Original Article

C-reactive protein testing to reduce antibiotic prescribing for acute respiratory infections in adults: a systematic review and meta-analysis

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Background: Antimicrobial resistance (AMR) has become a worldwide public health problem. Abuse of antibiotic in acute respiratory tract infections (ARI) contributes to the increasing AMR. C-reactive protein (CRP) testing may help reduce antibiotic overprescribing, but the available evidence quality varies widely. There is no meta-analysis of CRP testing to guide the antibiotic prescribing for adult ARI. Therefore, we conducted this meta-analysis to determine the effectiveness of CRP testing to guide antibiotic prescribing in adult ARI.

Methods: We searched the Cochrane Library, PubMed, and EMBASE databases for randomized controlled trials (RCTs) involving our meta-analysis from the establishment of these databases until January 16, 2021. Two reviewers extracted the data separately and pooled the data using RevMan5.3. The evidence quality was appraised strictly with GRADE system.

Results: Seven studies included with 3,614 patients. Compared with routine care, CRP testing reduced antibiotic prescribing rate at the index consultation significantly [risk ratio (RR) =0.76; 95% confidence interval (CI): 0.68–0.85; P<0.00001], and during 28 days follow-up (RR =0.77; 95% CI: 0.73–0.81; P<0.00001). There were no significant differences between CRP testing and routine care in clinical recovery of patients within 7 days (RR =0.95; 95% CI: 0.90–1.01; P=0.08). Moreover, adverse events were not significantly different between CRP testing and routine care.

Discussion: CRP testing can reduce the antibiotic prescribing rate at index consultation and during 28 days follow-up. These findings support the conclusion that CRP testing is valuable to guide the antibiotic prescribing for adult ARI.

Keywords: C-reactive protein (CRP); antibiotic; acute respiratory infections; randomized controlled trials (RCTs); meta-analysis

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Introduction

Antimicrobial resistance (AMR) has become one of the major public health problems because of antibiotic abuse (1-4). AMR not only increases the mortality of infectious diseases, but also brings some social problems and economic burden (5,6). The prescription of inappropriate antimicrobials is directly related to the AMR (7). The available evidences indicate that some biomarkers guide the antibiotic prescribing can reduce mortality and antibiotic prescribing rate (8-11). However, this remains controversial (12).

Acute respiratory tract infections (ARI) is one of the most common acute diseases that promotes the general practitioner (GP) to prescribe antibiotic in primary care. However, the pathogens of ARI are most virals and bacterias with mild self-limited (13,14). Therefore, the antibiotic prescribing for ARI need appropriate guidance. C-reactive protein (CRP) is a biomarker of inflammatory process (15,16). CRP activates the classical complement pathway to stimulate bacterial phagocytosis in bacterial infection. When the bacterial inflammatory factors are eliminated, the level of CRP decreases rapidly (17-19).

At present, several guidelines recommend CRP testing to guide antibiotic prescribing (20-22). Therefore, it is necessary to design reasonable meta-analysis for high-quality clinical studies. A Cochrane review confirmed that CRP could reduce the antibiotic prescription in ARI patients (23). However, this review was published in 2014, and many high-quality clinical studies have been published recently. A review includes intervention studies and observational studies, and the participants were adults and children, resulting in greater heterogeneity (24). A systematic review focused on acute infections in ambulatory care of adults and children, including randomized controlled trials (RCTs) and non-RCTs (25). A recent review included RCTs and cluster RCTs, while the participants were adults and children (26). In summary, the four related reviews (23-26) conducted the meta-analysis of CRP testing to guide antibiotic prescribing, but none of those reviews analysed adults separately. Moreover, the quality of the studies was varied, which affected the reliability of the conclusion. Therefore, we conducted a meta-analysis based on RCTs instead of cluster trials and only adults were chosen, to provide high-quality clinical evidence for CRP testing to reduce antibiotic prescribing in adult ARI.

We present the following article in accordance with the PRISMA reporting checklist (available at https://jtd.amegroups.com/article/view/10.21037/jtd-21-705/rc).

Methods

Search strategy

We searched databases of PubMed, Cochrane clinical trial database and Embase using search terms comprising medical subject headings (MeSH) and free-text terms from their inception to January 16, 2021 without language restrictions. The key search terms as following: C-reactive protein, antibacterial agents, RCT. We also checked references of the previous reviews to identify additional potentially eligible studies. The retrieval strategy is shown in Appendix 1.

