SUPPLEMENT

Management of Community-Acquired Pneumonia in Adults: the 2024 Practice Guideline from The Dutch Working Party on Antibiotic Policy (SWAB) and Dutch Association of Chest Physicians (NVALT)

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Contents

Potential conflicts of interest

The SWAB employs strict guidelines with regard to potential conflicts of interests, as described in the SWAB Format for Guideline Development (www.swab.nl). The SWAB is funded by the National Institute for Public Health and the Environment (RIVM), Bilthoven, the Netherlands. See Table S1 for disclosures of the members of the Guideline committee.

Table S1. Disclosures of the members of the Guideline committee.

Member	**Potential conflict of interest**
F.V. van Daalen	None
W.G. Boersma	Member advisory board Pfizer and MSD
E.M.W. van de Garde	None
F.M. van der Mooren	None
N. Roescher	None
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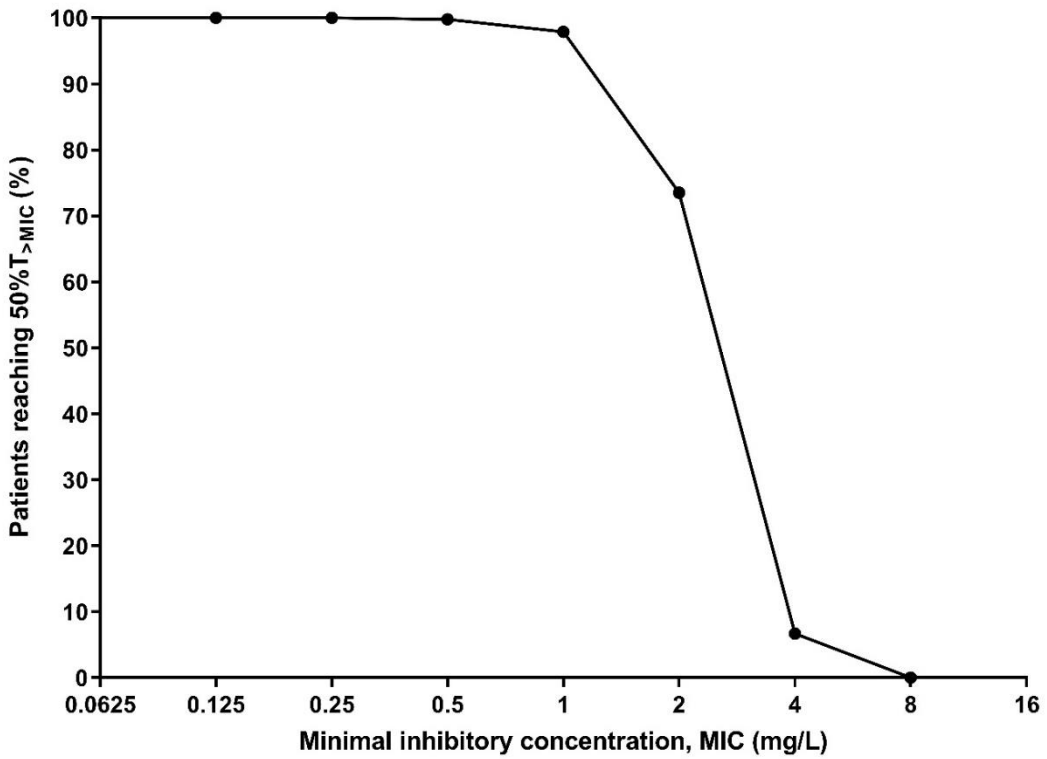
AGREE II scoring results of the ATS/IDSA guideline CAP[1]

Domain	**Sum of total score of two appraisers (minimum score – maximum score)**	**Domain score**
Scope and purpose	37 (6-42)	86%
Stakeholder involvement	14 (6-42)	22%
Rigour of development	74 (17-112)	60%
Clarity of presentation	29 (6-42)	63%
Applicability	9 (8-56)	2%
Editorial independence	26 (4-28)	92%

Probability of target attainment for oral amoxicillin

Figure S1. Probability of target attainment for oral amoxicillin[2]



Probability of target attainment of amoxicillin 500 mg three times daily. Shown are percentages of 1000 simulated patients per minimum inhibitory concentration (MIC) value achieving an amoxicillin concentration above the MIC during at least half of the first 24 h of treatment (i.e. at least 12 h, 50%$T_{>MIC}$). Simulated patients all had a CKD-EPI of 90 mL/min. The epidemiological cut-off for *Streptococcus pneumonia*, *Streptococcus pyogenes* and *Haemophilus influenzae* according to EUCAST is 0.0625, 0.0625 and 2 mg/L, respectively.

Search strategy per PICO

General inclusion criteria

Language: English or Dutch

Population:

- Adults = patients ≥ 18 years
- If a study includes patients <18 and >18 years, the study can be included provided that the total population includes > 50% of patients ≥ 18 years.

Definitions:

- CAP: community-acquired pneumonia, defined by an acute symptomatic infection of the lower respiratory tract and a new pulmonary infiltrate on chest X-ray, chest CT scan or lung ultrasonography, in a non-hospitalized patient or a patient <48hours hospitalized.[1,3]
- Symptoms and signs of an acute symptomatic infection are: new or increased cough, sputum production, shortness of breath, pleuritic chest pain, altered mental status, fever, rales, and leucocytosis (or suppressed white blood cell count with increased band forms).[1]
-

1a.Which are the causative aetiologies of CAP in the Netherlands?

For chapter 1a we searched for epidemiological studies on aetiology of community-acquired pneumonia. The search was done for the last 5 years (2016-Octobre 2021), as our previous guideline included studies until 2016. We searched Ovid Medline, assuming that all Dutch articles are published in this database.

