in the standard arm received an antibiotic prescription compared to 38/42 in the procalcitonin arm.
c. Few events

Author(s):
Date:
Question: Clinical prediction rules compared to clinical judgment for determination of treatment location in adults with CAP
Setting:
Bibliography: Marrie 2000; Yealy 2005

Certainty assessment							Impact	Certainty	Importance
Nº of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**			
Outpatient treatment									
2	randomised trials [a]	not serious	not serious	serious [b]	not serious	none	In Marrie 2000, fewer low-risk patients (PSI classes I-III) where managed as inpatients at the critical pathway sites (31% vs 49% at conventional management sites). Admission rates of patients with PSI classes IV and V were similar in the 2 groups (87% at critical pathway vs 88% at conventional management sites). In Yealy 2005, low-risk patients (determined by the level of arterial oxygenation and PSI risk class) in the moderate-intensity (61%) and high-intensity groups (61.9%) were more likely to be treated as outpatients compared with those in the low-intensity (37.5%) group (adjusted odds for outpatient treatment of low-risk patients were 2.7 (95% CI 1.4-5.0) in the moderate-intensity group and 2.5 (95% CI 1.3-4.6) in the high-intensity group, compared to the low-intensity group). Higher-risk patients in the moderate-intensity group were more likely to be treated as outpatients (9.6%) compared with those in the low-intensity (2.4%) and high-intensity (3.2%) groups (adjusted odds for outpatient treatment of high-risk patients of 4.5 (95% CI 1.6-14.3) in the moderate-intensity group and 1.1 (95% CI 0.4-2.6) in the high-intensity group, compared to the low-intensity group).	⊕⊕⊕◯ MODERATE	CRITICAL
Hospital length of stay									
1	randomised trials [c]	not serious	not serious	serious [d]	not serious	none	In Marrie 2000, median length of stay was lower at critical pathway sites (5 days vs 6.7 days at conventional management sites).	⊕⊕⊕◯ MODERATE	CRITICAL
Hospital readmission									
1	randomised trials [c]	not serious	not serious	serious [d]	not serious	none	In Marrie 2000, the absolute difference in hospital readmission between the critical pathway and conventional management sites was 0.7% (upper limit of the 1-sided 95% confidence limit of 3.6% for readmission gives an estimate of the outermost deleterious effect of the critical pathway compared with conventional management).	⊕⊕⊕◯ MODERATE	IMPORTANT
Mortality									
2 [e]	randomised trials [a]	not serious	not serious	serious [b]	serious [f]	none	In Marrie 2000, the absolute difference in mortality between the critical pathway and conventional management sites was -0.1% (upper limit of the 1-sided 95% confidence limit of 2.5% for mortality gives an estimate of the outermost deleterious effect of the critical pathway compared with conventional management). In Yealy 2005, adjusted odds for 30-day mortality of low-risk patients were 0.5 (95% CI 0.2-1.4) in the moderate-intensity group and 0.7 (95% CI 0.3-1.9) in the high-intensity group, compared to the low-intensity group. Adjusted odds for 30-day mortality of high-risk patients were 1.1 (95% CI 0.7-2.0) in the moderate-intensity group and 1.1 (95% CI 0.7-1.9) in the high-intensity group, compared to the low-intensity group.	⊕⊕◯◯ LOW	IMPORTANT
ICU admission									

2	randomised trials [a]	not serious	not serious	serious [b]	serious [f]	none	In Marrie 2000, the absolute difference in ICU admission between the critical pathway and conventional management sites was 0.3% (upper limit of the 1-sided 95% confidence limit of 2.0% for ICU admission gives an estimate of the outermost deleterious effect of the critical pathway compared with conventional management). In Yealy 2005, adjusted odds for ICU admission in low-risk inpatients were 1.0 (95% CI 0.5-2.2) in the moderate-intensity group and 1.8 (95% CI 0.9-3.6) in the high-intensity group, compared to the low-intensity group.	⊕⊕◯◯ LOW	IMPORTANT
Subsequent hospitalization among low-risk outpatients									
1	randomised trials [g]	not serious	not serious	serious [g]	serious [f]	none	In Yealy 2005, adjusted odds for subsequent hospitalization of low-risk outpatients was 1.1 (95% CI 0.4-2.7) in the moderate intensity group and 1.0 (95% CI 0.4-2.7) in the high intensity group, compared to the low-intensity group.	⊕⊕◯◯ LOW	IMPORTANT

CI: Confidence interval

Explanations

a. Marrie 2000 compared a critical pathway for management of CAP to conventional management. The critical pathway had 3 components: use of a clinical prediction rule (Pneumonia Severity Index - PSI) to assist the admission decision, treatment with levofloxacin, and practice guidelines for the care of inpatients. Yealy 2005 compared the effectiveness and safety of 3 guideline implementation strategies (low, moderate, and high intensity). Each strategy included the PSI, with escalating emphasis on its use as one went from the low to high-intensity strategy.
b. Two cluster randomized trials that compare multifaceted interventions that include a prediction rule to usual practice (not a direct comparison of the rule to usual practice).
c. Marrie 2000 compared a critical pathway for management of CAP to conventional management. The critical pathway had 3 components: use of a clinical prediction rule (Pneumonia Severity Index - PSI) to assist the admission decision, treatment with levofloxacin, and practice guidelines for the care of inpatients.
d. Marrie 2000 compared a multifaceted intervention that include a prediction rule to usual practice (not a direct comparison of the rule to usual practice). Per the authors of Marrie 2000, "the trial was not designed to evaluate the effectiveness of the separate components of the critical pathway."
e. The timing of follow-up for mortality is unclear in Marrie 2000. In Yealy 2005, 30-day mortality was assessed.
f. CI does not exclude an appreciable increase or reduction in the absolute risk.
g. Yealy 2005 compared the effectiveness and safety of 3 guideline implementation strategies (low, moderate, and high intensity). Each strategy included the PSI, with escalating emphasis on its use as one went from the low to high-intensity strategy (not a direct comparison of the rule to usual practice).

Author(s):
Date:
Question: Clinical prediction rules compared to clinical judgment for determination of treatment location in adults with CAP
Setting:
Bibliography: Atlas 1998 (PSI); Renaud 2007 (PSI); Jo 2012 (PSI); Julian-Jimenez 2013 (PSI); Dean 2015 (CURB-65)