Eligibility criteria

(I) Participants: adults (≥18 years) were diagnosed with ARI. (II) Intervention: the intervention was CRP testing; the comparator was routine care. (III) Outcomes: the primary outcomes were antibiotic prescribing rate at the index consultation and during 28 days follow-up. The secondary outcome measures were patient clinical recovery within 7 days and the adverse events. (IV) Studies type: RCTs.

Exclusion criteria

(I) Conference abstracts with no corresponding full article published in journal. (II) Duplicate publications. (III) Study protocol. (IV) Cluster RCTs.

Study selection

First of all, duplicated and non-relevant studies were excluded, then non-ARI studies, non-adult related studies, non-RCTs and cluster-RCTs were excluded through examining titles and abstracts. And literatures that satisfactory with the enrolling criteria were screened out by reading the full text finally.

Data extraction

Two reviewers (YL and ZC) extracted the data, assessed the quality and content of the data independently. Disagreements were solved by consultation with the third reviewers (KZ). The contents of information were extracted as follow: first author, years of publication, country, characteristics of participants, CRP level as the recommended threshold, treatment duration, follow-up duration and outcomes.

Quality assessment

Three reviewers (KX, KZ and CZ) independently assessed the quality of the included studies. We used the Cochrane Collaboration's tool to assess risk of bias (27). The assessment details included sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessors, incomplete outcome data, selective reporting, and other sources of bias. Each domain was assessed as "low risk", "high risk" or "unclear risk".

Statistical analysis

The data analyses were accomplished by Review Manager 5.3 software. All the outcomes are consistent with dichotomous outcomes, so we use risk ratio (RR) with 95% confidence interval (CI) to calculate the data. The heterogeneity was high among the studies (I^2 >50%) of antibiotic prescribing rate at the index consultation, and the random effect model was chosen. The heterogeneity was low among the studies (I^2 <50%) of the others outcomes, and the fixed effect model was selected for data analysis. The factors that affect the heterogeneity were found out by sensitivity analysis and subgroup analysis.

Evidence quality assessment

We use the GRADE system (28) to evaluate the evidence quality for the outcome measures, and the evidence quality was divided into four levels: high, moderate, low, or very low. Evidence of RCTs is regarded as high quality, but the credibility would be decreased if there were inconsistency of results.

Results

Studies retrieved

A total of 2,028 studies were identified. After removing duplicates and screening of the titles and abstracts, 34 studies were deemed potentially eligible. After reviewing the full-text articles, 7 trials (29-35) were included in the final analysis. The screening process was summarized in a flow diagram (*Figure 1*).

Characteristics of included studies

A total of 3,614 patients were included, and 1,868 patients were in the CRP testing group, while the others were in the routine care group. Six of seven studies included only adults (29-31,33-35), while one study included both adults and children (32). We only extracted data about adults. Patients in three studies were low ARI, included only acute exacerbation of chronic obstructive pulmonary disease (AECOPD) (29,30,35), while in four studies were upper ARI, included rhinosinusitis, rhinitis, pharyngitis and acute cough (31-34). The detailed information of included studies is shown in *Table 1*.

Assessment of risk of bias

Six of seven studies (29,30,32-35) reported funding or conflicts of interest which showed there were no interest-related and conflicts among researchers. All of these seven studies were RCTs. Moreover, specific randomized methods and specific random hidden assignments were mentioned. The blind method was not used in all studies. The detailed assessment was provided in *Figures 2,3*.

Antibiotic prescribing rate at the index consultation

Antibiotic prescribing rate at the index consultation was reported in seven studies (29-35). There was significant heterogeneity (I^2 =63%), hence, the random effect model was used. The antibiotic prescribing rate in the CRP group was lower compared with the routine care significantly (RR =0.76; 95% CI: 0.68–0.85; P<0.00001) (*Figure 4*). The factors affecting the heterogeneity were found out by sensitivity analysis. We found that the heterogeneity disappeared when one studies was excluded (31). Therefore, we infered that heterogeneity mentioned above might come from this study (Table S1).

Antibiotic prescribing rate during 28 days

Antibiotic prescribing rate during 28 days follow-up was reported in four studies (30,32,34,35). The between-study heterogeneity was low (I^2 =0%), therefore, the fixed effect model was used. It showed that CRP testing significantly decreased the antibiotic prescribing rate during 28 days follow-up compared with the routine care (RR =0.77; 95% CI: 0.73–0.81; P<0.00001) (*Figure 5*).