Included patients	Adults with CAP in the Netherlands*^
Outcome	Causative agents (viral or bacterial) of CAP
Included studies	Systematic reviews, RCTs, cohort studies
Time period of search	2016-2021

** exclusion of patients who have recently (≤2 weeks) completed foreign travel.*

^ inclusion of patients presenting at the general practitioner, patients presenting at the emergency department, and patients < 48hours hospitalized.

	Query	**Items found (21-10-2021)**
#8	Limit #7 to yr="2016-Current"	99
#7	(#5 AND #6)	215
#6	Nederlands in.	524061

#5	(#3 OR #4)	6651
#4	Community acquired pneumonia ti.	6036
#3	(# 1 AND #2)	1803
#2	Exp *Pneumonia/	17989
#1	Community-Acquired Infections [mh]	7935

After screening 99 titles and abstracts, 23 were considered potentially relevant after title and abstract review. After full review, 15 were excludes because of using (a part of) the same database (n=11) or patient selection (n=4). Since the outcome of this key question concerns pathogens and not patient related outcomes, we did not perform a GRADE analysis.

1b. Which risk factors (COPD, influenza, colonisation with Pseudomonas aeruginosa, colonisation with ESBL, aspiration) are associated with specific pathogens?

For chapter 1b, we searched Ovid Medline and Embase for three risk factors, namely COPD, influenza and colonisation with *P. aeruginosa*. Colonisation with ESBL and aspiration are discussed in the SWAB sepsis guideline, and therefore no additional search was done for these risk factors.

P	Adults with CAP^
I	Diagnosed with COPD[a]
	Influenza virus[b]
	Colonisation with pseudomonas aeruginosa[c]
C	Not diagnosed with COPD[a]
	No influenza virus[b]
	No colonisation with pseudomonas aeruginosa[c]
O	Causative agents (viral or bacterial) of CAP
S	Systematic reviews, RCTs, cohort studies
T	2000-2021

^inclusion of patients presenting at the emergency department, and patients < 48hours hospitalized.

[a]COPD gold I-IV, diagnosed by a general practitioner with spirometry, or diagnosed by a lung specialist

[b]infection with influenza virus, conformed with a diagnostic test.

[c]colonisation, defined by the presence of microorganisms in or on a host with growth and multiplication, but without tissue invasion or damage, and thus no clinical expression and no immune response. Colonisation should be diagnosed before clinical suspicion of CAP.

	Query	**Items found (15-11-'21) Medline**	**Items found (15-11-'21) Embase**
#11	Limit #10 to Embase		288
#10	(#8 AND #9)	221	413

#9	((?etiolog* adj3 (microbial or bacterial or diagn*)) or pathogen or microbial-agent* or genotyp*).ti,ab,kf.	534867	681545
#8	(#6 AND #7)	1305	2419
#7	Validat$.tw. or Predict$.ti. or Rule$.tw. or (Predict$ and (Outcome$ or Risk$ or Model$)).tw. or ((History or Variable$ or Criteria or Scor$ or Characteristic$ or Finding$ or Factor$) and (Predict$ or Model$ or Decision$ or Identif$ or Prognos$)).tw. or (Decision$.tw. and ((Model$ or Clinical$).tw. or logistic models/)) or (Prognostic and (History or Variable$ or Criteria or Scor$ or Characteristic$ or Finding$ or Factor$ or Model$)).tw. or exp Prognosis/ or exp Risk Factors/ or exp Multivariate Analysis/	6285411	7512454
#6	(#1 AND #5)	3084	6338
#5	(#2 OR #3 OR #4)	343510	566302
#4	exp Pseudomonas aeruginosa/ or aeruginosa.ti,ab,kf.	77559	131530
#3	exp Influenza A virus/ or exp Influenza, Human/ or (influenza or flu).ti,ab,kf.	122947	170339
#2	chronic obstructive lung disease/ or ((obstruct$ adj3 (pulmonary or lung$ or airway$ or airflow$ or bronch$ or respirat$)) or (chronic$ adj3 bronchiti$) or emphysema$ or COPD).ti,ab,kf.	145426	271500
#1	exp Community-Acquired Infections/ or (cap or (community-acquired adj2 (infection* or pneumon*))).ti,ab,kf.	62413	87220

After deduplication, 370 studies were found in the original searches, of which 24 were considered potentially relevant after title and abstract review. After full review 16 were excluded, because the results were not specified per risk factor of interest (n=5), narrative review (n=3), wrong study design (n=2), <10 patients included with a risk factor of interest (n=2), no differentiation between colonisation and infection with *P. aeruginosa* (n=2), data was too outdated (n=1), or wrong patient selection (n=1).

Since the outcome of this key question concerns pathogens and not patient related outcomes, we did not perform a GRADE analysis.

2. What is the susceptibility of the most common bacterial species causing CAP in the Netherlands?

For chapter 2 we used data from 2021 from the Dutch national antimicrobial resistance surveillance system (Infectious Diseases Surveillance Information System for Antimicrobial Resistance (ISIS-AR)). In 2021, 46 of 52 Dutch microbiological laboratories were participating in this system. The results of lower respiratory tract cultures were available from 33 laboratories.

Resistance percentages are calculated based on minimal inhibitory concentrations (MIC's) and zone diameters for antimicrobials of isolates cultured from the lower respiratory tract, and reinterpreted according to the clinical breakpoints reported by EUCAST[4] . Since 2021, EUCAST uses a stepped wise approach for the susceptibility testing for β-lactam antibiotics, to reduce the number of specific tests for β –lactam antibiotics, to reduce the number of specific tests for β -lactam agents. For *S. pneumoniae*, EUCAST susceptibility testing for β -lactam antibiotics starts with an oxacillin 1µg disk diffusion screening test. When this test is negative, all β -lactam agents for which clinical breakpoints are available, are considered susceptible. When the screening is positive, a flowchart should be used to determine whether the pathogen is susceptible. It depends on the oxacillin zone and the antibiotic whether the bacteria is said to be susceptible or resistant for the β-lactam antibiotic. For *H. influenzae*, EUCAST susceptibility testing for β-lactam antibiotics starts with benzylpenicillin screen test. When this test is negative, all β-lactam agents for which clinical breakpoints are available, are considered susceptible. When the screening is positive, it depends on the β -lactamase test, the antibiotic and in some cases the amoxicillin-clavulanic acid 2-1 µg disk whether the pathogen is considered susceptible or resistant.

