Antibiotic prescription strategies for acute sore throat: a prospective observational cohort study

Paul Little, Beth Stuart, F D Richard Hobbs, Chris C Butler, Alastair D Hay, Brendan Delaney, John Campbell, Sue Broomfield, Paula Barratt, Kerenza Hood, Hazel Everitt, Mark Mullee, Ian Williamson, David Mant, Michael Moore, for the DESCARTE investigators

Summary

Background Data from trials suggest that antibiotics reduce the risk of complications of sore throat by at least 50%, but few trials for complications have been done in modern settings, and datasets of delayed antibiotic prescription are underpowered. Observational evidence is important in view of poor compliance with antibiotic treatment outside trials, but no prospective observational cohort studies have been done to date.

Methods We generated a large prospective cohort from the DESCARTE study, and the PRISM component of DESCARTE, of 12 829 adults presenting with sore throat (≤2 weeks duration) in primary care. Our follow-up of the cohort was based on a detailed and structured review of routine medical records, and analysis of the comparison of three antibiotic prescription strategies (no antibiotic prescription, immediate antibiotic prescription, and delayed antibiotic prescription) to control for the propensity to prescribe antibiotics. Information about antibiotic prescription was recorded in 12 677 individuals (4805 prescribed no antibiotics, 6088 prescribed antibiotics immediately, and 1784 prescribed delayed antibiotics). We documented by review of patients' notes (n=11 950) the development of suppurative complications (eg, quinsy, impetigo and cellulitis, otitis media, and sinusitis) or reconsultation with new or non-resolving symptoms). We used multivariate analysis to control for variables significantly related to the propensity to prescribe antibiotics and for clustering by general practitioner.

Findings 164 (1·4%) of the 11 950 patients with information available developed complications; otitis media and sinusitis were the most common complications (101 patients [62%]). Compared with no antibiotic prescription, immediate antibiotic prescription was associated with fewer complications (adjusted risk ratio [RR] 0·62, 95% CI 0·43–0·91, estimated number needed to treat [NNT 193) as was delayed prescription of antibiotics (0·58, 0·34–0·98; NNT 174). 1787 of the 11 950 patients (15%) reconsulted with new or non-resolving symptoms; the risk of reconsultation was also reduced by immediate (0·83, 0·73–0·94; NNT 40) or delayed antibiotics (0·61, 0·50–0·74; NNT 18).

Interpretation Suppurative complications are not common in primary care and most are not serious. The risks of suppurative complications or reconsultation in adults are reduced by antibiotics, but not as much as the trial evidence suggests. In most cases, no antibiotic is needed, but a delayed prescription strategy is likely to provide similar benefits to an immediate antibiotic prescription.

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See Comment page 177

Primary Care and Population Sciences Division, University of Southampton, Southampton, UK (Prof P Little FMedSci, B Stuart, S Broomfield MSc, P Barratt PhD, M Mullee MSc, I Williamson MD, H Everitt PhD, M Moore FRCGP); **Department of Primary Care Health Sciences, Oxford University, New Radcliffe House, Oxford, UK** (Prof F D R Hobbs FMedSci, Prof D Mant FMedSci); **Institute of Primary Care and Public Health** (Prof C C Butler FRCGP) **and South East Wales Trials Unit** (Prof K Hood PhD), **School of Medicine, Cardiff University, Cardiff, UK; Centre for Academic Primary Care, School of Social and Community Medicine, University of Bristol, Bristol, UK** (Prof A D Hay FRCGP); **Department of Primary Care and Public Health Sciences, Kings College London, London, UK** (Prof B Delaney FRCGP); **and University of Exeter Medical School, Exeter, UK** (Prof J Campbell FRCGP)

Correspondence to: Prof Paul Little, University of Southampton, Aldermoor Health Centre, Southampton SO16 5ST, UK **p.little@soton.ac.uk**

