# Point of Care Testing

## Evidence-based developments following NICE guidelines

A report to the London RMOC Antimicrobial Stewardship Subcommittee

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## Background

In December 2014, NICE published it Clinical Guideline "Pneumonia in adults: diagnosis and management", which looked at the clinical and cost-effectiveness evidence of testing C-reactive protein, procalcitonin or performing a chest X-ray over using clinical assessment to inform antibiotic prescribing decisions and the need for hospital admission.

NICE made the following recommendation following a review of the evidence: [1]
"*For people presenting with symptoms of lower respiratory tract infection in primary care, consider a point of care C-reactive protein test if after clinical assessment a diagnosis of pneumonia has not been made and it is not clear whether antibiotics should be prescribed. Use the results of the C-reactive protein test to guide antibiotic prescribing in people without a clinical diagnosis of pneumonia as follows:*

- *Do not routinely offer antibiotic therapy if the C-reactive protein concentration is less than 20 mg/litre*
- *Consider a delayed antibiotic prescription (a prescription for use at a later date if symptoms worse) if the C-reactive protein concentration is between 20 mg/litre and 100 mg/litre*
- *Offer antibiotic therapy if the C-reactive protein concentration is greater than 100 mg/litre*"

### Summary of NICE

In forming its recommendation, NICE considered antibiotic prescription rates to be the outcome most directly relevant to this intervention. Other outcomes considered were mortality, hospital admission rates and quality of life, though NICE felt that these are indirectly associated with use of point of care testing in this indication. NICE identified eleven studies suitable for inclusion in their review. Three RCTs comparing CRP with usual care (four papers), two RCTs comparing PCT with usual care, one systematic review (2 papers) of 14 RCTs [only partially applicable because included patients with any acute respiratory infection, presenting in any setting, looking at both initial and follow-up measurements], and two observational studies looking at diagnostic test accuracy of PCT and CRP.

- Two studies (moderate quality evidence, N=538) showed a statistically significant reduction in antibiotic prescribing rate initially when CRP testing used: RR 0.61 [95% CI 0.5 to 0.75]
- Three studies (low quality evidence, N=4,802) showed a statistically significant reduction in antibiotic treatment at 28 days when CRP testing used: RR 0.69 [95% CI 0.6 to 0.8]
- Three studies (moderate quality evidence, N=4,802) showed no difference in terms of mortality at 28 days.
- Three studies showed a small, numerical trend towards additional hospitalisations in the CRP arm compared to standard care (moderate quality evidence, N=4,805). NICE noted that this did not clearly indicate whether the hospital admissions were appropriate
- There was no statistically significant impact on resolution of symptoms, the 28 day re-consultation rate, or mean patient reablement score [QoL] (moderate to very-low quality evidence)

There was a cost-utility analysis considered by NICE which calculated the incremental cost effectiveness ration for introduction of point-of-care CRP to be £7,364 per QALY gained. NICE chose to treat this analysis with caution because it was conducted in Scandinavia, and was based on an analysis that saw hospital admissions lower in the CRP group than the control group (which was contrary to NICE's findings). They conducted their own analysis and calculated an ICER of £15,763

per QALY (below the £20,000 per QALY threshold that NICE considers cost-effective). NICE felt that CRP testing had clinical advantages over PCT testing and cost less.

NICE reported on the areas of uncertainty within their analysis. They could not say, for instance, whether benefits from introduction of point-of-care testing would be equal across all practitioners (who have variable antibiotic prescribing rates). Whether increases in hospitalisation and re-consultation following CRP testing were appropriate is unknown. It is based on their uncertainties that NICE chose to phrase the recommendation as "consider" rather than to "offer" point-of-care testing.

There are some patient groups that have smaller CRP rises following serious infection (e.g. elderly, cirrhotic liver disease). NICE notes that the threshold for prescribing antibiotics following clinical assessment would be lower for these groups of patients.

The use of laboratory measurement of CRP (as opposed to point-of-care testing) was considered by NICE. It was felt that there are differences in these two approaches which may prejudice the applicability of findings across the groups. Specifically, it was felt that the interaction with the patient whilst point-of-care testing was being carried out would facilitate delivery of the message of rational antibiotic prescribing.