The downside is that ISIS-AR did not always receive all data from the laboratories that is required for this stepped wise approach. Therefore, a trustworthy re-interpretation of the data was not always possible. To diminish bias, ISIS-AR only reports resistance percentages when at least 50% of the laboratories has tested at least 50% of the cultured isolates for the particular antibiotic, and for at least 80% of the isolates it should be possible to re-interpreter the results according to EUCAST[4].

3. In adults with a clinical suspicion of CAP, what is the sensitivity of a CT scan or lung ultrasound compared with X-ray?

Recently, Cochrane Netherlands performed a comprehensive systematic search on the utility of lung ultrasound (LUS) for the diagnosis of pneumonia[5]. For the comparison between LUS and CXR, we used the search of the Cochrane report and we did an additional search for the remaining time period (2020-2021). For the comparison between CT scan and CXR we adapted the Cochrane search as described below.

P	Adults with clinical suspicion of CAP^
I	Use of Lung ultrasound Use of CT scan**
C	Use of Chest X-ray
O	Mortality, hospital admission, ICU admission, length of hospital stay, duration of antibiotic treatment. Radiographic confirmation of CAP***, sensitivity, specificity, positive predictive value, negative predictive value of radiographic imaging
S	Systematic reviews, RCTs, cohort studies
T	2011-2021

^ inclusion of patients presenting at the emergency department, and patients <48hours hospitalized.

** clinical suspicion of community acquired pneumonia, defined by symptoms or signs of pneumonia (temperature ≥37.8C or hypothermia <36C, cough, dyspnoea, sputum production, chest pain, new focal chest signs, altered mental status, crackles on auscultation, arterial oxygen saturation ≤95%, respiratory rate ≥24/min, heart rate ≥100/min, or systolic blood pressure ≤ 90 mm Hg), in a non-hospitalized patient or a patient <48hours hospitalized.*

*** including low dose and normal dose CT*

****the diagnosis is confirmed with a lobar consolidation, interstitial infiltrate or cavitation*

	Query	**Items found (29-11-'21) Medline**
#13	(#11 NOT #12)	631
#12	exp COVID-19/ or (corona or covid*).ti,ab,kf.	203995
#11	Limit 10 to yr="2011 -Current"	1289
#10	(#4 OR #9)	1667
#9	(#1 AND #7 AND #8)	373
#8	((CT adj3 (cine or scan* or x-ray* or xray*)) or ((electron beam* or comput* or axial) adj3 tomography) or tomodensitometry or (ct or mdct)).ti.	159240
#7	(#5 OR #6)	3532259
#6	(diagn* adj3 (utility or impact)).ti.	3708
#5	("randomized controlled trial" or "controlled clinical trial").pt. or random*.ab. or placebo.ab. or trial.ab. or groups.ab.	3529128
#4	(#1 AND #2 AND #3)	1422
#3	"sensitivity and specificity"/ or "mass screening"/ or "reference values"/ or "false positive reactions"/ or "false negative reactions"/ or (specificit* or sensitivit* or screening or false positive* or false negative* or accuracy or predictive value* or reference value* or roc* or likelihood ratio*).tw.	2548500
#2	((CT adj3 (cine or scan* or x-ray* or xray*)) or ((electron beam* or comput* or axial) adj3 tomography) or tomodensitometry).ti,ab,kf. or (ct or mdct).ti.	440322

#1	Pneumonia/ or exp community acquired infection/ or (cap or pneumonia* or (community-acquired adj2 infection*)).ti,ab,kf.	257863

	Query	**Items found (29-11-'21) Embase**
#14	Limit 13 to embase	1279
#13	(#11 NOT #12)	2484
#12	coronavirus disease 2019/ or severe acute respiratory syndrome/ or (corona or covid* or SARS).ti,ab,kf.	235070
#11	limit 10 to yr="2011 -Current"	3329
#10	(#4 OR #9)	4186
#9	(#1 AND #5 AND #8)	1133
#8	(#6 OR #7)	5033182
#7	(diagn* adj3 (utility or impact)).ti.	5661
#6	(Randomized controlled trial/ or Controlled clinical study/ or Random$.ti,ab. or randomization/ or intermethod comparison/ or placebo.ti,ab. or (compare or compared or comparison).ti. or ((evaluated or evaluate or evaluating or assessed or assess) and (compare or compared or comparing or comparison)).ab. or (open adj label).ti,ab. or ((double or single or doubly or singly) adj (blind or blinded or blindly)).ti,ab. or double blind procedure/ or parallel group$1.ti,ab. or (crossover or cross over).ti,ab. or ((assign$ or match or matched or allocation) adj5 (alternate or group$1 or intervention$1 or patient$1 or subject$1 or participant$1)).ti,ab. or (assigned or allocated).ti,ab. or (controlled adj7 (study or design or trial)).ti,ab. or (volunteer or volunteers).ti,ab. or human experiment/ or trial.ti.) not (((random$ adj sampl$ adj7 ("cross section$" or questionnaire$1 or survey$ or database$1)).ti,ab. not (comparative study/ or controlled study/ or randomi?ed controlled.ti,ab. or randomly assigned.ti,ab.)) or (Cross-sectional study/ not (randomized controlled trial/ or controlled clinical study/ or controlled study/ or randomi?ed controlled.ti,ab. or control group$1.ti,ab.)) or (((case adj control$) and random$) not randomi?ed controlled).ti,ab. or ((Systematic review not (trial or study)).ti. or (nonrandom$ not random$).ti,ab.) or "Random field$".ti,ab. or (random cluster adj3 sampl$).ti,ab. or ((review.ab. and review.pt.) not trial.ti.) or ("we searched".ab. and (review.ti. or review.pt.)) or "update review".ab. or (databases adj4 searched).ab. or ((rat or rats or mouse or mice or swine or porcine or murine or sheep or lambs or pigs or piglets or rabbit or rabbits or cat or cats or dog or dogs or cattle or bovine or monkey or monkeys or trout or marmoset$1).ti. and animal experiment/) or (Animal experiment/ not (human experiment/ or human/)))	5028959