Quality assessment							Impact	Quality	Importance
Nº of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**			
Mortality (follow up: 30 days)									
4	observational studies	not serious	not serious	serious [a]	serious [b]	none	In Atlas 1998, no patient in either the intervention group or the retrospective cohort control group was known to have died (95% CI 0-2.2% for patients in the intervention group). In Renaud 2007, 9.1% of patients at PSI-user EDs died and 12.1% of patients at non-PSI user EDs died (adjusted OR 0.52, 95% CI 0.29-0.94). In Julian-Jiminez 2013, more patients in the pre-intervention group died than in the post-intervention group (15% vs. 8.5%, no CI provided). In Dean 2015, the severity-adjusted OR for mortality between intervention and usual care EDs post–tool deployment was 0.53 among patients with CAP (95% CI 0.28-0.99).	⊕◯◯◯ VERY LOW	CRITICAL
Outpatient treatment									
5	observational studies	not serious	serious [c]	serious [d]	not serious [e]	none	In Atlas 1998, 57% of low-risk patients were initially treated as outpatients during the intervention period compared to 42% of low-risk patients in the retrospective cohort group (95% CI 8-72%). In Renaud 2007, the adjusted odds ratios for outpatient treatment were higher for patients in PSI risk classes I and II who were treated in PSI-user EDs, compared with PSI-nonuser EDs (adjusted OR, 7.0 [95% CI, 2.0–25.0] and 4.6 [95% CI, 1.3–16.2], respectively), whereas the adjusted odds ratio did not differ by PSI-user status among patients in risk class III or among patients at high risk. In Jo 2012, the admission rate of the PSI group was lower than that of the non-PSI group (30.4% vs. 68.2%, no CI provided). In Julian-Jiminez 2013, discharge directly from the ED was more common in the pre-intervention group than the post-intervention group (36.5% vs. 19.5%, no CI provided). In Dean 2015, 712 patients were hospitalized in the baseline group (57%, 95% CI 54-59%) and 865 patients were admitted in the post-deployment group (60%, 95% CI 58-63%).	⊕◯◯◯ VERY LOW	CRITICAL
Subsequent hospitalization (follow up: 7-30 days)									
5	observational studies	not serious	not serious	serious [d]	serious [b]	none	In Atlas 1998, the proportion of patients without admission to the study hospital during the 4-week follow-up period was 52% for the intervention cohort and 42% in the retrospective group (relative increase 25%, 95% CI -2% to 59%). In Renaud 2007, subsequent hospitalization occurred for 10.1% of patients in the PSI-user EDs and 12.3% of patients in the PSI-nonuser EDs (adjusted OR 0.83, 95% CI 0.22-3.10). In Jo 2012, subsequent hospitalization occurred for 4.2% of patients in the PSI group and 7.8% of patients in the non-PSI group (no CI provided). In Julian-Jiminez 2013, subsequent hospitalization occurred for 7% of patients in the pre-intervention group and 1% of the post-intervention group (no CI provided). In Dean 2015, 37 patients had subsequent hospitalizations in the baseline group (6.8%) compared to 28 patients in the post-deployment group (4.9%) (no CI provided).	⊕◯◯◯ VERY LOW	CRITICAL

ICU admission									
2	observational studies	not serious	not serious	serious [f]	serious [b]	none	In Atlas 1998, 4% of patients in the intervention group has ICU admission compared with 2% of controls. In Renaud 2007, ICU admission for inpatients occurred for 11.8% of patients in the PSI-user EDs and 10.6% of patients in the PSI-nonuser EDs (adjusted OR 0.99, 95% CI 0.49-1.98).	⊕◯◯◯ VERY LOW	CRITICAL
Hospital length of stay									
3	observational studies	not serious	not serious	serious [g]	not serious	none	In Atlas 1998, the median length of hospitalization was 4 days during both the intervention and control periods. In Julian-Jiminez 2013, the mean length of hospitalization was 8.73 days (SD 5.49) in the pre-intervention group and 7.59 (SD 3.97) in the post-intervention group. In Dean 2015, median length of stay in the baseline group was 3 days (95% CI 2.8-3.2) compared to 2.9 days (95% CI 2.8-3.0) in the post-deployment group.	⊕◯◯◯ VERY LOW	CRITICAL

CI: Confidence interval

a. 3 of the 4 studies include additional components that might affect decision-making and outcomes, including: outpatient services (Atlas 1998), application of clinical practice guidelines (Julian-Jimenez 2013), and use of a multi-faceted decision-support tool (Dean 2015).
b. CI does not exclude either an appreciable increase, reduction, or absence of difference in the absolute risk.
c. 3 studies demonstrate that the use of clinical prediction rules is associated with more outpatient treatment, whereas 2 studies demonstrate that the use of clinical prediction rules is associated with less outpatient treatment.
d. 3 of the 5 studies include additional components that might affect decision-making and outcomes, including: outpatient services (Atlas 1998), application of clinical practice guidelines (Julian-Jimenez 2013), and use of a multi-faceted decision-support tool (Dean 2015).
e. Although estimates from individual studies are not imprecise, comparisons across studies show inconsistency in the results, thus raising the concern that overall, there is imprecision in the evidence.
f. 1 of the 2 studies includes additional components that might affect decision-making and outcomes, including outpatient services (Atlas 1998).
g. All 3 studies include additional components that might affect decision-making and outcomes, including: outpatient services (Atlas 1998), application of clinical practice guidelines (Julian-Jimenez 2013), and use of a multi-faceted decision-support tool (Dean 2015).

References

Author(s):
Date:
Question: A cephalosporin compared to a penicillin for treatment of CAP in adults in the outpatient setting
Setting: Outpatient
Bibliography: Higuera 1996, Fogarty 2002

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**a cephalosporin**	**a penicillin**	**Relative (95% CI)**	**Absolute (95% CI)**		
Clinical response												
2 [a]	randomised trials	not serious [b]	not serious	not serious	serious [c]	none	198/243 (81.5%)	179/222 (80.6%)	**RR 1.00** (0.93 to 1.07)	**0 fewer per 1,000** (from 56 fewer to 56 more)	⊕⊕⊕◯ MODERATE	CRITICAL
Any adverse effects												
2 [a]	randomised trials	not serious [b]	not serious	not serious	serious [c]	none	97/353 (27.5%)	110/345 (31.9%)	**RR 0.88** (0.71 to 1.10)	**38 fewer per 1,000** (from 32 more to 92 fewer)	⊕⊕⊕◯ MODERATE	CRITICAL
Serious adverse effects												
1 [a]	randomised trials	not serious	not serious	not serious	serious [c,d]	none	8/269 (3.0%)	14/267 (5.2%)	**RR 0.57** (0.24 to 1.33)	**23 fewer per 1,000** (from 17 more to 40 fewer)	⊕⊕⊕◯ MODERATE	CRITICAL
Bacteriologic response												
2 [a]	randomised trials	not serious [b]	not serious	not serious	serious [c]	none	103/118 (87.3%)	97/115 (84.3%)	**RR 1.03** (0.94 to 1.13)	**25 more per 1,000** (from 51 fewer to 110 more)	⊕⊕⊕◯ MODERATE	IMPORTANT
Pathogen eradication												
1 [a]	randomised trials	not serious	not serious	not serious [e]	serious [c]	none	109/123 (88.6%)	95/115 (82.6%)	**RR 1.07** (0.97 to 1.19)	**58 more per 1,000** (from 25 fewer to 157 more)	⊕⊕⊕◯ MODERATE	IMPORTANT

CI: Confidence interval; **RR:** Risk ratio

Explanations

a. Fogarty 2002 compared oral cefditoren 200 and 400 mg BID with oral amoxicillin/clavulanate 875/125 mg BID for 14 days in adult outpatients with CAP. Because 400mg is the most commonly used dose at this time, data here is for that dose only.

b. No blinding of patients in Higuera 1996
c. CI does not exclude an appreciable increase or reduction in the absolute risk
d. Few events
e. Not a pre-specified outcome for this group of PICOs

Author(s):
Date:
Question: A ketolide compared to a respiratory fluoroquinolone for treatment of CAP in adults in the outpatient setting
Setting: Outpatient
Bibliography: Kohno 2003, Oldach 2013