The clinical recovery of patients within 7 days

Two studies (31,33) reported the clinical recovery of patients within 7 days. There was no significant heterogeneity

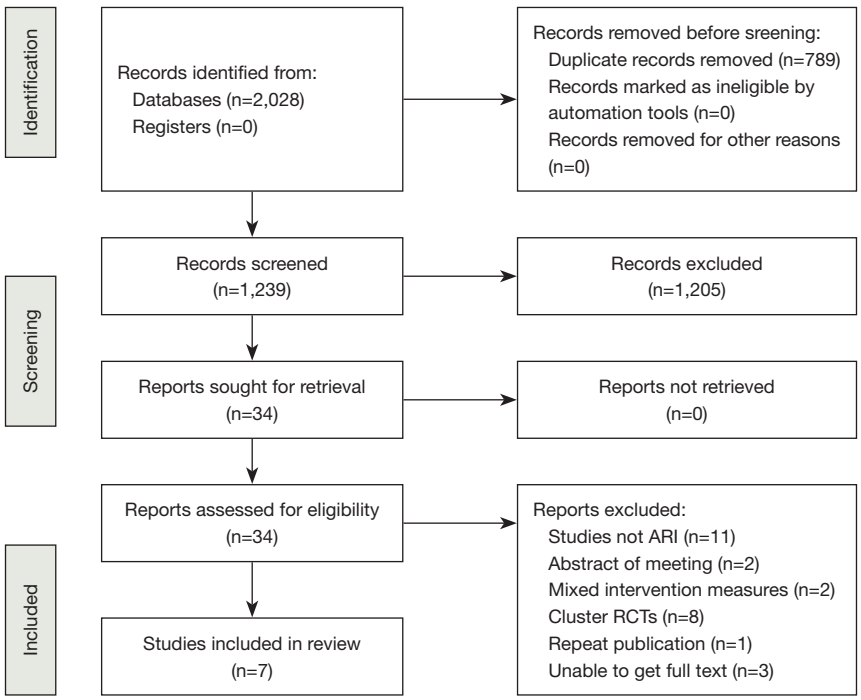

Figure 1 Study identification and process for selection of studies included in the review. ARI, acute respiratory tract infections; RCTs, randomized controlled trials.

(I^2 =0%), therefore, the fixed effect model was chosen. It showed that there were no significant differences about the recovery of patients within 7 days between the CRP testing and routine care (RR =0.95; 95% CI: 0.90–1.01; P=0.08) (*Figure 6*).

Adverse events

Five studies (29,30,32,33,35) reported the adverse events. Trails-related adverse events were found in three (29,30,32) studies. We gave up the meta-analysis of adverse events and only made a descriptive analysis because of great heterogeneity. All of the studies showed that there were no differences between the two groups about adverse events. Detailed adverse events were showed in Table S2.

Subgroup analysis

We made the subgroup analyses of antibiotic prescribing rate at the index consultation. The subgroup analysis was conducted by different types of ARI and different CRP levels as recommended of antibiotic prescribing. It showed that CRP testing reduce the antibiotic prescribing rate compared with the routine care in low ARI significantly (RR =0.71; 95% CI: 0.65–0.78; P<0.00001), but not in upper ARI (RR =0.83; 95% CI: 0.66–1.03; P=0.09). Subgroup analyses by different CRP levels as recommended threshold showed that using of 40 mg/L as the recommended threshold was the most obvious to reduce the antibiotic prescribing compared with the routine care. However, there were no significant differences between CRP testing and routine care using 50 mg/L as the recommended (Table S3).

Quality of evidence

According to the outcome's measures, the quality of antibiotic prescribing rate at the index consultation was moderate, and the quality of antibiotic prescribing rate during 28 days follow-up, patient clinical recovery within 7 days and adverse events were high. The GRADE evidence profiles of the primary outcomes are shown in *Table 2*.

Discussion

Main findings

This review included seven trials about CRP testing reducing antibiotic prescribing for ARI. The participants