#5	((CT adj3 (cine or scan* or x-ray* or xray*)) or ((electron beam* or comput* or axial) adj3 tomography) or tomodensitometry or (ct or mdct)).ti.	220979
#4	(#1 AND #2 AND #3)	3480
#3	x-ray computed tomography/ or ((CT adj3 (cine or scan* or x-ray* or xray*)) or ((electron beam* or comput* or axial) adj3 tomography) or tomodensitometry).ti,ab,kf. or (ct or mdct).ti.	660621
#2	exp "sensitivity and specificity"/ or exp mass screening/ or false negative result/ or false positive result/ or diagnostic accuracy/ or diagnostic test accuracy study/ or reference value/ or (specificit* or sensitivit* or screening or false positive* or false negative* or accuracy or predictive value* or reference value* or roc* or likelihood ratio*).tw.	3391432
#1	Pneumonia/ or exp community acquired infection/ or (cap or pneumonia* or (community-acquired adj2 infection*)).ti,ab,kf.	480859

There were 631 studies in the Medline search, and 1279 in the Embase search. After deduplication, 1467 studies were screened, of which 19 were considered potentially relevant after title and abstract review. After full review, five were excluded because of wrong study design (n=2), wrong patient selection (n=1), primary care (n=1), comment (n=1).

Since the search of Cochrane Netherlands included also patients suspected of HAP or VAP, we performed our own GRADE analysis for the comparison between LUS and CXR in patients suspected of CAP, as shown in table S1 (evidence summaries). For the comparison between CT and CXR the GRADE analyses are shown in table S2 and S3.

4. What is the role of (rapid) diagnostic tests in the treatment decisions in adults hospitalized with CAP?

For chapter 4, we used the searches of the ATS/IDSA guideline and we did an additional search in Ovid Medline for the period 2015-2021.

4.1. In adults with CAP, should gram stain and culture of lower respiratory secretions be obtained at the time of diagnosis?

This search was combined with the search for 4.2 concerning sputum cultures, as described below.

4.2 In adults with CAP, should blood cultures be obtained at the time of diagnosis?

P	Adults with CAP^
I	Blood culture
	Sputum culture
C	No blood culture

	No sputum culture
O	death <30 days after start of therapy, clinical improvement within 72 hours, ICU admission, length of hospital stay, duration of antibiotic treatment, duration of IV antibiotic treatment, duration of broad-spectrum antibiotic treatment
S	Systematic reviews, RCTs, cohort studies
T	2015-2021

^ inclusion of patients presenting at the emergency department, and patients <48hours hospitalized.

	Query	**Items found (IDSA)**	**Items found (8-11-2021) Medline**
#10	Limit #9 to [not COVID]		482
#9	Limit #8 to yr=”2015-Current”		550
#8	(#4 AND #7)	1407	1927
#7	(#5 OR #6)	21534	30314
#6	sputum culture*[tw]	2092	3053
#5	blood culture*[tw]	19573	27453
#4	(#1 OR #2 OR #3)	83866	222065
#3	community acquired pneumonia[tw]	7188	10850
#2	pneumonia[mh]	76881	212342
#1	Infections, Community-Acquired[mh]	11021	15126

For this PICO there were 482 studies in the original search, with 16 considered potentially relevant after title and abstract review. After full review, six were excluded because of wrong study design (n=2), wrong outcome (n=3), concerned other diagnostics (n=1). In our search there was no study reporting direct patient outcomes. One study described culture-based changes of antibiotic treatment, however there was no comparison group without cultures. Therefore we could not generate an evidence table for this outcome.

The ATS/IDSA search resulted in three studies concerning patient outcomes, and therefore we used their GRADE analysis on these outcomes[1].

4.3 In adults with CAP, should legionella and pneumococcal urinary antigen testing be performed at the time of diagnosis?

P	Adults with CAP^
I	urine antigen testing
C	No urine antigen testing

O	death <30 days after start of therapy, narrowing antibiotic therapy, clinical improvement, length of hospital stay, diagnostic accuracy
S	Systematic reviews, RCTs, cohort studies
T	2015-2021

^ inclusion of patients presenting at the emergency department, and patients <48hours hospitalized.

	Query	**Items found (IDSA)**	**Items found (1-11-2021) Medline**
#22	Limit #21 to [not COVID]		828
#21	Limit #20 to yr="2015-Current"		871
#20	(#13 AND #19)	1207	2052
#19	(#14 OR #15 OR #16 OR #17 OR #18)	1349068	1819816
#18	assay[tiab]	536377	766838
#17	urine antigen[tiab]	141	263
#16	urin*[tw]	574730	707874
#15	viral*[tiab]	280466	402828
#14	binax*[tw]	239	347
#13	(#8 AND #12)	5289	8414
#12	(#9 OR #10 OR #11)	3782872	5829471
#11	diagnos*[tiab]	1874315	2750586
#10	testing[tw]	473655	735476
#9	test*[tiab]	2114563	3526966
#8	(#3 AND #7)	15079	22064
#7	(#4 OR #5 OR #6)	1688542	2434190
#6	Infecti*[tiab]	1216514	1762847
#5	Lung[tiab]	466696	668993
#4	Pneumonia[tiab]	90235	136189
#3	(#1 OR #2)	17579	25358
#2	Community-acquired[tiab]	14158	20972
#1	Infections, Community-Acquired[mh]	10953	15110

For this PICO there were 828 studies in the original search, with 34 considered potentially relevant after title and abstract review. After full review, seven were excluded because of wrong outcome (n=2), wrong patient selection (n=2), narrative review (n=2), and wrong study design (n=1). We used the GRADE analysis performed by ATS/IDSA for patients' outcomes in terms of mortality, duration of antibiotic use, hospital length of stay and ICU admission[1]. For the outcome narrowing antibiotic therapy, we performed a GRADE analysis as presented in table S4.