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**a ketolide**	**a respiratory fluoroquinolone**	**Relative (95% CI)**	**Absolute (95% CI)**		
Clinical response												
2	randomised trials	not serious	not serious	not serious	serious [a]	none	121/134 (90.3%)	110/121 (90.9%)	**RR 0.99** (0.93 to 1.06)	**9 fewer per 1,000** (from 55 more to 64 fewer)	⊕⊕⊕◯ MODERATE	CRITICAL
Any adverse effects												
1	randomised trials	not serious	not serious	not serious	serious [a,b]	none	7/64 (10.9%)	13/68 (19.1%)	**RR 0.57** (0.24 to 1.34)	**82 fewer per 1,000** (from 65 more to 145 fewer)	⊕⊕⊕◯ MODERATE	CRITICAL
Serious adverse effects												
1	randomised trials	not serious	not serious	not serious	serious [a,b]	none	2/64 (3.1%)	6/68 (8.8%)	**RR 0.35** (0.07 to 1.69)	**57 fewer per 1,000** (from 61 more to 82 fewer)	⊕⊕⊕◯ MODERATE	CRITICAL
Bacteriologic response												
1	randomised trials	not serious	not serious	not serious	serious [a,b]	none	14/18 (77.8%)	10/14 (71.4%)	**RR 1.09** (0.72 to 1.65)	**64 more per 1,000** (from 200 fewer to 464 more)	⊕⊕⊕◯ MODERATE	IMPORTANT

CI: Confidence interval; **RR:** Risk ratio

a. CI does not exclude an appreciable increase or reduction in the absolute risk
b. Few events

References

Author(s):
Date:
Question: A ketolide compared to a macrolide for treatment of CAP in adults in the outpatient setting
Setting: Outpatient
Bibliography: Tellier 2004, MathersDunbar 2004, English 2012A, English 2012A

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**a ketolide**	**a macrolide**	**Relative (95% CI)**	**Absolute (95% CI)**		
Clinical response												
4 [a,b]	randomised trials	not serious	not serious	not serious	serious [a,c]	none	745/909 (82.0%)	748/900 (83.1%)	**RR 0.98** (0.94 to 1.03)	**17 fewer per 1,000** (from 25 more to 50 fewer)	⊕⊕⊕◯ MODERATE	CRITICAL
Hospital admission												
2 [d]	randomised trials	not serious	not serious	not serious	serious [c,e]	none	20/417 (4.8%)	24/411 (5.8%)	**RR 0.82** (0.46 to 1.47)	**11 fewer per 1,000** (from 27 more to 32 fewer)	⊕⊕⊕◯ MODERATE	CRITICAL
Any adverse effects												
2 [a]	randomised trials	not serious	not serious	not serious	serious [c]	none	209/414 (50.5%)	193/409 (47.2%)	**RR 1.07** (0.89 to 1.29)	**33 more per 1,000** (from 52 fewer to 137 more)	⊕⊕⊕◯ MODERATE	CRITICAL
Serious adverse effects												
2 [a]	randomised trials	not serious	not serious	not serious	serious [c,e]	none	20/414 (4.8%)	25/409 (6.1%)	**RR 0.79** (0.45 to 1.40)	**13 fewer per 1,000** (from 24 more to 34 fewer)	⊕⊕⊕◯ MODERATE	CRITICAL
Bacteriologic response												
4 [a,b]	randomised trials	not serious	not serious	not serious	serious [c]	none	241/293 (82.3%)	240/283 (84.8%)	**RR 0.98** (0.92 to 1.06)	**17 fewer per 1,000** (from 51 more to 68 fewer)	⊕⊕⊕◯ MODERATE	IMPORTANT
Pathogen eradication (late follow-up)												

1	randomised trials	not serious	not serious	not serious [f]	serious [c,e]	none	28/32 (87.5%)	29/30 (96.7%)	**RR 0.91** (0.78 to 1.05)	**87 fewer per 1,000** (from 48 more to 213 fewer)	⊕⊕⊕◯ MODERATE	IMPORTANT

CI: Confidence interval; **RR:** Risk ratio

Explanations

a. In the study by Tellier et al, Telithromycin 800 mg PO once daily was given for 5 days or 7 days; included data from 5 day intervention as same efficacy and shorter duration of therapy.
b. The study by English et al 2012 included two phase III, prospective, double-blinded, randomized, parallel-group, multicenter, multinational studies. Study CL05-001 was conducted from January 2006 to October 2007 at 113 sites in the United States, Canada, and South Africa. Study CL06-001 was conducted from July 2006 to May 2007 at 90 sites in South America, Europe, and Israel.
c. CI does not exclude an appreciable increase or reduction in the absolute risk
d. Two post-hoc analyses were performed, one assessing the Mathers Dunbar 2004 study and another the Tellier 2004 study. Hospital admission was included as an outcome in both post-hoc analyses.
e. Few events
f. Not a pre-specified outcome for this group of PICOs

Author(s):
Date:
Question: A macrolide compared to a B-lactam for treatment of CAP in adults in the outpatient setting
Setting: Outpatient
Bibliography: Salvarezza 1998, Bonvehi 2003

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**a macrolide**	**a B-lactam**	**Relative (95% CI)**	**Absolute (95% CI)**		
Clinical response												
2	randomised trials	not serious [a]	not serious	not serious	serious [b]	none	144/154 (93.5%)	145/159 (91.2%)	**RR 1.03** (0.97 to 1.10)	**27 more per 1,000** (from 27 fewer to 91 more)	⊕⊕⊕◯ MODERATE	CRITICAL
Bacteriologic response												
2	randomised trials	not serious [a]	not serious	not serious	serious [b]	none	84/104 (80.8%)	96/115 (83.5%)	**RR 0.97** (0.88 to 1.06)	**25 fewer per 1,000** (from 50 more to 100 fewer)	⊕⊕⊕◯ MODERATE	IMPORTANT
Pathogen eradication												
1	randomised trials	not serious	not serious	not serious [c]	serious [b]	none	103/113 (91.2%)	126/135 (93.3%)	**RR 0.98** (0.91 to 1.05)	**19 fewer per 1,000** (from 47 more to 84 fewer)	⊕⊕⊕◯ MODERATE	IMPORTANT
Radiographic response												
1	randomised trials	not serious	not serious	serious [c,d]	serious [b]	none	112/118 (94.9%)	113/126 (89.7%)	**RR 1.06** (0.98 to 1.14)	**54 more per 1,000** (from 18 fewer to 126 more)	⊕⊕◯◯ LOW	NOT IMPORTANT

CI: Confidence interval; **RR:** Risk ratio

a. Salvarezza 1998 was open label. Not expected to be a risk for study outcomes.
b. CI does not exclude an appreciable increase or reduction in the absolute risk
c. Not a pre-specified outcome for this group of PICOs
d. Very indirect

References

Author(s):
Date:
Question: A macrolide compared to doxycycline for treatment of CAP in adults in the outpatient setting
Setting: Outpatient
Bibliography: Wesner 1993

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**a macrolide**	**doxycycline**	**Relative (95% CI)**	**Absolute (95% CI)**		
Clinical response												
1	randomised trials	not serious	not serious	not serious	serious [a]	publication bias strongly suspected [b]	9/11 (81.8%)	12/13 (92.3%)	**RR 0.89** (0.64 to 1.22)	**102 fewer per 1,000** (from 203 more to 332 fewer)	⊕⊕◯◯ LOW	CRITICAL

CI: Confidence interval; **RR:** Risk ratio

a. Only 21 events among 24 patients
b. Only one small trial, suspect publication bias

References

Author(s):
Date:
Question: A macrolide compared to a respiratory fluoroquinolones for treatment of CAP in adults in the outpatient setting
Setting: Outpatient
Bibliography: Fogarty 1999, Gotfried 2002, D'Ignazio 2005