Table 1 Basic information of included studies

Study ID	Country	Upper ARI/ low ARI	n (male/female)		Average age (year)		CRP threshold	Treatment duration	Follow-up duration	Outcome measurements
			CRP testing	Routine care	CRP testing	Routine care				
Prins 2019 (29)	The Netherlands	Low ARI	101 (41/60)	119 (67/52)	68.4±12.0	70.8±11.8	50 mg/L	–	1 year	①④
Butler 2019 (30)	United Kingdom	Low ARI	325 (162/163)	324 (173/151)	67.8±9.53	68.3±9.31	40 mg/L	4 weeks	6 months	①②④
Diederichsen 2000 (31)	Denmark	Upper ARI	414 (182/232)	398 (165/233)	37 (0–84)	37 (0–90)	50 mg/L	1 week	–	①③
Do 2016 (32)	Vietnam	Upper ARI	507	501	16 (8–39)	15 (8–41)	100 mg/L	5 days	2 weeks	①②④
Cals 2010 (33)	The Netherlands	Upper ARI	129 (41/88)	129 (38/91)	43.0	45.5	100 mg/L	7 days	28 days	①③
Gonzales 2011 (34)	United States	Upper ARI	67 (23/44)	61 (19/42)	–	–	100 mg/L	–	30 days	①②
Francis 2020 (35)	United Kingdom	Low ARI	325 (162/163)	324 (173/151)	68.7±9.53	68.3±9.31	40 mg/L	4 weeks	6 months	①②

Outcomes: ①, antibiotic prescribing rate at the index consultation; ②, antibiotic prescribing rate in 28 days follow-up; ③, patient recovery within 7 days; ④, adverse reactions. ARI, acute respiratory tract infections; CRP, C-reactive protein.

were adults, and all the included studies were RCTs. We assessed the outcomes of antibiotic prescribing rate at the index consultation and during 28 days follow-up, patient clinical recovery within 7 days and the adverse events. We concluded that CRP testing could reduce antibiotic prescribing in adult ARI.

At present, the prescribing of antibiotic is unreasonable seriously (36,37). Antibiotic abuse is the main reason of drug resistance and makes adverse reaction risk increase (38-40). Therefore, rational reduction of antibiotic prescriptions is worthwhile and meaningful. The results of this study showed that CRP testing can reduce the antibiotic prescribing in ARI. Subgroup analysis by different types of ARI showed that CRP testing significantly reduce the antibiotic prescribing rate compared with the routine care in low ARI (Table S2).

Inappropriate antibiotics prescription is not only abuse of antibiotics, but also lack of antibiotics prescription, which makes the infection uncontrollable and increases the mortality of infectious diseases. Meta-analysis of the clinical recovery of patients within 7 days and adverse events found that CRP testing guide the antibiotic prescribing in ARI did not affect patient clinical recovery, and there was no evidence of serious adverse events associated with CRP testing. It showed that CRP testing was safe to guide the use of antibiotics for ARI, and would not affect the therapeutic effects.

Previous similar reviews (23-26) found that CRP testing might reduce the antibiotic prescribing, but showed uncertain degree of antibiotic reduction. The Cochrane review (23) showed that CRP testing could reduce antibiotic prescribing, but might increase hospital admissions. Subgroup analysis found that individual RCTs showed non-significant relative reduction of antibiotic prescribing. Petel *et al.* (24) found that CRP testing can reduce antibiotic prescribing in newborns and adults, but the numbers of studies were small relatively, including interventional and observational studies, with high heterogeneity. A review (25) showed that CRP testing could reduce the antibiotic prescribing combined with clinical guidance, but the differences disappeared in two groups when absence of clinical guidance. A recent study (26) observed that CRP testing could reduce immediate antibiotic prescribing in primary care, but might increase re-consultations. Our review showed that CRP testing could reduce the antibiotic prescribing in adult ARI based on the individual RCTs. We excluded deviations due to enrolled population and study type, and the conclusion had high credibility.

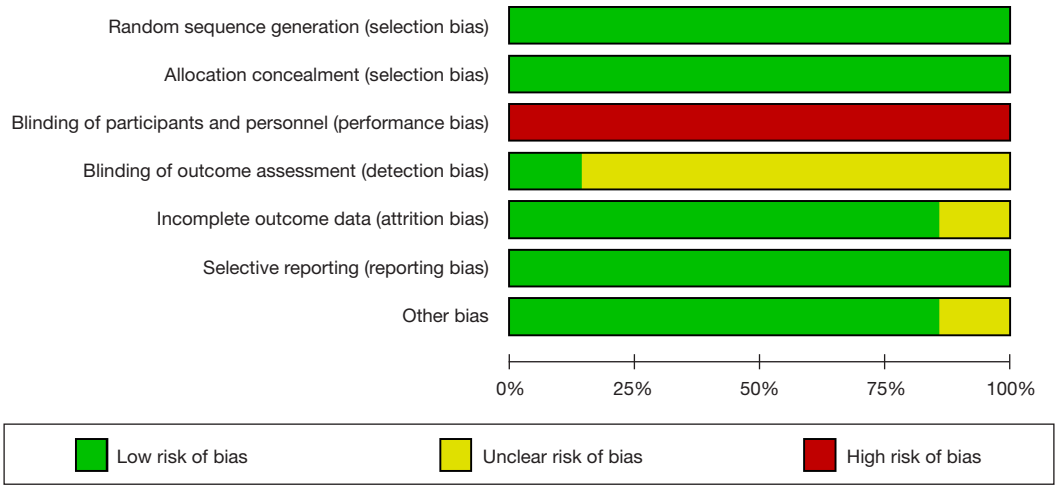

Figure 2 Risk of bias graph.