## Methods

A rapid review was conducted using Medline, EMBASE and Cochrane. The search terms were the same as those used by NICE to prepare Clinical Guideline 191 (see Appendix 1). Papers were excluded from this search if they related to children or infants, if the clinical condition under consideration wasn't LRTI or suspected community acquired pneumonia, if the studies were looking only at the prognostic benefit of CRP/PCT (as opposed to benefit as a diagnostic factor), or if they did not consider either CRP or PCT point-of-care testing. Date limits of 2014 to 2018 were applied to avoid duplication. As systematic review / meta-analysis data were available to augment NICE, lower-quality evidence was also excluded from this rapid review.

| | Systematic Review | Excluded | Reviewed |
|---|---|---|---|
| **EMBASE** | 112 | 107 | 5 |
| **Medline** | 17 | 16 | 1 (duplicate) |
| **Cochrane** | 7 | 5 | 2 (duplicate) |

All five reviews are discussed below.

## Systematic reviews

**Aabenhus *et al* (2014)** [2] conducted a systematic review of RCTs (3,284 participants, 139 children; 6 RCTs) looking at primary care treatment of acute respiratory tract infections, assessing the benefits and harms of using biomarkers as point-of-care tests to guide antibiotic treatment. Trials were included if they randomised individual patients or clusters of patients. Mean age of participants was 46 years (sd 17). The outcomes considered by this review were: impact on antibiotic use, impact on duration of/recovery from infection, complications (re-consultations, hospitalisations, mortality), and patient satisfaction. The authors of this Cochrane review contributed their findings to the NICE guideline. [1]

- Antibiotic prescribing: RR 0.78 [95CI 0.66 to 0.92] $I^2$=68% (6 trials)
    - Antibiotic prescribing (individually randomised trials): RR 0.90 [95CI 0.80 to 1.02] $I^2$=5%. Number needed to test (NNT) to save one antibiotic prescription is 20. (3 trials)

    - Antibiotic prescribing (cluster randomised trials): RR 0.68 [95CI 0.61 to 0.75] $I^2$=0%. Number needed to test (NNT) to save one antibiotic prescription is 6. (3 trials)
- Antibiotic prescribed within 28 days: RR 0.80 [95CI 0.67 to 0.96], $I^2$=40% (4 trials)
    - Antibiotic prescribed within 28 days (individually randomised trials): RR 0.87 [95CI 0.75 to 1.02], $I^2$=7% (2 trials)
    - Antibiotic prescribed within 28 days (cluster randomised trials): RR 0.68 [95CI 0.51 to 0.91], $I^2$=19% (2 trials)
- Patient recovery at 7 days: RR 1.03 [95CI 0.93 to 1.14], $I^2$=0% (3 trials)
- Mortality at 28 days: no deaths or serious complications were reported
- There were no significant differences in need of a re-consultation at 28 days
- Hospitalisations
    - Five of six studies reported no hospitalisation
    - One study reported 30/4264 hospitalisations (22 in CRP group vs. 8 in control, crude RR 2.53, 95% CI 1.13 to 5.66)
    - An adjustment was made to account for design effect of cluster RCTs, which removed the statistical significance (RR 2.45, 95CI 0.65 to 9.19)
    - Not all hospitalisations may have been related to use of the intervention. Absolute rate of hospitalisation was low. Data are not available to determine proportion of hospitalised patients initially withheld antibiotic treatment.
- Duration of acute respiratory infection: pooled analysis could not be performed
- Number of satisfied patients: no differences detected. $I^2$=45%, two studies only.
- Patients with substantial improvement at 28 days: No differences

The review authors could only identify studies that used C-reactive protein as a point-of-care test performed in primary care. The authors concluded that CRP can guide antibiotic use to treat acute respiratory tract infections in primary care, but the degree of antibiotic use reduction is uncertain. It should be used as an adjunct to clinical examination. There is a risk of increased hospitalisation.

**McDonagh *et al* (2018)** [3] published the findings of a structured review (only Medline, Cochrane and references were searched) looking at the impact of different interventions to reduce inappropriate use of antibiotics for acute respiratory tract infections. Twenty six interventions were identified in 95 studies. Included studies were RCTs and comparative observational studies.

This review looked at a range of different interventions to improve antibiotic use. There were seven studies included that looked specifically at CRP concentration. Measurement of CRP reduced overall antibiotic prescribing for acute respiratory tract infections by between 13% and 33%, with the range being driven in part by baseline prescribing level. There was an increase in return visits at 28 days (RR=1.64, 95CI 1.35 to 2.00, $I^2$=0%).