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**a macrolide**	**a respiratory fluoroquinolones**	**Relative (95% CI)**	**Absolute (95% CI)**		
Clinical response												
3	randomised trials	not serious	not serious	not serious	serious [a]	none	471/529 (89.0%)	480/532 (90.2%)	**RR 0.99** (0.96 to 1.03)	**9 fewer per 1,000** (from 27 more to 36 fewer)	⊕⊕⊕◯ MODERATE	CRITICAL
Any adverse effects												
3	randomised trials	not serious	not serious	not serious	serious [a]	none	243/603 (40.3%)	211/593 (35.6%)	**RR 1.15** (0.96 to 1.37)	**53 more per 1,000** (from 14 fewer to 132 more)	⊕⊕⊕◯ MODERATE	CRITICAL
Serious adverse effects												
2	randomised trials	not serious	not serious	not serious	serious [a,b]	none	13/367 (3.5%)	9/355 (2.5%)	**RR 1.40** (0.61 to 3.24)	**10 more per 1,000** (from 10 fewer to 57 more)	⊕⊕⊕◯ MODERATE	CRITICAL
Bacteriologic response												
3	randomised trials	not serious	not serious	not serious	serious [a]	none	277/304 (91.1%)	311/337 (92.3%)	**RR 0.99** (0.95 to 1.03)	**9 fewer per 1,000** (from 28 more to 46 fewer)	⊕⊕⊕◯ MODERATE	IMPORTANT
Pathogen eradication												
1	randomised trials	not serious	not serious	not serious [c]	serious [a]	none	134/154 (87.0%)	136/155 (87.7%)	**RR 0.99** (0.91 to 1.08)	**9 fewer per 1,000** (from 70 more to 79 fewer)	⊕⊕⊕◯ MODERATE	IMPORTANT
Radiographic response												

1	randomised trials	not serious	not serious	serious [c,d]	not serious	none	117/123 (95.1%)	104/118 (88.1%)	**RR 1.08** (1.00 to 1.17)	**71 more per 1,000** (from 0 fewer to 150 more)	⊕⊕⊕◯ MODERATE	NOT IMPORTANT

CI: Confidence interval; **RR:** Risk ratio

a. CI does not exclude an appreciable increase or reduction in the absolute risk
b. Few events
c. Not a pre-specified outcome for this group of PICOs
d. Very indirect outcome

References

Author(s):
Date:
Question: A respiratory fluoroquinolone compared to a B-lactam + macrolide in adults hospitalized with CAP
Setting: Inpatient
Bibliography: Frank 2002, Fogarty 2004, Zervos 2004, Portier 2005, Xu 2006, Lin 2007, Lee 2012, Postma 2015 (Cluster RCT)

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	a respiratory fluoroquinolone	a B-lactam + macrolide	Relative (95% CI)	Absolute (95% CI)		
Clinical response												
7	randomised trials	not serious [a]	not serious	not serious	not serious	none	473/574 (82.4%)	458/593 (77.2%)	**RR 1.05** (1.00 to 1.11)	**39 more per 1,000** (from 0 fewer to 85 more)	⊕⊕⊕⊕ HIGH	CRITICAL
Any adverse effect												
7	randomised trials	not serious [a]	not serious	not serious	serious [b]	none	247/584 (42.3%)	269/604 (44.5%)	**RR 0.98** (0.88 to 1.09)	**9 fewer per 1,000** (from 40 more to 53 fewer)	⊕⊕⊕◯ MODERATE	CRITICAL
Serious adverse effects												
4	randomised trials	not serious [a]	not serious	not serious	serious [b]	none	34/406 (8.4%)	45/423 (10.6%)	**RR 0.57** (0.16 to 2.04)	**46 fewer per 1,000** (from 89 fewer to 111 more)	⊕⊕⊕◯ MODERATE	CRITICAL
Mortality (follow up: 90 days)												
1	randomised trials	not serious	not serious	not serious [c]	serious [b]	none	From Postma 2015, a cluster RCT: BLM vs FQ: adjusted OR 1.37 (95% CI 0.96 - 1.97), in favor of a respiratory fluoroquinolone.				⊕⊕⊕◯ MODERATE	CRITICAL
Bacteriologic response												
6	randomised trials	not serious [a]	not serious	not serious	serious [b]	none	144/184 (78.3%)	160/213 (75.1%)	**RR 1.02** (0.90 to 1.16)	**15 more per 1,000** (from 75 fewer to 120 more)	⊕⊕⊕◯ MODERATE	IMPORTANT

CI: Confidence interval; **RR:** Risk ratio; **OR:** Odds ratio

a. No blinding of participants, personnel; however, not believed to a significant risk for study outcomes
b. CI does not exclude an appreciable increase or reduction in the absolute risk
c. 90-day mortality was not pre-specified as an outcome for these PICOs

References

Author(s):
Date:
Question: A B-lactam compared to a B-lactam + macrolide in adults hospitalized with CAP
Setting: Inpatient
Bibliography: Garin 2014, Postma 2015 (Cluster RCT)

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	a B-lactam	a B-lactam + macrolide	Relative (95% CI)	Absolute (95% CI)		
Mortality (follow up: 30 days)												
1	randomised trials	not serious [a]	not serious	not serious	serious [b,c]	none	14/291 (4.8%)	10/289 (3.5%)	**RR 1.39** (0.63 to 3.08)	**13 more per 1,000** (from 13 fewer to 72 more)	⊕⊕⊕◯ MODERATE	CRITICAL
Complicated pleural effusion												
1	randomised trials	not serious [a]	not serious	not serious	serious [b,c]	none	8/291 (2.7%)	14/289 (4.8%)	**RR 0.57** (0.24 to 1.33)	**21 fewer per 1,000** (from 16 more to 37 fewer)	⊕⊕⊕◯ MODERATE	CRITICAL
Clinical response												
1	randomised trials	not serious [a]	not serious	not serious	not serious	none	171/291 (58.8%)	192/289 (66.4%)	**RR 0.88** (0.78 to 1.00)	**80 fewer per 1,000** (from 0 fewer to 146 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL
Any adverse effects												
1	randomised trials	not serious [a]	not serious	not serious	serious [b,c]	none	3/291 (1.0%)	3/289 (1.0%)	**RR 0.99** (0.20 to 4.88)	**0 fewer per 1,000** (from 8 fewer to 40 more)	⊕⊕⊕◯ MODERATE	CRITICAL
Serious adverse effects												
1	randomised trials	not serious [a]	not serious	not serious	serious [b,c]	none	1/291 (0.3%)	3/289 (1.0%)	**RR 0.33** (0.03 to 3.16)	**7 fewer per 1,000** (from 10 fewer to 22 more)	⊕⊕⊕◯ MODERATE	CRITICAL
Hospital readmission (follow up: 30 days)												