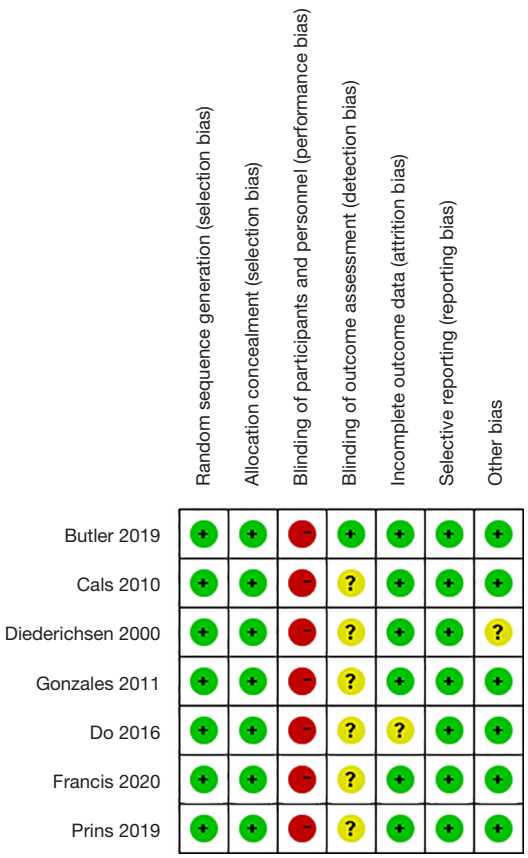

Figure 3 Risk of bias graph.

CRP and COVID-19

COVID-19 is the highly pathogenic SARS coronavirus pneumonia that infects human. Inflammatory reaction plays a critical role in COVID-19. Inflammatory storm can increase the severity of COVID-19 and leads to serious complications and death (41-43). CRP is a biomarker of inflammatory response, which can predict the severity and prognosis of COVID-19 (44,45). A retrospective study conducted in China found that patients with CRP level >41.8 mg/L in COVID-19 were more vulnerable to develop severe disease (46). A study on COVID-19 patients who need mechanical ventilation shows that CRP testing can be used to guide escalation of treatment in patients with COVID-19–related hyperinflammatory syndrome (47). However, the pathogen of COVID-19 is coronavirus, while antibiotics are aimed at bacterial infection. Therefore, CRP testing cannot be used as the guide to antibiotic prescribing for patients with COVID-19. For patients with overactivated inflammatory response in COVID-19, recent research recommended glucocorticoid for anti-inflammatory treatment (48,49).

Suggestions for future research

There is no unified standard for using antibiotic according to the level of CRP at present. One guidance suggested

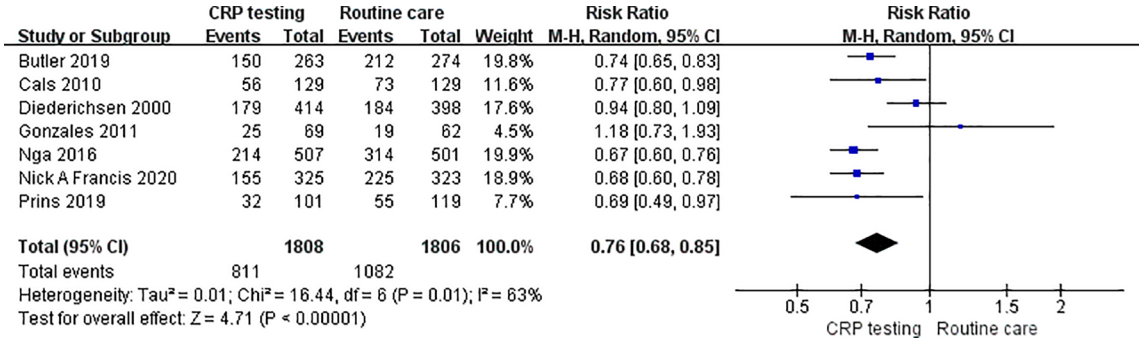

Figure 4 CRP testing group versus routine care group, antibiotic prescribing rate at the index consultation. CRP, C-reactive protein; M-H, Mantel-Haenszel; CI, confidence interval.