Conversely, this review highlighted the benefit from procalcitonin point of care testing. Antibiotic prescribing reduced by a mean of 12% to 72% (OR 0.14, 95% CI 0.09 to 0.22). No adverse effects were seen with use of procalcitonin (e.g. days limited activity, symptoms at 28 days, hospitalisations).

**Schuetz *et al* (2017)** published a Cochrane Review looking at the effects of using procalcitonin to guide starting or discontinuing antibiotics in people with acute respiratory infections. [4] The same systematic review was later published by the same authors in Lancet Infectious Diseases. [5] The Cochrane publication has been used for this summary.

The review included RCTs of adults with acute respiratory infections who received an antibiotic treatment following either a procalcitonin (PCT) guided algorithm, or usual care. Trials predominantly

in children, or focusing on use of PCT for something other than initiation or discontinuation of antibiotics were excluded. The primary end-points of this systematic review were “all-cause mortality” and “treatment failure at 30 days”. Antibiotic use, side-effects and length of hospital stay were secondary end-point.

**Table 4. Clinical endpoints overall and stratified by setting and ARI diagnosis**

| | Control group | PCT group | Measures of effect: adjusted OR or difference (95% CI), P value | P for interaction |
|---|---|---|---|---|
| **Overall** | 3372 | 3336 | | |
| 30 days mortality, n (%) | 336 (10.0%) | 286 (8.6%) | 0.83 (0.70 to 0.99), P = 0.037 | NA |
| Treatment failure, n (%) | 841 (24.9%) | 768 (23.0%) | 0.90 (0.80 to 1.01), P = 0.068 | NA |
| Length of ICU stay, mean (±SD) | 13.3 ± 16.0 | 13.7 ± 17.2 | 0.39 (-0.81 to 1.58), P = 0.524 | NA |
| Length of hospital stay, mean (±SD) | 13.7 ± 20.6 | 13.4 ± 18.4 | -0.19 (-0.96 to 0.58), P = 0.626 | NA |
| Antibiotic-related side effects, n (%) | 336 (22.1%) | 247 (16.3%) | 0.68 (0.57 to 0.82), P < 0.001 | NA |
| **According to setting** | | | | |
| **Primary care** | 501 | 507 | | |
| 30 days mortality, n (%) | 1 (0.2%) | 0 (0.0%) | NA | NA |
| Treatment failure, n (%) | 164 (32.7%) | 159 (31.4%) | 0.96 (0.73 to 1.25), P = 0.751 | 0.715 |
| Days with restricted activities, mean (±SD) | 8.9 ± 4.2 | 8.9 ± 4.1 | 0.07 (-0.44 to 0.59), P = 0.777 | NA |
| Antibiotic-related side effects, n (%) | 128 (25.7%) | 102 (20.2%) | 0.65 (0.46 to 0.91), P = 0.012 | 0.596 |

The only outcome statistically significant for the primary care cohort was an improvement in antibiotic-related side effects in the PCT group, which supports the argument that use of near patient testing will help reduce the burden of side effects from these medicines. Unfortunately, it was not possible to estimate impact on mortality in the primary care setting (due to the very low absolute rate), though overall there was a statistically significant reduction in 30 day mortality by using PCT testing.

Table 6. Antibiotic treatment overall and stratified by setting and ARI diagnosis

| Parameter | Control group | PCT group | Measures of effect: adjusted OR or difference (95% CI), P value | P for interaction |
|---|---|---|---|---|
| **Overall** | 3372 | 3336 | | |
| Initiation of antibiotics, n (%) | 2894 (86.3%) | 2351 (71.5%) | 0.27 (0.24 to 0.32), P < 0.001 | |
| Duration of antibiotics (days), mean (±SD) | 9.4 ± 6.2 | 8.0 ± 6.5 | -1.83 (-2.15 to -1.50), P < 0.001 | |
| Total exposure of antibiotics (days), mean (±SD) | 8.1 ± 6.6 | 5.7 ± 6.6 | -2.43 (-2.71 to -2.15), P < 0.001 | |
| **Setting-specific outcomes** | | | | |
| **Primary care** | 501 | 507 | | |
| Initiation of antibiotics, n (%) | 316 (63.1%) | 116 (22.9%) | 0.13 (0.09 to 0.18), P < 0.001 | < 0.001 |
| Duration of antibiotics (days), mean (±SD) | 7.3 ± 2.5 | 7.0 ± 2.8 | -0.52 (-1.07 to 0.04), P = 0.068 | 0.064 |
| Total exposure of antibiotics (days), mean (±SD) | 4.6 ± 4.1 | 1.6 ± 3.2 | -3.02 (-3.45 to -2.58), P < 0.001 | 0.101 |

Initiation of antibiotics and total exposure to antibiotics was statistically significantly reduced in the PCT testing, primary care cohort.