4.4 In adults with CAP, should serum procalcitonin plus clinical judgement versus clinical judgment alone be used to withhold initiation of antibiotic treatment?

P	Adults with CAP^
I	Procalcitonine + clinical judgement
C	Clinical judgement alone
O	Distinction of viral vs bacterial pneumonia, start of antibiotic treatment, clinical improvement, ICU admission, length of hospital stay, death <30 days after start of therapy
S	Systematic reviews, RCTs, cohort studies
T	2016-2021

^ inclusion of patients presenting at the GP, at the emergency department, and patients <48hours hospitalized.

	Query	**Items found (IDSA)**	**Items found (5-11-2021) Medline**
#12	Limit #11 to [not COVID]		191
#11	Limit #10 to yr="2015-Current"		216
#10	(#8 AND #9)	239	437
#9	procalcitonin*[tw]	3356	7390
#8	(#3 AND #7)	15079	22078
#7	(#4 OR #5 OR #6)	1688452	2435616
#6	infecti*[tiab]	1216514	1764144
#5	lung[tiab]	466696	669118
#4	pneumonia[tiab]	90235	136296
#3	(#1 OR #2)	17579	25373
#2	community-acquired[tiab]	14158	20984
#1	Infections, Community-Acquired[mh]	10953	15122

For this PICO there were 191 studies in the original search, with 35 considered potentially relevant after title and abstract review. After full review, 19 were excluded because of wrong study design (n=13), procalcitonin was used a reference (n=2), wrong outcome (n=2) and wrong patient selection (n=2). We used the GRADE analysis performed by ATS/IDSA for patients' outcomes in terms of mortality, clinical failure, hospital length of stay or ICU admission[1]. For the outcome diagnostic accuracy, we used the systematic review by Kamat et al[6]. We assessed this review using the ROBIS tool[7].

5. What is the optimal initial treatment for adults with CAP?

For chapter 5, we developed searches based on the searches of the IDSA. We adapted their search for our key questions. We performed these searches in Ovid Medline and Embase.

P	Adults with CAP^
I	Treatment with β-lactam combination therapy
C	Treatment with a β-lactam monotherapy
O	death <30 days after start of therapy, clinical improvement, readmission, length of hospital stay, bacteriological response
S	Systematic reviews, RCTs, cohort studies
T	2015-2021

P	Adults with CAP^
I	Treatment with quinolones monotherapy or quinolone combination therapy
C	Treatment with β-lactam monotherapy or combination therapy
O	death <30 days after start of therapy, clinical improvement, readmission, length of hospital stay, bacteriological response
S	Systematic reviews, RCTs, cohort studies
T	2015-2021

^ inclusion of patients presenting at the emergency department, and patients <48hours hospitalized.

	Query	**Items found (14-10-'21) Medline**	**Items found (2-11-'21) Embase**
#E32	#E31 (2015-2021)		6113
#E31	#29 NOT #E30		24977
#E30	COVID		
#E29	#25 NOT #34		27396
#36	((#25 AND #35))	6580	
#35	((#33 NOT #34)	4525954	nvt
#34	((animals [mh] NOT humans [mh]))	4897783	5647869
#33	((#26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32))	5196339	Nvt
#32	groups[tiab]	2289258	Nvt
#31	trial[tiab]	674095	Nvt
#30	randomly[tiab]	368454	Nvt
#29	drug therapy[sh]	2385457	Nvt
#28	randomized[tiab]	583972	Nvt
#27	controlled clinical trial[pt]	636996	Nvt
#26	randomized controlled trial[pt]	547425	Nvt

#25	((#8 AND #11 AND #24))	10127	27700
#24	#12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23	893384	4260827
#23	((doxycyclin* OR tetracyclin*))	64444	162765
#22	((co-trimoxazole OR trimethoprim*))	25448	47225
#21	clavulan*[tiab]	9136	13394
#20	((quinolone* OR fluoroquinolon* OR ciprofloxacin* OR gemifloxacin* OR levofloxacin*))	69377	169617
#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*))	185200	414945
#18	((macrolide* OR makrolide* OR azithromycin* OR clarithromycin* OR erythromycin* OR roxithromycin* OR telithromycin* OR clindamycin*))	73147	207780
#17	Tetracyclines[mh]	49986	196875
#16	Quinolones[mh]	50185	187490
#15	beta-lactams[mh]	132861	8295
#14	Macrolides[mh]	115067	352946
#13	antibiotic*[tw]	412853	522400
#12	Anti-Bacterial Agents[mh]	405664	4108873
#11	(#9 OR #10)	279368	417704
#10	pneumonia[tiab]	135630	210379
#9	pneumonia[mh]	206565	371510
#8	((#3 OR #4 OR #5 OR #6 OR #7))	470959	716335
#7	hospitali*[tw]	351067	476737
#6	inpatient*[tw]	143405	205840
#5	inpatients[mh]	25221	207247
#4	inpatient[tiab]	97729	157944
#3	(#1 OR #2)	25293	34440
#2	community-acquired[tiab]	20912	30166
#1	Infections, Community-Acquired[mh]	15064	17261

There were 2777 studies in the original search of Ovid Medline and Embase. In Ovid Medline 71 were considered potentially relevant after title and abstract review. After full review, 21 were excluded because it concerned a background article or comment (n=9), the outpatient setting (n=3), a phase 3 study (n=3), wrong study design (n=2), wrong patient selection (n=2), or was based on outdated data (n=2).