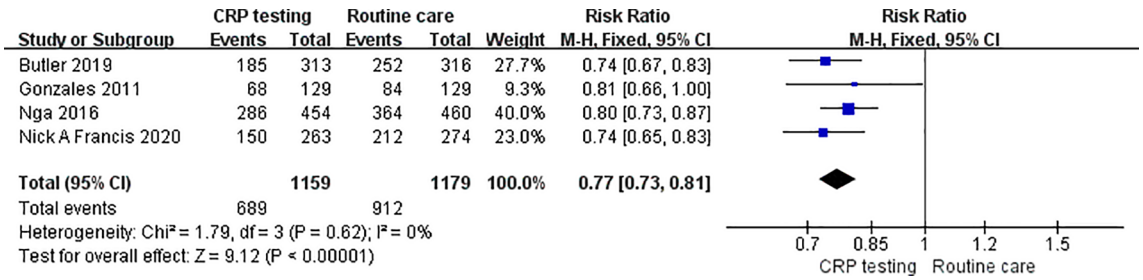

Figure 5 CRP testing group versus routine care group, antibiotic prescribing rate during 28 days follow-up. CRP, C-reactive protein; M-H, Mantel-Haenszel; CI, confidence interval.

Figure 6 CRP testing group versus routine care group, the recovery of patients within 7 days. CRP, C-reactive protein; M-H, Mantel-Haenszel; CI, confidence interval.

that antibiotic prescribing was beneficial when CRP level was higher than 40 mg/L (50). DCGP guidelines suggest that antibiotic should not be used when the CRP level is lower than 20 mg/L, while should be used immediately when CRP level was higher than 100 mg/L (51). One trial conducted in Thailand and Myanmar (52) using CRP testing with a threshold of 20 and 40 mg/L to guide antibiotic prescribing in febrile patients, and found that CRP testing with a threshold of 40 mg/L could reduce antibiotic prescribing significantly. Therefore, it is meaningful to choose different CRP level to guide the use of antibiotic, and further experiments can be designed to verify the best recommended threshold of CRP. Our review showed that CRP testing did not affect therapeutic effects.

Table 2 Quality of evidence

Certainty assessment							No. of patients		Effect		Certainty	Importance
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	CRP testing	Routine care	Relative (95% CI)	Absolute (95% CI)		
Antibiotic prescribing rate at the index consultation												
7	Randomised trials	Not serious	Serious[a]	Not serious	Not serious	None	811/1,808 (44.9%)	1,082/1,806 (59.9%)	RR: 0.75 (0.70 to 0.80)	150 fewer per 1,000 (from 180 fewer to 120 fewer)	⊕⊕⊕○ Moderate	Critical
Antibiotic prescribing rate during 28 days follow-up												
4	Randomised trials	Not serious	Not serious	Not serious	Not serious	None	689/1,159 (59.4%)	912/1,179 (77.4%)	RR: 0.77 (0.73 to 0.81)	178 fewer per 1,000 (from 209 fewer to 147 fewer)	⊕⊕⊕⊕ High	Critical
Patient clinical recovery within 7 days												
2	Randomised trials	Not serious	Not serious	Not serious	Not serious	None	384/525 (73.1%)	384/509 (75.4%)	RR: 0.95 (0.90 to 1.01)	38 fewer per 1,000 (from 75 fewer to 8 more)	⊕⊕⊕⊕ High	Important
Adverse events												
3	Randomised trials	Not serious	Not serious	Not serious	Not serious	None	16/1,423 (1.1%)	25/1,440 (1.7%)	RR: 0.65 (0.35 to 1.21)	6 fewer per 1,000 (from 11 fewer to 4 more)	⊕⊕⊕⊕ High	Important

[a], the heterogeneity was high among the studies (I^2 >50). CRP, C-reactive protein; CI, confidence interval; RR, risk ratio.

But the Cochrane review (23) found that CRP testing may increase the hospital admissions, and a recent study (26) showed that CRP testing may increase re-consultations. We infer that CRP testing does not affect the short-term efficacy of ARI, but it is necessary to evaluate the long-term effects of CRP testing.