1	randomised trials	not serious [a]	not serious	not serious	serious [b,c]	none	23/291 (7.9%)	9/289 (3.1%)	**RR 2.54** (1.19 to 5.39)	**48 more per 1,000** (from 6 more to 137 more)	⊕⊕⊕◯ MODERATE	CRITICAL
ICU admission												
1	randomised trials	not serious [a]	not serious	not serious	serious [b,c]	none	12/291 (4.1%)	14/289 (4.8%)	**RR 0.85** (0.40 to 1.81)	**7 fewer per 1,000** (from 29 fewer to 39 more)	⊕⊕⊕◯ MODERATE	CRITICAL
Hospital length of stay												
2	randomised trials	not serious [a]	not serious	not serious	not serious	none	Median and IQR provided for both studies. Garin: BL=8 (6-13) days and for BLM=8 (6-12) days. Postma: BL=6 (4-8) days and BLM=6 (4-10) days.				⊕⊕⊕⊕ HIGH	CRITICAL
New pneumonia (follow up: 30 days)												
1	randomised trials	not serious [a]	not serious	not serious	serious [b,c]	none	10/291 (3.4%)	6/289 (2.1%)	**RR 1.66** (0.61 to 4.49)	**14 more per 1,000** (from 8 fewer to 72 more)	⊕⊕⊕◯ MODERATE	CRITICAL
In-hospital mortality												
1	randomised trials	not serious [a]	not serious	not serious [d]	serious [b,c]	none	8/291 (2.7%)	7/289 (2.4%)	**RR 1.14** (0.42 to 3.09)	**3 more per 1,000** (from 14 fewer to 51 more)	⊕⊕⊕◯ MODERATE	CRITICAL
Mortality (follow up: 90 days)												
2	randomised trials	not serious [a]	not serious	not serious [d]	serious [b,c]	none	One cluster RCT (Postma 2105) reported the absolute difference in the adjusted risk of death with BL strategy compared to BLM strategy: 19 fewer deaths per 1000 patients (90% CI: from 44 fewer to 6 more). Another RCT (Garin 2014) reported 24/291 (8.2%) deaths in BL group and 20/289 (6.9%) in BLM group (RR 1.19, 95% CI: 0.67 to 2.11; risk difference: 13 more per 1000, 95% CI: from 23 fewer to 77 more).				⊕⊕⊕◯ MODERATE	CRITICAL

CI: Confidence interval; **RR:** Risk ratio; **MD:** Mean difference

a. Garin 2014 had no blinding of participants or personnel; outcomes assessors were blinded. Not believed to be a significant risk for study outcomes.
b. CI does not exclude an appreciable increase or reduction in the absolute risk
c. Few events
d. Not one of the pre-specified outcomes for this group of PICOs

References

Author(s):
Date:
Question: A macrolide compared to a B-lactam + macrolide in adults hospitalized with CAP
Setting: Inpatient
Bibliography: Vetter 1997, Vergis 2000

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	a macrolide	a B-lactam + macrolide	Relative (95% CI)	Absolute (95% CI)		
Clinical response												
2	randomised trials	not serious [a]	not serious	not serious	serious [b]	none	128/201 (63.7%)	129/203 (63.5%)	**RR 0.99** (0.79 to 1.25)	**6 fewer per 1,000** (from 133 fewer to 159 more)	⊕⊕⊕◯ MODERATE	CRITICAL
In-hospital mortality												
1	randomised trials	not serious [a]	not serious	not serious	serious [b,c]	none	3/83 (3.6%)	1/86 (1.2%)	**RR 3.11** (0.33 to 29.29)	**25 more per 1,000** (from 8 fewer to 329 more)	⊕⊕⊕◯ MODERATE	CRITICAL
Any adverse effects												
1	randomised trials	not serious [a]	not serious	not serious	serious [b]	none	77/118 (65.3%)	91/117 (77.8%)	**RR 0.84** (0.71 to 0.99)	**124 fewer per 1,000** (from 8 fewer to 226 fewer)	⊕⊕⊕◯ MODERATE	CRITICAL
Serious adverse effects												
1	randomised trials	not serious [a]	not serious	not serious	serious [b,c]	none	10/118 (8.5%)	13/117 (11.1%)	**RR 0.76** (0.35 to 1.67)	**27 fewer per 1,000** (from 72 fewer to 74 more)	⊕⊕⊕◯ MODERATE	CRITICAL
Bacteriologic response												
1	randomised trials	not serious [a]	not serious	not serious	serious [b,c]	none	16/24 (66.7%)	16/23 (69.6%)	**RR 0.96** (0.65 to 1.42)	**28 fewer per 1,000** (from 243 fewer to 292 more)	⊕⊕⊕◯ MODERATE	IMPORTANT

CI: Confidence interval; **RR:** Risk ratio

a. No blinding of participants, personnel; however, not believed to a significant risk for study outcomes

b. CI does not exclude an appreciable increase or reduction in the absolute risk
c. Few events

References

Author(s):
Date:
Question: Corticosteroids compared to no corticosteroids in adults hospitalized with CAP (any severity)
Setting:
Bibliography: All Studies: Blum 2015, Confaloneiri 2005, El-Ghamrawy 2006, Fernández-Serrano 2011, Marik 1993, McHardy 1972, Meijvis 2011, Mikami 2007, Nafae 2013, Sabry 2011, Snijders 2010, Torres 2015, Wagner 1956; Severe CAP: Confaloneiri 2005, El-Ghamrawy 2006, Marik 1993, Nafae 2013, Sabry 2011, Torres 2015

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**corticosteroids**	**no corticosteroids**	**Relative (95% CI)**	**Absolute (95% CI)**		
All-cause Mortality (All Studies)												
12	randomised trials	not serious	not serious [a]	not serious	serious [b]	none	52/977 (5.3%)	79/997 (7.9%)	**RR 0.67** (0.47 to 0.97)	**26 fewer per 1,000** (from 2 fewer to 42 fewer)	⊕⊕⊕◯ MODERATE	CRITICAL
Need for Mechanical Ventilation (All Studies)												
5	randomised trials	not serious	not serious	not serious	serious [b]	none	17/550 (3.1%)	29/510 (5.7%)	**RR 0.45** (0.25 to 0.82)	**31 fewer per 1,000** (from 10 fewer to 43 fewer)	⊕⊕⊕◯ MODERATE	CRITICAL
ICU Admission												
3	randomised trials	not serious	not serious	not serious	serious [c]	none	27/566 (4.8%)	37/568 (6.5%)	**RR 0.73** (0.45 to 1.18)	**18 fewer per 1,000** (from 12 more to 36 fewer)	⊕⊕⊕◯ MODERATE	CRITICAL
Duration of hospitalization (assessed with: mean number of days)												
9	randomised trials	not serious	serious [e]	not serious	serious [b]	none	846	812	-	MD **2.96 days fewer** (4.84 fewer to 1.09 fewer)	⊕⊕◯◯ LOW	CRITICAL
Hyperglycemia requiring treatment												
5	randomised trials	not serious	not serious	not serious	serious [f]	none	114/687 (16.6%)	63/647 (9.7%)	**RR 1.42** (1.00 to 2.02)	**41 more per 1,000** (from 0 fewer to 99 more)	⊕⊕⊕◯ MODERATE	CRITICAL
Gastrointestinal bleeding												

7	randomised trials	not serious	not serious	not serious	serious [c,d]	none	8/628 (1.3%)	9/595 (1.5%)	**RR 0.82** (0.33 to 2.03)	**3 fewer per 1,000** (from 10 fewer to 16 more)	⊕⊕⊕◯ MODERATE	CRITICAL

CI: Confidence interval; **RR:** Risk ratio; **MD:** Mean difference

Explanations

a. Possible important subgroup differences (see separate analysis)
b. The CI does not exclude an appreciable benefit or no effect.
c. CI does not exclude an appreciable increase or reduction in the absolute risk.
d. Few events.
e. Heterogeneity of results, potential explained by large number of studies with high risk of bias.
f. CI does not exclude an appreciable increase in the absolute risk or no difference.