Introduction

Acute pharyngitis constitutes roughly a third of all respiratory-tract infections in primary care,[1] and is the reason for about a third of antibiotic prescriptions for such infections. Although major complications are rare in acute pharyngitis, most patients are still given antibiotics.[1] Antibiotic prescription in primary care is rising, and has now exceeded the peak in the late 1990s.[2] This increase is driving antibiotic resistance,[3] which could lead to serious infections becoming untreatable.[4,5]

Concern about complications is one of the key drivers of antibiotic prescription.[6] Data from trials of antibiotics in acute sore throat suggest moderate symptomatic benefit, and prevention of both suppurative complications (eg, quinsy, otitis media, sinusitis, and cellulitis) and non-suppurative complications, although the latter are rare.[7–9] In 2008, the UK National Institute for Health and Care Excellence (NICE) recommended a strategy of either no antibiotic or delayed antibiotic prescription for acute sore throat and other respiratory infections.[10] However, few data for complications associated with delayed prescribing were available to NICE, so further evidence to justify the recommendations is needed.

Three efficacy trials of delayed antibiotics for pharyngitis have been done in which the delay has been both masked and fixed.[11–13] In these trials, participants were given drugs every day, but one group had placebo for the first few days (ie, masked); because it was not the participants choosing when to delay, the delay time was fixed by the provision of drugs. Findings from reviews showed only one open pragmatic effectiveness trial[14,15] that was designed to realistically assess antibiotic use (because patients have control over the delay) and reconsultations (because patients' knowledge of their treatment can affect reconsultation). Although the trial data for acute sore throat and chest infections tentatively suggest that immediate or delayed antibiotics reduce reconsultation compared with a no prescription strategy,[15,16] the trials

were underpowered for this outcome. Findings from systematic reviews of trials of delayed antibiotic prescription[17,18] show useful reductions in antibiotic use for both no prescription and delayed prescription, but the reviews[17,18] were underpowered to address symptom progression and complications. The selection bias in trial recruitment always compromises the generalisability of trial evidence, and trial settings probably result in much greater drug adherence than do observational settings, perhaps especially for antibiotics.[14,19] Therefore, the effect of antibiotic prescription in routine practice might be smaller than the trial evidence suggests. Findings of observational studies are useful alongside trial data, and are important for policy making. Although observational studies have the drawback of confounding by indication, the effects of this confounding can be assessed by use of techniques to control for the propensity to prescribe.[20,21] We are aware of no adequately powered prospective observational studies documenting symptom progression and complications that compare the use of either immediate antibiotics or delayed antibiotics with a no prescription strategy.

We recorded the likely effect of different antibiotic prescription strategies on complications associated with acute sore throat, and the effect on the non-resolution or progression of symptoms in a large prospective clinical cohort.

Methods

Selection criteria

We aimed to develop a simple one-page clinical proforma (on paper or website) that documented key clinical features to help generate a large prospective cohort. If successful, we aimed to use this method in other studies of other respiratory infections. Follow-up of the cohort was based on a detailed and structured review of the routine medical records, and analysis of the comparison of three antibiotic prescription strategies (no antibiotic prescription, immediate antibiotic prescription, and delayed antibiotic prescription) to control for the propensity to prescribe antibiotics. Within the main observational study (DESCARTE: Decision rule for Symptoms and Complications or Acute Red Throat in Everyday practice, n=11722), smaller diagnostic studies were nested to develop a clinical scoring method for bacterial infection (PRISM [PRImary Care Streptococcal Management study] diagnostic studies, n=1107). We did not include patients from the PRISM randomised trial (n=1781), unlike the companion paper on prognosis.[22] All studies shared the same baseline clinical proforma and outcome measures, the only difference was that in the diagnostic studies, a throat swab was taken and sent for microbiological analysis.

We recruited general practitioners in England and Wales who reported prescribing immediate antibiotics to 50% or less of patients with tonsillitis so that the effect of antibiotics could be explored.