Strengths and limitations

Due to CRP testing did not have a high predictive value for severe infections in children and newborn infants (53,54), only adults were included in this review, which reduced the heterogeneity caused by age. Considering that this type of studies would increase study bias risks, we did not include cluster-RCTs. We assessed the bias risk of the included studies and found that the methodological quality of the included literatures was high. Seven studies were included from five countries, reducing regional bias. But there are also inadequacies in our research. The CRP level as the recommended threshold of antibiotic were different in including studies (Table S2). Two studies used 40 mg/L as the recommended threshold of antibiotic, while two studies used 50 mg/L as the recommended threshold, and three studies used 100 mg/L as the recommended threshold. The subgroup analysis showed that 40 mg/L as the recommended threshold could reduce the antibiotic prescribing great significantly. However, considering the small number of references and large heterogeneity, reasonable researches should be designed in further researches to verify the best recommended threshold of CRP.

Conclusions

CRP testing can reduce the antibiotic prescribing in adult ARI, which is safe and would not affect therapeutic effects. However, the CRP level as the recommended threshold of antibiotic prescribing is not consistent. Considering the individuals difference of patients, physicians should make clinical decisions combined with patient's preferences, best available evidence and experience of professionals.

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Footnote

Reporting Checklist: The authors have completed the PRISMA reporting checklist. Available at https://jtd.amegroups.com/article/view/10.21037/jtd-21-705/rc

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://jtd.amegroups.com/article/view/10.21037/jtd-21-705/coif). All authors report that this work is supported by the National Natural Science Foundation of China (No. 81774222; No. 82074411); the Chinese Medicine Top-notch Talents Training Project of Henan Province (No. 2019ZYBJ05); the Program for Key Subjects of Henan Province (No. STS-ZYX2017002). This work has no relationship with any manufacturers of antibiotic medication. The authors have no other conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy and integrity of any part of the work are appropriately investigated and resolved.

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Supplementary

Appendix 1 Details of the literature search strategy

(1) PubMed (1977 to January 16, 2021)

Search	Query	Items found
#1	"Anti-Bacterial Agents"[Mesh]	385232
#2	((((((((((((((((((Anti Bacterial Agents[Title/Abstract]) OR Agents, Antibacterial[Title/Abstract]) OR Bacteriocidal Agents[Title/Abstract]) OR Bacteriocides[Title/Abstract]) OR Antimycobacterial Agent*[Title/Abstract]) OR antibiotic*[Title/Abstract]) OR antibacterial[Title/Abstract]) OR anti-acterial[Title/Abstract]) OR amoxicillin[Title/Abstract]) OR amoxycillin[Title/Abstract]) OR penicillin[Title/Abstract]) OR ampicillin[Title/Abstract]) OR cotrimoxazole[Title/Abstract]) OR chloramphenicol[Title/Abstract]) OR trimethoprim[Title/Abstract]) OR sulphamethoxazole[Title/Abstract]) OR tmp smx[Title/Abstract]) OR tmp- mx[Title/Abstract]	506080
#3	#1OR#2	687035
#4	"C-Reactive Protein"[Mesh]	47029
#5	((c reactive protein[Title/Abstract]) OR c-reactive protein[Title/Abstract]) OR CRP[Title/Abstract]	87077
#6	#4 OR #5	95790
#7	#3 AND #6	5215
#8	#7 AND ("Randomized Controlled Trial" [Publication Type] OR "Controlled Clinical Trial" [Publication Type] OR "Clinical Trials as Topic"[Mesh:NoExp] OR randomized[Title/Abstract] OR placebo [Title/Abstract] OR randomly[Title/Abstract] OR trial[Title/Abstract]) NOT ("Animals"[Mesh] NOT "Humans"[Mesh])	341

(2) Embase (1974 to January 16, 2021)

Search	Query	Items found
#1	'anti bacterial agents':ab,ti OR 'agents, antibacterial':ab,ti OR 'bacteriocidal agents':ab,ti OR bacteriocides:ab,ti OR 'antimycobacterial agent*':ab,ti OR antibiotic*:ab,ti OR antibacterial:ab,ti OR 'anti-bacterial':ab,ti OR amoxicillin:ab,ti OR amoxycillin:ab,ti OR penicillin:ab,ti OR ampicillin:ab,ti OR cotrimoxazole:ab,ti OR chloramphenicol:ab,ti OR trimethoprim:ab,ti OR sulphamethoxazole:ab,ti OR 'tmp smx':ab,ti OR 'tmp-smx':ab,ti	645998
#2	'c reactive protein'/exp	187951
#3	'c reactive protein':ab,ti OR 'c-reactive protein':ab,ti OR crp:ab,ti	151134
#4	#2 OR #3	230851
#5	#1 AND #4	13894
#6	random*:ab,ti	1615319
#7	#5 AND #6	805