In Embase, eight studies were considered potentially relevant after title and abstract review. After full review, five studies were excluded because of a wrong patient population (n=2), phase 3 study (n=2), in vitro results (n=1).

Two randomised controlled trials compare treatment of beta-lactam monotherapy and beta-lactam combination therapy. The certainty of evidence based on these randomized controlled trials is described in the ATS/IDSA guideline using GRADE, and we used this analysis[1].

For the comparison between treatment with narrow-spectrum and broad-spectrum beta-lactam treatment, we performed a GRADE analysis, as shown in table S5 (evidence summaries).

Treatment of patients with (moderate) severe CAP with respiratory fluorquinolones vs beta-lactam therapy with or without macrolides was evaluated in two systematic reviews (Liu et al. and Raz-Pasteur et al.). We assessed the quality of both reviews using the AMSTAR-2 checklist[7]. Liu et al. scored slightly higher on the assessment of publication bias and funding, while Raz-Pasteur et al. had a more comprehensive literature search strategy. The examination of the effect of risk of bias is limited in both studies: Raz-Pasteur et al. report that the paucity of the trials limits the ability of risk of bias examination. Therefore, we used the two systematic reviews as a basis for our GRADE analysis, but when information was lacking, we checked the original RCT. The final GRADE analysis is shown in table S6.

Treatment of patients with severe CAP with moxifloxacin vs beta-lactam therapy was evaluated in a GRADE analysis, as shown in table S7. One systematic review by Sligl et al. compared – amongst others – treatment with beta-lactam-macrolide and beta-lactam-fluorquinolones, and treatment with- and treatment without macrolides in critically ill patients with CAP. The quality of this review was assessed by the AMSTAR-2. Based on our PICO search, we performed a GRADE analysis only for the comparison between fluorquinolone-based regimen and macrolide-based regimen as shown in table S8. Due to unreported data on the control groups, studies by Ito et al. and Pereira et al. were not suitable for the GRADE analysis.

6. What is the optimal initial treatment for patients with CAP caused by Legionella?

For chapter 6, we used the same searches as described in chapter 5, but this time we checked the studies specifically for CAP caused by Legionella species. Again, we performed these searches in Ovid Medline and Embase.

P	Adults with CAP^ with a culture of urinary antigen test positive for *Legionella species*
I	Treatment with quinolone monotherapy or treatment with tetracycline monotherapy

C	Treatment with macrolides therapy
O	death <30 days after start of therapy, clinical improvement, readmission, length of hospital stay, bacteriological response
S	Systematic reviews, RCTs, cohort studies
T	2015-2021

^ inclusion of patients at the general practitioner, presenting at the emergency department, and patients <48hours hospitalized.

7a. In adults with CAP, is the optimal duration of treatment five days or longer?

For chapter 7, we used the same searches as described in chapter 5, but this time we checked the studies for the duration of treatment of CAP. Again, we performed these searches in Ovid Medline and Embase.

P	Adults with CAP^*
I	Treatment duration ≤5 days
C	Treatment duration >5 days
O	Clinical recovery, death <30 days after discharge, readmission <30 days after discharge
S	Systematic reviews, RCTs
T	2011-2021

^ inclusion of patients presenting at the general practitioner, patients presenting at the emergency department, and patients <48hours hospitalized.
**exclusion of patients with a culture/PCR/urinary antigen test positive for Legionella species, Mycoplasma pneumoniae*, or *S aureus*

7b. In adults with a CAP caused by an atypical pathogen, what is the optimal duration of treatment?

7.b.1. Legionella species – 7 days

P	Adults with CAP^ with a culture, PCR or urinary antigen test positive for *Legionella species*
I	Treatment duration <7 days
C	Treatment duration ≥7 days

O	Clinical recovery, death <30 days after discharge, readmission <30 days after discharge
S	Systematic reviews, RCTs, cohort studies
T	2011-2021

^ inclusion of patients presenting at the general practitioner, patients presenting at the emergency department, and patients <48hours hospitalized.

7.b.2. Mycoplasma pneumoniae – 14 days

P	Adults with CAP^ with a culture or PCR test positive for *Mycoplasma pneumoniae*
I	Treatment duration <14 days
C	Treatment duration ≥14 days
O	Clinical recovery, death <30 days after discharge, readmission <30 days after discharge
S	Systematic reviews, RCTs, cohort studies
T	2011-2021

^ inclusion of patients presenting at the general practitioner, patients presenting at the emergency department, and patients <48hours hospitalized.

7.b.3. Staphylococcus aureus – 14 days

P	Adults with CAP^ with a culture positive for *Staphylococcus aureus*
I	Treatment duration <14 days
C	Treatment duration ≥14 days
O	Clinical recovery, death <30 days after discharge, readmission <30 days after discharge
S	Systematic reviews, RCTs, cohort studies
T	2011-2021

^ inclusion of patients presenting at the general practitioner, patients presenting at the emergency department, and patients <48hours hospitalized.

8. Should adults with CAP be treated with corticosteroids in addition to antibiotics?

P	Adults with CAP^
I	Systemic corticosteroid treatment, given as adjunct to antibiotic treatment*
C	Antibiotic treatment alone, or antibiotic treatment with placebo
O	Mortality < 30 days after start of therapy, clinical improvement within 72 hours, ICU admission, length of hospital stay, readmission < 30 days after discharge, adverse

	events including hyperglycaemia, gastrointestinal bleeding and neuropsychiatric events
S	Systematic reviews
T	2015-2021

^ inclusion of patients at the emergency department, and patients <48hours hospitalized.

** including prednisone, dexamethasone, hydrocortisone, either orally or intravenously. All doses.*

Since the committee was aware of the existence of several systematic reviews on this topic, we performed a search in Epistemonikos database, which is a collaborative, multilingual database of health evidence, considered the largest source of systematic reviews relevant for health-decision making[8].