Eligible patients were previously healthy, aged 16 years and older, with an acute illness (duration 14 days or less), who presented with sore throat as the main symptom, or whose pharynx was abnormal on examination (ie, identical criteria to our previous studies[15]). The baseline clinical proforma consisted of one clinical sheet documenting age, sex, smoking status, previous duration of illness, and the presence and severity of baseline symptoms (eg, sore throat, difficulty in swallowing, fever during the illness, runny nose, cough, feeling unwell, diarrhoea, headache, aching muscles, sleep disturbance, earache, vomiting, and abdominal pain). Symptoms were recorded on four-point Likert scales (none, a slight problem, a moderately bad problem, or a severe problem), and the presence of signs (pus, nodes, cervical nodes, temperature, fetor, palatal oedema, and difficulty in speaking because of sore throat) to include those used in previous clinical scores.[8,23–25] Clinicians also recorded their prescribing strategy (ie, immediate antibiotics, delayed antibiotics, or no antibiotics).

Documentation of outcomes

Complications (the main outcome) were assessed by staff in general practices or by staff of the primary care research network based on review of patients' notes with a standardised proforma. To minimise the need for judgments by the reviewing staff, the proforma was separated into several terms showing the possible consultation diagnosis or symptom presentation. Reviewers were not told that the aim of the study was to assess effect of antibiotic prescription strategies. The inter-rater reliability of the assessment of complications and of progression of illness was documented by a second rater without knowledge of the first rating in 153 patients in two of the sites. A complication was defined as a new clinical diagnosis of otitis media, sinusitis, and quinsy (the major complications based on previous systematic review[7]), and including cellulitis or impetigo (based on a recent Dutch trial[8,26]), made in the month after the presentation was recorded in the clinical record. When information about complications was not available from notes, we obtained information from a freepost card returned directly to the study centre by patients.

The secondary outcome was reconsultation with non-resolving symptoms or development of a new respiratory diagnosis, symptom, or sign, within a month of the index presentation. This outcome was similar to outcomes used previously in a cohort of children[27] and in a large trial of antibiotics for lower respiratory infection in adults.[28]

Sample size

We used the NQuery sample-size programme for sample size calculations, which assumed 5% two-sided significance and 80% power. The sample-size calculations were limited by the need to power the cohort to detect

complications to detect variables with 80% power that would predict complications with an odds ratio (OR) of at least 2·5 (predictors of complications will be reported elsewhere. On the assumption that the group not receiving immediate antibiotics might be the most appropriate group in which to develop a model, we estimated that 6749 participants in those groups would be needed, or 13 498 to allow for other patients receiving immediate antibiotics, which we assumed was no more than half the cohort. Our previous data suggested little clustering by general practitioner, but assuming an intracluster correlation coefficient of 0·01 to allow for potential clustering, we estimated we might need to recruit up to 17 412 patients. Thus, we aimed to recruit a minimum of 6749 participants not receiving immediate antibiotics, and a maximum of 17 412 in total.

Statistical analyses

To assess the role of immediate or delayed antibiotics in the prevention of complications compared with a no prescription strategy, we used logistic regression, accounting for clustering by general practitioner, and controlling for any potential confounder of the association between prescription strategy and outcome. We did not impute missing variables, and assessed the effect of controlling for a wide range of case report form variables. We generated another model that controlled just for significant covariates (from backward fitting of the regression model, retaining all variables with p≤0·20). We converted odds ratios (OR) to risk ratios (RR) by use of standard formulae.[29] We also did a secondary analysis by a stratified propensity score method,[20,21] which allowed us to investigate whether more rigorous control for confounding by indication would change the estimates. A limitation of this approach was that propensity score analyses cannot allow for missing data, so power is reduced compared with a model that simply includes the most significant variables. A further secondary analysis with the propensity scores merged immediate and delayed antibiotics to provide more power to assess the effect of antibiotics. Our secondary analysis also allowed us to assess the likely effect of missing data by multiple imputation methods. Finally, we did secondary posthoc analyses of individual complications; we recognise that power and precision are lower for subgroups.