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(3) Cochrane Library (January 16, 2021)

Search	Query	Items found
#1	MeSH descriptor: [Anti-Bacterial Agents] explode all trees	12180
#2	(“Anti Bacterial Agents”):ti,ab,kw OR (“Agents, Antibacterial”):ti,ab,kw OR (Bacteriocidal Agents):ti,ab,kw OR (“Bacteriocides”):ti,ab,kw OR (“Antimycobacterial Agent*”):ti,ab,kw	12986
#3	(“antibiotic* ”):ti,ab,kw OR (“antibacterial ”):ti,ab,kw OR (“anti-bacterial ”):ti,ab,kw OR (“amoxicillin ”):ti,ab,kw OR (“amoxycillin”) ti,ab,kw	40350
#4	(“penicillin”):ti,ab,kw OR (“ampicillin”):ti,ab,kw OR (cotrimoxazole):ti,ab,kw OR (“chloramphenicol ”):ti,ab,kw OR (“trimethoprim”):ti,ab,kw	6942
#5	(“sulphamethoxazole”):ti,ab,kw OR (“tmp smx”):ti,ab,kw OR (tmp-smx):ti,ab,kw	416
#6	#1 OR #2 OR #3 OR #4 OR #5	45850
#7	MeSH descriptor: [C-Reactive Protein] explode all trees	4637
#8	(“c reactive protein”):ti,ab,kw OR (c-reactive protein):ti,ab,kw OR (CRP):ti,ab,kw	25632
#9	#7 OR #8	25632
#10	#6 AND #9	1194
#11	(“antibiotic* ”):ti,ab,kw	1037710
#12	#10 AND #11	885

Table S1 Results of sensitivity analysis

Outcomes	Deletion	Result	
Antibiotic prescribing rate at the index consultation	Prins 2019	χ^2=16.25; P=0.006; I^2 =69%	RR: 0.75; 95% CI: 0.71–0.80
	Butler 2019	χ^2=16.41; P=0.006; I^2 =70%	RR: 0.75; 95% CI: 0.71–0.81
	Diederichsen 2000	χ^2=5.96; P=0.31; I^2 =16%	RR: 0.71; 95% CI: 0.66–0.76
	Do 2016	χ^2=13.20; P=0.02; I^2 =62%	RR: 0.78; 95% CI: 0.73–0.84
	Cals 2010	χ^2=16.37; P=0.006; I^2 =69%	RR: 0.75; 95% CI: 0.70–0.80
	Gonzales 2011	χ^2=12.85; P=0.02; I^2 =61%	RR: 0.74; 95% CI: 0.70–0.79
	Francis 2020	χ^2=14.63; P=0.01; I^2 =66%	RR: 0.77; 95% CI: 0.71–0.82

RR, risk ratio; CI, confidence interval.

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Table S2 Adverse events

Study	Adverse events	The number of events	
		CRP testing	Routine care
Prins 2019 (29)	Hyperglycaemia	1	5
	Steroid induced myopathy		
	Oral candidiasis		
	Urinary retention bladder		
Butler 2019 (30)	Pneumonia	9	12
Do 2016 (32)	Hospital admissions	6	8
Cals 2010 (33)	Death or hospitalization	These serious adverse events were not related to the intervention or to trial participation	
Francis 2020 (35)	Died	These serious adverse events were not related to the intervention or to trial participation	

CRP, C-reactive protein.

Table S3 Summary of subgroup analyses about antibiotic prescribing rate at the index consultation

Basis of subgroup	Subgroup	No. of trials	No. of participants	Mean difference (95% CI)	Heterogenity (I^2)
Type of ARI	Low ARI	3	1,405	0.71 (0.65–0.78); P<0.00001	0%
	Upper ARI	4	2,209	0.83 (0.66–1.03); P=0.09	78%
CRP level as recommended	40 mg/L	2	1,185	0.71 (0.65–0.78); P<0.00001	0%
	50 mg/L	2	1,032	0.83 (0.62–1.12); P=0.23	62%
	100 mg/L	3	1,397	0.77 (0.61–0.98); P=0.03	62%

CI, confidence interval; ARI, acute respiratory tract infections; CRP, C-reactive protein.

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