**Minnaard *et al* (2017)** [6] conducted a systematic review and meta-analysis of individual patient data to assess the value of adding CRP-measurement into the diagnostic process for community acquired pneumonia in primary care. Included studies where participants were adults, and suspected by their doctor of having a lower respiratory tract infection. The outcomes measured were correct identification of pneumonia ("discrimination between patients with and without pneumonia") and improved risk classification. The authors created a model to estimate diagnostic prediction of pneumonia. There were eight studies (n=5308) included in this meta-analysis. Risk of bias or external validity were assessed; 5 studies were found to have a risk of bias, relating in 3 studies to the way chest x-ray was ordered.

The study authors reported that adding CRP measurement to the diagnosis of suspected pneumonia in primary care improved discrimination and risk classification of patients. This meta-analysis reported results in a different way from Cochrane discussed above, for example by not focussing on mortality, antibiotic use, or duration of antibiotics.

**Tonkin-Crine *et al* (2017)** [7] published an overview of systematic reviews to synthesise evidence about interventions used to influence antibiotic prescribing behaviour in acute respiratory tract infections. There were two systematic reviews identified by these authors which looked at the effect of CRP testing on the change in antibiotic prescribing: Aabenhus 2014 (discussed above, [2]) and Huang 2013 (published before NICE released its guideline). These provided moderate-quality evidence that CRP testing *probably* reduces antibiotic prescribing in general practice. The authors of this review commented on the three trials in Huang 2013 that were not also reported in Aabenus 2014. Two of these trials looked at antibiotic prescribing in general practice, and showed that CRP testing decreased antibiotic prescriptions compared to usual care (Cals 2011: RR 0.57 [95CI 0.44 to 0.71; 330 participants] and Cals 2013: RR 0.58 [95CI 0.45 to 0.74; 379 participants]).

Aabenhus 2014 reported moderate-quality evidence that there was little or no difference in adverse events between CRP testing and usual care.

The review authors concluded that there was moderate-quality evidence that point-of-care CRP testing safely reduced antibiotic prescribing in acute respiratory tract infection management, without impacting on symptom duration, patient satisfaction or reconsultation.

## Summary

NICE Clinical Guideline 191 advised that clinicians should consider a point of care test if there are symptoms of lower respiratory tract infection but diagnosis of pneumonia is not made and it is unclear whether antibiotics should be prescribed. This recommendation was published in 2014.

Point-of-care CRP testing falls within the cost-effectiveness ration that NICE considers a good use of NHS resources, but there was uncertainty in their analysis.

The word “consider” is used within this NICE guideline rather than “recommend”. “Consider” is a weaker term that reflects the uncertainty with regards to clinical evidence base. It should be noted that “consider” is a more positive suggestion than “do not recommend”.

Of the systematic reviews considered in this paper, the most relevant (Aabenhus et al) was published soon after the NICE Clinical Guideline, and contributed its data to the CG. They concluded that there is a degree of reduction in antibiotic use following use of CRP testing, but this is uncertain, it may increase hospitalisation, but is something that could be used as an adjunct to clinical diagnosis.

One review identified that CRP measurement as part of diagnostic workup in primary care could improve discrimination of pneumonia and contribute to the risk assessment.

A review of reviews concluded, based on the findings of two systematic reviews, that there is moderate quality evidence that CRP testing probably reduces antibiotic prescribing. This was without impact on symptom duration, patient satisfaction or reconsultation.

Two of the reviews were looking at procalcitonin rather than CRP testing.

These additional systematic reviews are consistent with NICE’s findings, therefore consideration should be given to adding CRP-testing to the diagnostic workup when pneumonia is suspected.

A limitation of this rapid review is that it did not look at RCT evidence, which means some trials that have not yet found their way into systematic reviews will not have been picked up in this review.

## References


[1] NICE, “Pneumonia: Diagnosis and management of community and hospital acquired pneumonia in adults. CG 191,” NICE, Manchester, 2014.

[2] R. Aabenhus, J. Jensen, K. Jorgensen, A. Hrobjartsson and L. Bjerrum, “Biomarkers as point-of-care tests to guide prescription of antibiotics in patients with acute respiratory infections in primary care (Review),” *Cochrane Database of Systematic Reviews,* no. 11, p. CD010130, 2014.