Author(s):
Date:
Question: Corticosteroids compared to no corticosteroids in adults hospitalized with CAP (any severity)
Setting:
Bibliography: All Studies: Blum 2015, Confaloneiri 2005, El-Ghamrawy 2006, Fernández-Serrano 2011, Marik 1993, McHardy 1972, Meijvis 2011, Mikami 2007, Nafae 2013, Sabry 2011, Snijders 2010, Torres 2015, Wagner 1956; Severe CAP: Confaloneiri 2005, El-Ghamrawy 2006, Marik 1993, Nafae 2013, Sabry 2011, Torres 2015

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**corticosteroids**	**no corticosteroids**	**Relative (95% CI)**	**Absolute (95% CI)**		
All-cause Mortality (Non-severe CAP)												
6	randomised trials	serious [b]	not serious	not serious	serious [c]	none	36/762 (4.7%)	41/824 (5.0%)	**RR 1.00** (0.64 to 1.56)	**0 fewer per 1,000** (from 18 fewer to 28 more)	⊕⊕◯◯ LOW	CRITICAL
All-cause Mortality (Severe CAP)												
6	randomised trials	serious [b]	not serious	not serious	not serious	none	16/215 (7.4%)	38/173 (22.0%)	**RR 0.39** (0.22 to 0.67)	**134 fewer per 1,000** (from 72 fewer to 171 fewer)	⊕⊕⊕◯ MODERATE	CRITICAL
Need for Mechanical Ventilation (Non-severe CAP)												
2	randomised trials	serious [b]	not serious	not serious	serious [a,d]	none	2/415 (0.5%)	11/415 (2.7%)	**RR 0.18** (0.04 to 0.78)	**22 fewer per 1,000** (from 6 fewer to 25 fewer)	⊕⊕◯◯ LOW	CRITICAL
Need for Mechanical Ventilation (Severe CAP)												
3	randomised trials	serious [b]	not serious	not serious	serious [c]	none	15/135 (11.1%)	18/95 (18.9%)	**RR 0.54** (0.28 to 1.04)	**87 fewer per 1,000** (from 8 more to 136 fewer)	⊕⊕◯◯ LOW	CRITICAL

CI: Confidence interval; **RR:** Risk ratio; **MD:** Mean difference

Explanations

a. The CI does not exclude an appreciable benefit or no effect.
b. Subgroup analysis not planned a priori.
c. CI does not exclude an appreciable increase or reduction in the absolute risk.
d. Few events.

Author(s):
Date:
Question: De-escalation of antibiotic coverage compared to no change in antibiotic coverage for inpatients with CAP and cultures that fail to reveal MDR pathogens at 48-72 hours
Setting: Inpatient
Bibliography: Yamana 2016

Certainty assessment							Impact	Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**			
Mortality (follow up: 15 days)									
1	observational studies	not serious	not serious	not serious	not serious	none	In propensity-matched patients, 15-day mortality rate was 5.0% in both the de-escalation and continuation groups (14/278; 95% CI of the difference in mortality rate, -3.6 to 3.6).	⊕⊕◯◯ LOW	CRITICAL
In-hospital mortality									
1	observational studies	not serious	not serious	not serious	not serious	none	In propensity-matched patients, the in-hospital mortality rate was 14.4% (40/278) in the de-escalation group and 13.3% (37/278) in the continuation group; the difference in mortality rate was 1.1% (95% CI, -4.7 to 6.8).	⊕⊕◯◯ LOW	CRITICAL

CI: Confidence interval

Author(s):
Date:
Question: De-escalation of antibiotic coverage compared to no change in antibiotic coverage for inpatients with CAP and cultures with identified pathogens
Setting: Inpatient
Bibliography: Cremers 2014, Khasawneh 2014, Carugati 2015, Viasus 2016, Yamana 2016

Certainty assessment							Impact	Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**			
Mortality (in-hospital, 15-day, and 30-day)									
5	observational studies	not serious [a,b]	not serious	not serious	not serious	none	In Cremers 2014, for pneumonia cases, mortality was 5.5% (6/109) with streamlining versus 12.5% (15/120) without streamlining; adjusted OR for in-hospital mortality of 0.35 (95% CI: 0.12–0.99) upon streamlining. Khasawneh 2014 provided an unadjusted comparison in which 3/33 patients (9.1%) in the de-escalation group died versus 7/27 patients (25.9%) in the no de-escalation group. In Carugati 2015, de-escalation of therapy was not associated with a higher risk of 30-day mortality (RR 0.78 (95% CI 0.47–1.27), after adjusting for potential confounders. In Viasus 2016, when a propensity score was entered in the multivariable models, antibiotic de-escalation was not associated with a higher risk of mortality (OR=0.83, 95%CI 0.24–2.81). In Yamana 2016, for propensity-matched patients, 15-day mortality rate was 5.3% (26/489) in the de-escalation group and 4.3% (21/489) in the continuation group (difference in mortality rate of 1.0% [95% CI, -1.7 to 3.7]); in-hospital mortality was 8.0% (39/489) in the de-escalation group and 8.8% (43/489) in the continuation group (difference in mortality rate was 0.8% [95% CI, -4.3 to 2.7]).	⊕⊕◯◯ LOW	CRITICAL
Hospital length of stay									
5	observational studies [c]	serious [d]	not serious	not serious	not serious	none	In Cremers 2014, among CAP survivors, 103 patients who had streamlining of therapy had a median hospital LOS of 11 days (IQR 8-15) whereas 105 who did not have streamlining had a median LOS of 10 days (IQR 7-15). In Khasawneh 2014, the de-escalation group (n=33) had a mean hospital LOS of 10.1 days (SD 8.4); the non de-escalation group (n=27) had a mean hospital LOS of 10.9 days (SD 10.2). In Carugati 2015, the de-escalation group (n=165) had a median hospital LOS of 8 days (IQR 5-15); the non de-escalation group (n=96) had a median hospital LOS of 9 days (IQR 5-16). In Viasus 2016, median hospital LOS was 5 days (IQR 4-8) in the de-escalation group (n=166) and 9 days (IQR 6-13) in the non de-escalation group (n=1117). In Yamana 2016, length of hospitalization in the de-escalation group (n=489) was a median 13 days (IQR 9-21) and in the non de-escalation group (n=489) it was a median 13 days (IQR 9-22 days).	⊕◯◯◯ VERY LOW	CRITICAL
Clinical failure (follow up: 28 days)									
1	observational studies	not serious	not serious	not serious	not serious	none	In Carugati 2015, a lower rate of clinical failure was detected in the de-escalation group than in the no de-escalation group (28/104 patients (26.9%) vs. 27/66 patients (40.9%)). The risk of clinical failure was not higher among those patients whose antibiotic therapy was de-escalated (RR 0.89 [95% CI 0.63–1.27]).	⊕⊕◯◯ LOW	CRITICAL
Duration of antibiotic therapy									

2	observational studies	serious [d]	not serious	not serious	not serious	none	In Carugati 2015, median duration of antibiotic therapy was 8 days (IQR 5-15) in the de-escalation group (n=165), compared to 9 days (IQR 5-16) in the non de-escalation group (n=96). In Viasus 2016, median duration of antibiotic therapy was 3 days (IQR 2-3) in the de-escalation group (n=166), compared to 5 days (IQR 4-9) in the non de-escalation group (n=1117).	⊕◯◯◯ VERY LOW	IMPORTANT
Hospital readmission (follow up: 30 days)									
1	observational studies	serious [d]	not serious	not serious	not serious	none	In Viasus 2016, 2.4% (4/166) of patients in the de-escalation group experienced a subsequent hospital admission in < 30 days, whereas 2.9% (31/1117) of patients in the non de-escalation group had a readmission.	⊕◯◯◯ VERY LOW	

CI: Confidence interval

Explanations

a. Khasawneh 2014 did not include adjustment for potential confounders. The other studies did employ multivariable analysis, adjusting for a variety of factors.
b. In Khasawneh, mortality data in Table 2 differs from mortality data included in the text. Data from the Table are presented here.
c. In Carugati 2015, the length of hospital stay reported in Table 1 differs from the LOS reported in the text. Here, the values from Table 1 are used.
d. Comparisons were not adjusted for potential confounders.