Search terms: *(advanced_title_en:((community-acquired OR pneumon* OR CAP) AND (corticosteroid* OR predniso* OR hydrocortisone* OR dexame*)) OR advanced_abstract_en:((community-acquired OR pneumon* OR CAP) AND (corticosteroid* OR predniso* OR hydrocortisone* OR dexame*))) [Filters: protocol=no, classification=systematic-review, min_year=2012, max_year=2022]*

There were 176 search results. No duplicates were detected. Therefore, 176 studies were screened, of which 16 were considered potentially relevant after title and abstract review. After full review, 2 were excluded because they did not concern an original systematic review and 2 were excluded because they included only patients with influenza. Six systematic reviews included only patients with severe CAP (Wu 2018, Wan 2016, Jiang 2019, Huang 2019, Cheng 2014, Bi 2016). Of the remaining 6 systematic reviews, one was a Cochrane review from 2017, including 13 RCTs concerning adult patients with CAP. We found that none of the other systematic reviews included important data that was not included in the Cochrane review 2017, except for one systematic review by Briel et al, which included an individual patient data meta-analysis. Briel et al. included 6 RCTs, which were all included in the Cochrane. The 7 studies that were included in the Cochrane but not in Briel et al. were 4 studies published before 2010 (Mikami 2007, Marik 1993, McHardy 1972 and Hatakeyama 1995), and 3 studies of which the authors did not provide individualised patients data (Nafae 2013, Sabry 2011, El-Ghamraway 2006). We used the AMSTAR-2 checklist for both the Cochrane review and the systematic review by Briel et al, and the AMSTAR-2 scores were both high, but the Cochrane review does not investigate or discuss heterogeneity between the studies. Since there is substantial heterogeneity between the studies with a high risk of ecological bias, we decided to use the systematic review by Briel et al. for our recommendations.

9. In adults with CAP who are improving, should follow-up chest imaging be obtained after discharge?

For chapter 9, we used the searches of the ATS/IDSA guideline and we did an additional search in Ovid Medline for the period 2015-2021.

P	Adults with CAP^
I	Follow-up imaging with chest X-ray <100 days after discharge
C	No follow-up imaging with chest X-ray
O	Lung malignancy, abnormal non-malignant pathology of the lung, ongoing infection, mortality, quality of life
S	Systematic reviews, RCTs, cohort studies
T	2015-2021

^ inclusion of patients at the emergency department, and patients <48hours hospitalized.

	Query	**Items found (IDSA)**	**Items found (11-10-2021)**
#14	Limit #13 to [not COVID]		822
#13	Limit #12 to yr=”2015-Current”		1215
#12	(#4 AND #7 AND #11)	1385	2576
#11	(#8 OR #9 OR #10)	2884695	4105819
#10	Follow*[tiab]	2636630	3748082
#9	Convalesc*[tiab]	10290	14359
#8	Recovery*[tiab]	337392	487519
#7	(#5 OR #6)	1029294	1268236
#6	Radiograph*[tiab]	770452	251859
#5	Radiography[mh]	672804	1153329
#4	(#1 OR #2 OR #3)	85574	215498
#3	Community acquired pneumonia[tw]	7220	10789
#2	Pneumonia[mh]	78574	205808
#1	Infections, Community-Acquired[mh]	11086	15058

For this PICO 18 studies were considered potentially relevant after title and abstract review. After full review, no study directly addressed our PICO. Therefore, no evidence table was generated.

Evidence summaries

The following tables are developed using the GRADE Guideline Development Tool (https://gradepro.org/).

Table S1. Question: LUS compared to CXR for diagnosing CAP

Bibliography: Amatya 2019, Bourcier 2014, Corradi 2015, Cortellaro 2012, Liu 2015, Pagano 2015, Sezgin 2020, Taghizadieh 2015, Buda 2021, Linsalata 2020

Certainty assessment							№ of patients		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	LUS	CXR		
True positive										
10	observational studies	serious[a]	not serious	not serious	serious[b]	none	731/789 (92.6%)	559/789 (70.8%)	⨁◯◯◯ Very low	IMPORTANT
True negative										
10	observational studies	serious[a]	not serious	not serious	serious[b]	none	291/331 (87.9%)	273/331 (82.5%)	⨁◯◯◯ Very low	IMPORTANT

a. Risk of selection bias due to patient selection in each study except Liu 2015, Insalata 2020 and Buda 2021. Lack of blinding of the LUS performer in each study except Sezgin 2020 and Linsalata 2020.
b. Wide variation in true positive and true negative test results. Variation in training of LUS performer.

Table S2. Question: ULDCT compared to CXR for diagnosing CAP

Bibliography: van den Berk 2022

Certainty assessment							№ of patients		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ULDCT	CXR		
Mortality within 28 days (follow-up: 28 days)										
1	randomised trials	serious[a]	not serious	not serious	serious[b]	none	31/1208 (2.6%)	36/1210 (3.0%)	⨁⨁◯◯ Low	CRITICAL
Hospital admission										
1	randomised trials	serious[a]	not serious	not serious	not serious	none	638/1208 (52.8%)	659/1210 (54.5%)	⨁⨁⨁◯ Moderate	CRITICAL
Length of hospital stay										
1	randomised trials	serious[a]	not serious	not serious	not serious	none	1208	1210	⨁⨁⨁◯ Moderate	CRITICAL
ICU admission										
1	randomised trials	serious[a]	not serious	not serious	serious[b]	none	50/1208 (4.1%)	44/1210 (3.6%)	⨁⨁◯◯ Low	CRITICAL

a. Lack of concealment of allocation, lack of blinding
b. Small number of events

Table S3. Question: ULDCT compared to CXR for diagnosing CAP

Bibliography: Claesssens 2015, Prendki 2018

Certainty assessment							№ of patients		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ULDCT	CXR		
True positive										
2	observational studies	not serious	not serious	not serious	not serious	none	284/306 (92.8%)	270/306 (88.2%)	⊕⊕◯◯ Low	IMPORTANT
True negative										
2	observational studies	not serious	not serious	not serious	not serious	none	53/213 (24.9%)	143/213 (67.1%)	⊕⊕◯◯ Low	IMPORTANT

Table S4. Question: Pneumococcal UAT compared to no pneumococcal UAT in adults with suspected CAP

Bibliography: Schimmel 2020, Piso 2012

Certainty assessment							№ of patients		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	pneumococcal UAT	no pneumococcal UAT		
narrowing antibiotic therapy										
2	observational studies	not serious	not serious	not serious	serious[a]	none	1919/10099 (19.0%)	7537/51270 (14.7%)	⊕◯◯◯ Very low	IMPORTANT

a. Piso 2012 includes small sample sizes. Schimmel 2020 compares groups with large size differences.