[3] M. McDonagh, K. Peterson, K. Winthrop, A. Cantor, B. Lazur and D. Buckley, “Interventions to reduce inappropriate prescribing of antibiotics for acute respiratory tract infections: summary and update of a systematic review,” *Journal of International Medical Research,* vol. 46, no. 8, pp. 3337 - 3357, 2018.

[4] P. Schuetz, Y. Wirz, R. Sager, M. Christ-Crain, D. Stolz, M. Tamm, L. Bouadma, C. Luyt, M. Wolff, J. Chastre, F. Tubach, K. Kristoffersen, O. Burkhardt, T. Welte, S. Schroeder, V. Nobre, L. Wei, H. Bucher, N. Bhatnagar, D. Annane, K. Reinhart, A. Branche, P. Damas, M. Nijsten, D. de Lange, R. Deliberato, S. Lima, V. Maravic-Stojkovic, A. Verduri, B. Cao, Y. Shehabi, A. Beishuizen, J. Jensen, C. Corti, J. Van Oers, A. Falsey, E. de Jong, C. Oliveira, B. Beghe, M. Briel and B. Mueller, “Procalcitonin to initiate or discontinue antibiotics in acute respiratory tract infections.,” *Cochrane Database of Systematic Reviews,* no. 10, p. CD007498, 2017.

[5] P. Schuetz and et al, “Effect of procalcitonin-guided antibiotic treatment on mortality in acute respiratory infections: a patient level meta-analysis,” *Lancet Infectious Diseases,* vol. 18, pp. 95 - 107, 2018.

[6] M. Minnaard, J. de Groot, R. Hopstaken, A. Schierenberg, N. de Wit, J. Reitsma, B. Broekhuizen, S. van Vugt, A. Neven, A. Graffelman, H. Melbye, T. Rainer, J. Steurer, A. Holm, R. Gonzales, G. Dinant, A. van de Pol and T. Verheij, “The added value of C-reactive protein measurement in diagnosisng pneumonia in primary care: a meta-analysis of individual patient data,” *CMAJ,* no. doi: 10.1503/cmaj.151163, pp. E56-E63, 2017.

[7] S. Tonkin-Crine, P. Tan, O. van Hecke, K. Wang, N. Roberts, S. McCullough, M. Hansen, C. Butler and C. Del Mar, “Clinician-targeted interventions to influence antibiotic prescribing behaviour for acute respiratory infections in primary care: an overview of systematic reviews.,” *Cochrane Database of Systematic Reviews,* no. 9, p. CD012252, 2017.

# Appendix 1

## Medline

| # | Search term | Results |
|---|---|---|
| 1 | exp "PRIMARY HEALTH CARE"/ | 518099 |
| 2 | exp "PRACTICE PATTERNS, PHYSICIANS"'/ | 53410 |
| 3 | exp "FAMILY PRACTICE"/ | 64100 |
| 4 | exp "PHYSICIANS, PRIMARY CARE"/ | 2724 |
| 5 | exp "GENERAL PRACTICE"/ | 72440 |
| 6 | exp "PHYSICIANS, FAMILY"/ | 15887 |
| 7 | exp "GENERAL PRACTITIONERS"/ | 6451 |
| 8 | exp "REFERRAL AND CONSULTATION"/ | 69032 |
| 9 | ((primary OR communit*) ADJ5 care).ti,ab | 151685 |
| 10 | (family practi* OR family doctor* OR family physician* OR gp* OR general practi*).ti,ab | 319133 |
| 11 | exp "OUTPATIENT CLINICS, HOSPITAL"/ | 16661 |
| 12 | exp "AMBULATORY CARE"/ | 50456 |
| 13 | exp "COMMUNITY HEALTH SERVICES"/ | 289161 |
| 14 | (casualty).af | 6255 |
| 15 | "COMMUNITY-ACQUIRED INFECTIONS"/ | 12955 |
| 16 | (community acquired).ti,ab | 21037 |
| 17 | (1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7 OR 8 OR 9 OR 10 OR 11 OR 12 OR 13 OR 14 OR 15 OR 16) | 1317129 |
| 18 | "C-REACTIVE PROTEIN"/ | 41551 |
| 19 | (crp).ti,ab | 41024 |
| 20 | (c reactive protein).ti,ab | 70941 |
| 21 | (c reactive protein*).ti,ab | 73186 |
| 22 | (18 OR 19 OR 20 OR 21) | 93005 |
| 23 | (17 AND 22) | 4295 |
| 24 | 23 [DT 2014-2018] [Document type Meta-analysis] [Languages English] [Humans] | 17 |
| 25 | 23 [DT 2014-2018] [Document type Clinical Study OR Clinical Trial OR Clinical Trial, Phase I OR Clinical Trial, Phase Ii OR Clinical Trial, Phase Iii OR Clinical Trial, Phase Iv OR Controlled Clinical Trial OR Randomized Controlled Trial] [Languages English] [Humans] | 232 |