Author(s):
Date:
Question: ≤ 7 days of antibiotic therapy compared to > 7 days of antibiotic therapy in adults hospitalized with CAP
Setting:
Bibliography: Schonwald 1994; Bohte 1995; Rizzato 1995; Siegel 1999; Leophonte 2002; el Moussaoui 2006; Zhao 2014; Uranga 2016

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**≤ 7 days of antibiotic therapy**	**> 7 days of antibiotic therapy**	**Relative (95% CI)**	**Absolute (95% CI)**		
Clinical cure (Follow-up < 30 days)												
7	randomised trials [a]	not serious	not serious	not serious	serious [b]	none	442/580 (76.2%)	391/537 (72.8%)	**RR 1.03** (0.98 to 1.07)	**22 more per 1,000** (from 15 fewer to 51 more)	⊕⊕⊕◯ MODERATE	CRITICAL
Clinical cure (Follow-up >= 30 days)												
2	randomised trials [c,d]	not serious	not serious	not serious	serious [b]	none	168/189 (88.9%)	152/175 (86.9%)	**RR 1.03** (0.95 to 1.11)	**26 more per 1,000** (from 43 fewer to 96 more)	⊕⊕⊕◯ MODERATE	CRITICAL
In-hospital mortality												
1	randomised trials [c]	not serious	not serious	not serious	serious [b,e]	none	3/162 (1.9%)	2/150 (1.3%)	**RR 1.39** (0.24 to 8.20)	**5 more per 1,000** (from 10 fewer to 96 more)	⊕⊕⊕◯ MODERATE	CRITICAL
30-day mortality												
1	randomised trials [c]	not serious	not serious	not serious	serious [b,e]	none	3/162 (1.9%)	3/150 (2.0%)	**RR 0.93** (0.19 to 4.52)	**1 fewer per 1,000** (from 16 fewer to 70 more)	⊕⊕⊕◯ MODERATE	CRITICAL
Hospital length of stay												
2	randomised trials [c,f,g]	not serious	not serious	not serious	serious [b]	none	166	157	-	MD **0.16 higher** (0.43 lower to 0.75 higher)	⊕⊕⊕◯ MODERATE	CRITICAL
Clinical relapse or recurrence of pneumonia												

2	randomised trials [c,d]	not serious	not serious	not serious	serious [e]	none	In Siegel 1999, relapse was declared if there was initial improvement in signs and symptoms, then new signs symptoms and symptoms appeared after antibiotic completion. In this study, no episodes of relapse were observed in either study arm. In Uranga 2016, 4 of 162 patients who received antibiotics for a minimum of 5 days experienced recurrence compared to 6 of 150 patients in the arm with longer treatment duration.				⊕⊕⊕◯ MODERATE	CRITICAL
Any adverse effect												
6	randomised trials [h]	not serious	not serious	not serious	serious [b]	none	188/430 (43.7%)	192/396 (48.5%)	**RR 0.96** (0.86 to 1.06)	**19 fewer per 1,000** (from 29 more to 68 fewer)	⊕⊕⊕◯ MODERATE	CRITICAL
Serious adverse effect												
2	randomised trials	not serious	not serious	not serious	serious [b]	none	29/246 (11.8%)	36/239 (15.1%)	**RR 0.78** (0.51 to 1.20)	**33 fewer per 1,000** (from 30 more to 74 fewer)	⊕⊕⊕◯ MODERATE	CRITICAL

CI: Confidence interval; **RR:** Risk ratio; **MD:** Mean difference

Explanations

a. Data from studies comparing similar antibiotics. Additional characteristics of note: In Schonwald 1994, patients were hospitalized with atypical pneumonia. In Bohte 1995, data shown here are for the group of patients treated for non-pneumococcal CAP. A separate arm compared azithromycin to benzylpenicillin but this was considered a dissimilar comparison, thus these data are not included here. In Rizzato 1995, a previous antibiotic had been administered unsuccessfully in 20 cases. In Zhao 2014, data for clinical cure includes those who were considered cured and those considered improved, as improvement required no further antibiotic treatment. Although clinicians determined antibiotic type in Uranga 2016, it is included here (as opposed to excluding it due to "dissimilar comparisons"), because the majority (80%) of patients in both groups received a Quinolone.
b. CI does not exclude an appreciable increase or reduction in the absolute risk.
c. Although clinicians determined antibiotic type in Uranga 2016, it is included here (as opposed to excluding it due to "dissimilar comparisons"), because the majority (80%) of patients in both groups received a Quinolone.
d. In Siegel 1999, all included participants were male.
e. Includes very few events.
f. In Rizzato 1995, a previous antibiotic had been administered unsuccessfully in 20 cases.
g. el Moussaoui 2006 also included data about hospital length of stay, but the this was not reported in a standard format (e.g. mean [SD]). It was reported as follows: "the bootstrap estimated mean length of hospital stay was 7.9 days (6.5 to 9.3 days) in the three day treatment group compared with 8.9 days (6.8 to 11 days) in the eight day treatment group, with a bootstrap estimated mean difference of 1.0 day (− 1.3 to 3.2 days)."
h. The large number of adverse effects reported in Leophonte 2002 suggests that in this study, adverse effects were assessed differently compared to the other studies (reported adverse events in over 80% of patients, although only 20 (16%) patients in the 5 day group and 26 (21.8%) patients in the 10 day group presented with an adverse event considered by the investigator as possibly or probably linked to treatment).

Author(s):
Date:
Question: Antiviral therapy compared to no antiviral therapy in adults with CAP who test positive for influenza
Setting: Hospital
Bibliography: Oliveira 2001; Takayanagi 2006; Matsuno 2009; Lam 2011; Yang 2012

Certainty assessment							Impact	Certainty	Importance
Nº of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**			
Mortality									
5	observational studies	serious [a]	not serious	not serious	serious [b]	none	Combining mortality data from all included studies, death occurred in 18% of patients (14/79) not receiving any antiviral therapy, compared to 5% of patients who did receive antiviral therapy (47/941). [c]	⊕◯◯◯ VERY LOW	
ICU admission									
2	observational studies	serious [a]	not serious	not serious	serious [b]	none	In Oliveira 2011, 71% (10/14) of patients receiving antiviral therapy required ICU-level care, whereas 0% (0/3) of patients not receiving antiviral therapy were in the ICU. In Yang 2012, 25% (221/875) of patients receiving antiviral therapy were admitted to an ICU, compared to 16% (7/45) of those not receiving antiviral therapy. [c]	⊕◯◯◯ VERY LOW	
Mechanical ventilation									
3	observational studies	serious [a]	not serious	not serious	serious [b]	none	In Takayanagi 2006, 15% (6/41) of those receiving antiviral therapy required mechanical ventilation, compared to 18% (5/28) of those not receiving therapy. In Lam 2011, 65% (11/17) of patients on antiviral agents required mechanical ventilation, compared to 100% (1/1) patients not receiving antiviral therapy. In Yang 2012, 11% (100/875) of patients on antiviral agents required mechanical ventilation, compared to 13% (6/45) of patients not receiving antiviral therapy. [c]	⊕◯◯◯ VERY LOW	

CI: Confidence interval

Explanations

a. Of the included studies, only one accounts for any confounding factors when comparing data across treatment groups.
b. Few events in all studies, unable to detect evidence of harm versus benefit.
c. These observational studies are heterogeneous in nature, and differences between treatment groups are not adequately accounted for in this comparison nor in those in the original manuscripts.