Table S5. Question: Narrow spectrum (penicillin) compared to broad spectrum (cephalosporin or piperacillin/tazobactam) for empirical treatment of moderate severe CAP

Bibliography: Rhedin 2017

Certainty assessment							№ of patients		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	narrow spectrum (penicillin)	broad spectrum (cephalosporin or piperacillin/tazobactam)		
30-day mortality										
1	observational studies	not serious	not serious	not serious	not serious	none	57/524 (10.9%)	51/524 (9.7%)	⨁⨁◯◯ low	CRITICAL
90-day mortality										
1	observational studies	not serious	not serious	not serious	not serious	none	82/524 (15.6%)	80/524 (15.3%)	⨁⨁◯◯ low	CRITICAL
ICU admission										
1	observational studies	not serious	not serious	not serious	not serious	none	26/515 (5.0%)	44/515 (8.5%)	⨁⨁◯◯ low	CRITICAL

Table S6. Question: Fluorquinolones compared to beta-lactam based regimen for treatment of (moderate) severe CAP

Bibliography: Finch 2002, Frank 2002, Lode 2002, Leophonte 2004, Erard 2004, Portier 2005, Welte 2005, Lin 2006, Xu 2006, Postma 2015. **Used systematic reviews:** Liu 2019, Raz-Pasteur 2015

Certainty assessment							№ of patients		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	fluorquinolones monotherapy	beta-lactam with or without macrolides		
All-cause mortality										
8	randomised trials	serious[a]	not serious	not serious	serious[b]	none	109/2039 (5.3%)	188/2516 (7.5%)	⊕⊕◯◯ Low	CRITICAL
Clinical treatment success										
9	randomised trials	serious[c]	not serious	not serious[d]	not serious	none	1376/1551 (88.7%)	1174/1376 (85.3%)	⊕⊕⊕◯ Moderate	CRITICAL
Length of hospital stay										
6	randomised trials	serious[e]	serious[f]	not serious	not serious	none	1610	2095	⊕⊕◯◯ Low	CRITICAL
Microbiological treatment success										
8	randomised trials	serious[g]	not serious	not serious	not serious	none	209/251 (83.3%)	201/250 (80.4%)	⊕⊕⊕◯ Moderate	IMPORTANT

a. None of the RCTs, except for Leophonte 2004, applied blinding. Lode 2002 and Erard 2004 do not describe the process of randomisation. Erard 2004 does not apply the intention to treat principle.
b. In all RCTs, except for Postma 2015, the absolute number of deaths per study group is very small (less than 10 events per study group).
c. None of the RCTs, except for Leophonte 2004, applied blinding. Lode 2002 and Xu 2006 do not describe the process of randomisation. Lee 2012 does not apply the intention to treat principle.
d. Postma 2015 provides only numbers of insufficient clinical recovery. We do not expect this to be a significant risk for the study outcome.
e. None of the RCTs applied blinding. Lode 2002 and Erard 2004 do not describe the process of randomisation. Erard 2004 does not apply the intention to treat principle.
f. The systematic review by Liu 2019 report moderate heterogeneity when calculating the mean duration for all trials. Although not all included trials were available to us (two were in Chinese language) we adopted this calculation.
g. None of the RCTs, except for Leophonte 2004, applied blinding. Lode 2002 and Xu 2006 do not describe the process of randomisation. Lee 2012 does not apply the intention to treat principle.

Table S7. Question: Moxifloxacin compared to beta-lactam based regimen for treatment of CAP, including patients with severe CAP

Bibliography: Finch 2002, Torres 2008.

Certainty assessment							№ of patients		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	moxifloxacin	beta-lactam based regimen		
clinical response after completion of treatment (<14 days) (follow-up: range 4 days to 14 days)										
2	randomised trials	serious[a]	not serious	not serious	not serious	none	494/546 (90.5%)	489/558 (87.6%)	⨁⨁⨁◯ Moderate	CRITICAL
mortality due to pneumonia										
1	randomised trials	not serious	not serious	not serious	serious[b]	none	18/368 (4.9%)	12/365 (3.3%)	⨁⨁⨁◯ Moderate	CRITICAL
bacterial response after completion of treatment (<14 days) (follow-up: range 4 days to 14 days)										
2	randomised trials	serious[a]	not serious	not serious	serious[c]	none	166/191 (86.9%)	163/194 (84.0%)	⨁⨁◯◯ Low	IMPORTANT

a. No blinding of patients in Finch et al. 2002
b. Small number of events
c. Less patients with a known causative pathogen results in wide confident intervals in both Finch et al 2002 and Torres et al 2008.

Table S8 Question: Fluorquinolone based regimen compared to macrolide based regimen for treatment of patients with severe CAP at the ICU

Bibliography: Used systematic review: Sligl 2014

Certainty assessment							№ of patients		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	fluorquinolone based regimen	macrolide based regimen		
short-term mortality (follow-up: 30 days)										
19	observational studies	not serious	not serious	not serious	not serious	none	511/2561 (20.0%)	386/1680 (23.0%)	⊕⊕◯◯ Low	CRITICAL

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