## EMBASE

| # | Search term | Results |
|---|---|---|
| 1 | exp PRIMARY HEALTH CARE/ | 150291 |
| 2 | exp "PROFESSIONAL PRACTICE"/ | 328107 |
| 3 | exp "CLINICAL PRACTICE"/ | 248837 |
| 4 | exp "GENERAL PRACTICE"/ | 73570 |
| 5 | "PATIENT REFERRAL"/ | 95124 |
| 6 | ((primary OR communit*) ADJ5 care).ti,ab | 195125 |
| 7 | (family practi* OR family doctor* OR family physician* OR gp* OR general pract*).ti,ab | 306886 |
| 8 | exp "OUTPATIENT DEPARTMENT"/ | 55597 |
| 9 | exp "AMBULATORY CARE"/ | 44327 |
| 10 | exp "COMMUNITY CARE"/ | 107786 |
| 11 | "HEALTH CENTER"/ | 30276 |
| 12 | (casualty*).af | 6768 |
| 13 | (communicable disease).ti,ab | 3290 |
| 14 | (community acquired).ti,ab | 23735 |
| 15 | "COMMUNICABLE DISEASE"/ | 20581 |
| 16 | (1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7 OR 8 OR 9 OR 10 OR 11 OR 12 OR 13 OR 14 OR 15) | 1282905 |
| 17 | exp "C REACTIVE PROTEIN"/ | 149173 |
| 18 | (crp).ti,ab | 81482 |
| 19 | (c reactive protein*).ti,ab | 85235 |
| 20 | PROCALCITONIN/ | 9862 |
| 21 | (pro-calcitonin).ti,ab | 66 |
| 22 | (procalcitonin).ti,ab | 7501 |
| 23 | (17 OR 18 OR 19 OR 20 OR 21 OR 22) | 187934 |
| 24 | (16 AND 23) | 9968 |
| 25 | 24 [DT 2014-2018] [English language] [Humans] [Evidence based medicine Meta Analysis OR Systematic Review] | 110 |
| 26 | 24 [DT 2014-2018] [English language] [Humans] [Clinical trials Clinical Trial OR Randomized Controlled Trial OR Controlled Clinical Trial OR Phase 1 Clinical Trial OR Phase 2 Clinical Trial OR Phase 3 Clinical Trial OR Phase 4 Clinical Trial] | 427 |

## Cochrane

| | | |
|---|---|---|
| #1 | ((primary or communit* or ambulatory) near/5 (care or health)):ti,ab,kw | 29939 |
| #2 | (family practi* or family doctor* or family physician* or gp* or general practi*):ti,ab,kw | 26198 |
| #3 | casualty*:ti,ab,kw | 162 |
| #4 | community acquired:ti,ab,kw | 1978 |
| #5 | MeSH descriptor: [Referral and Consultation] explode all trees | 2074 |
| #6 | MeSH descriptor: [Outpatient Clinics, Hospital] explode all trees | 640 |
| #7 | MeSH descriptor: [Practice Patterns, Physicians'] explode all trees | 1147 |
| #8 | #1 or #2 or #3 or #4 or #5 or #6 or #7 | 53965 |
| #9 | ((chest or thorax or thoracic or lung* or bronch* or trachea*) near/2 (x-ray or xray or imag* or radiogra* or radiol*)):ti,ab,kw | 3300 |
| #10 | crp:ti,ab,kw | 9536 |
| #11 | c reactive protein*:ti,ab,kw | 13417 |
| #12 | (procalcitonin or pro-calcitonin):ti,ab,kw | 613 |
| #13 | MeSH descriptor: [Radiography, Thoracic] explode all trees | 345 |
| #14 | #9 or #10 or #11 or #12 or #13 | 19940 |
| #15 | #8 and #14 with Cochrane Library publication date Between Jan 2014 and Nov 2018, in Cochrane Reviews | 7 |

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