Supplementary Text on etiology of pneumonia

Pneumonia is generally defined as a newly recognized pulmonary infiltrate, together with two or more of the following symptoms: new or increased cough, sputum production, shortness of breath, pleuritic chest pain, confusion, fever, rales, and leukocytosis (or suppressed white blood cell count with increased band forms). The 2019 IDSA/ATS pneumonia guidelines confine themselves to community-acquired pneumonia (CAP), specifically pneumonia that develops in adults in the community. The guidelines' recommendations for diagnostic evaluation and treatment exclude persons who have congenital or acquired immune deficiency or drug-induced neutropenia, but not those who have secondary immune dysfunction related to age or comorbid diseases.

Pneumonia is a syndrome with widely diverse causes. This supplementary section will make 4 major points regarding the etiology of CAP: (1) some proportion of patients who present with a typical pneumonia syndrome have no infection; (2) the recognized etiologies have undergone a major evolution since the beginning of the antibiotic era; (3) the cause in some patients who do have an infection is not amenable to treatment with usually recommended antibiotics; and (4) nearly every systematic study in recent years has failed to identify a cause in more than one-half of cases.

(1) A prospective systematic study included every person hospitalized for a syndrome consistent with CAP during a one-year period. This study was done at a veterans hospital in the US and, therefore, was confined to older adults, mainly men (1). Of 259 consecutive patients, all were diagnosed with CAP in the Emergency Department; a treatable infectious etiology was assumed, and empiric antibiotics were begun in all. Nonetheless, 44 of 259 (17%) were finally diagnosed with causes for their lung conditions other than infection. Causes of the CAP syndrome in these patients included pulmonary edema, malignancy, interstitial lung disease, eosinophilic pneumonia, and diffuse alveolar hemorrhage.

(2) In the pre-antibiotic era, an infectious etiology was regularly identified in cases of pneumonia. *Streptococcus pneumoniae* (pneumococcus) caused 90-95% of cases, with most of the remainder being attributed to *Streptococcus pyogenes, Haemophilus influenzae, Staphylococcus aureus*, or *Klebsiella pneumoniae* (2). The proportion of cases attributable to pneumococcus among adults has steadily declined since the 1960's such that, in recent studies using diagnostic testing in the United States, only 5-15% of cases of CAP have been shown to be pneumococcal (1, 3, 4). An indirect finding of a 7-23% decrease in hospitalizations of older adults in the 10 years after implementation of the 7-valent pneumococcal vaccine suggests that a somewhat higher proportion of cases may still be due to pneumococcus (5, 6). In Europe, studies (generally done before widespread institution of conjugate pneumococcal vaccine in children), have continued to identify *S. pneumoniae* in 20-25% of cases (7). This difference between the US and Europe has been attributed to the lack of use of pneumococcal vaccine in adults, the unchanged prevalence of cigarette smoking and, perhaps, the use of nonvalidated diagnostic tests for *S. pneumoniae* in European countries, with further contribution in the first part of the present century by a delay in widespread use of conjugate vaccine.

(3) Of patients with CAP due to an identified infectious etiology, a variable proportion, perhaps 20-25% or more, may be caused by organisms that do not respond to usually recommended empiric antibacterial therapy (Table 1). Among these, respiratory viruses are most prominent. Importantly, secondary bacterial infection is present in an unknown proportion of

these, and the difficulty in excluding a bacterial etiology in patients in whom a respiratory virus is identified in the upper respiratory tract is thought to justify the recommendations for empiric antibiotics in all adults diagnosed with CAP. Some proportion of *S. aureus* are ceftriaxone-resistant, which has led to the use of ceftaroline as a recommended beta-lactam in influenza season. Patients who have had repeated hospitalizations and/or courses of antibiotics may be infected with drug-resistant Gram-negative rods. Other infectious organisms causing a CAP syndrome include *Pneumocystis jirovecii, Nocardia, Mycobacterium tuberculosis,* and, depending heavily upon geographic locale, *Histoplasma, Coccidioides* and *Coxiella burneti,* to name just a few, underscoring the problem of administering recommended antibiotics in all cases.

(4) Intensive, prospective studies that, in recent years, have used every available technique have generally failed to identify an etiologic agent in more than one-half of cases (Table 1).This is largely because: (1) blood cultures are only positive in a minority of cases (perhaps 20-25% depending upon the etiologic agent); (2) many patients are unable to provide a sputum sample; and (3) a proportion of those with a productive cough only provide a sputum sample after antibiotics have been given for $\geq$18 hours, which renders the test poorly sensitive. Many of these pneumonia patients without a determined etiology appear to have a clinical pattern that suggests a bacterial etiology (1) and clearly respond to antibiotic treatment, further justifying the recommendation of empiric antibiotics for patients with pneumonia. Some authorities have suggested that "normal respiratory flora," the most commonly observed laboratory finding in sputum cultures, may be responsible for some proportion of these cases (7, 8).

Table 1. Studies of etiology of community acquired pneumonia. Data presented are percentages of total patients studied whose specimens were positive for the particular pathogen listed. Patients who had both a bacterium and virus detected are listed in both the bacterial and viral rows

	VAMC (1) †	EPIC (3) ‡	CAPITA (9, 10) ¶
Number of patients	215	2,320	1240
Bacteria	29	15	22
S. pneumoniae	9	5	14
Haemophilus	6	<1	3
Staph aureus	5	2	1
Pseudomonas	3	<1	1
Legionella	1	1	1
Mycoplasma, Chlamydia	--	<3	1
Other bacteria	6	3	5
Mycobacteria	2	1	<1
Nocardia	1	0	0
Fungi (PCP)	3	1	3
Viruses*	20	27	14
Rhinovirus	13	9	3
Coronavirus	3	2	2
Human metapneumovirus	2	4	1
Influenza	1	6	3
Parainfluenza	2	3	--
RSV	2	3	1
Other viruses	--	2	--
No cause identified	55	62	74

*Data presented as percentages of total patients studied. Patients who were coinfected with a bacterium and with a virus are listed under in both the bacterial and viral column. About 25% of patients who had evidence for viral infection were recognized as being coinfected with bacteria.
† VAMC = Houston Veterans Affairs Medical Center. Prospective study to determine etiology of CAP, single medical center (veterans hospital). No exclusions. This study originally identified 259 patients who, at the time of hospitalization, met definition for CAP and were begun on empiric antibiotic therapy. *Mycoplasma* or *Chlamydia* were not studied.

‡ Prospective study by US Centers for Disease Control and Prevention to determine etiology of CAP, carried out in 8 medical centers around the US. Immunocompromised patients were excluded.

¶ Control (non-vaccinated) subjects in a prospective study of the efficacy of conjugate pneumococcal vaccine at 101 community-based sites in the Netherlands. These subjects were followed for a mean of 3.9 years. Immunocompromised patients were excluded. Main source of data from Huijts et al (10), with some additional information from Bonten et al (9)

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