Role of the funding source

The sponsor of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

12 829 adult patients were recruited between Nov 10, 2006, and June 1, 2009, from 616 recruiting practices. Notes review was possible in 560 practices (518 recruited to DESCARTE only, 26 to both DESCARTE and PRISM, and 16 to PRISM only). Clinicians reported that both recruitment and data collection were easy, so no changes in the format of data collection were needed after the study started. Antibiotic prescription strategy was recorded in 99% of patients (12 677: 4805 given no antibiotic, 6088 prescribed antibiotics immediately, and 1784 prescribed delayed antibiotics). Complications were assessed in 12 099 patients, but 149 of these did not have antibiotic prescribing strategy recorded in the case report form leaving 11 950 for analysis. Thus relevant information about prescribing and compliations was available for 11 950 of the 12 829 (93%) patients; this total included a few patients for whom notes review was not available, but we used postcards describing any further care (figure). The inter-rater reliability for assessment of complications was good (statistic 0·95); of 11 patients with complications, only one was deemed not to have a complication on the second assessment. The assessment of return with non-resolution of symptoms was good too (κ 0·84); of 29 patients documented as reconsulting with new or worsening symptoms, only one was changed on the second assessment.

Table 1 shows the clinical characteristics of patients recruited. 164 of 11 950 patients (1·4%) developed complications overall, and the patients prescribed antibiotics differed significantly from those not given a prescription in several characteristics (particularly fever, pus, and severity of inflammation). Compared with patients prescribed no antibiotics, the risk of suppurative complications was lower for both immediate antibiotics (RR 0·62, 95% CI 0·43–0·91; estimated number needed to treat [NNT] 193) and delayed antibiotics (RR 0·58, 0·34–0·98; NNT 174) when the analysis controlled for significant baseline covariates (table 2). Reconsultation with new or unresolving symptoms was also less common among patients prescribed immediate (RR 0·83, 0·73–0·94; NNT 40) or delayed antibiotics (RR 0·61, 0·50–0·74; NNT 18; table 3).

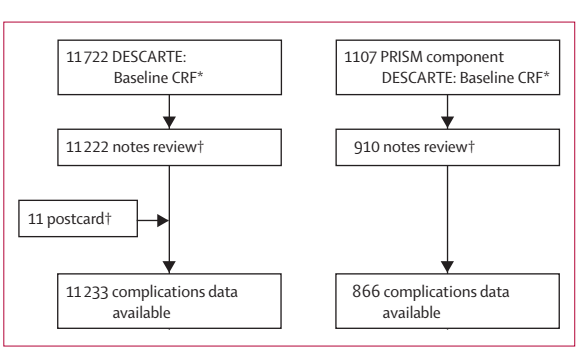

Figure: **Patient recruitment and follow-up**
CRF=case report form. *DESCARTE: baseline CRF and notes review. PRISM: same baseline and CRF, but patients also have throat swab sent for a microbiological diagnostic study. †Self-completed postcards were used for 87 people who had no complications data recorded from notes review, and for a further 11 people who were included in the notes review but had no baseline data.

See Online for appendix

The estimates changed very little when propensity scores were used (tables 2 and 3), but because of the reduction in power, the estimates for complications were no longer significant. The appendix shows a comparison of different approaches to use of propensity scores, and shows that the estimates are probably stable. When we combined immediate and delayed antibiotic groups, the propensity score shows a significant reduction in

	Not given antibiotics	Given antibiotics	Delayed antibiotics
Clinical assessment			
Mean (SD) severity of sore throat and difficulty in swallowing on a four-point Likert scale	2·92 (0·71)	3·31 (0·63)	3·02 (0·69)
Previous duration in days	4·88 (6·62)	4·65 (4·14)	4·11 (3·18)
Age in years	34·6 (15·4)	32·7 (14·2)	33·8 (14·4)
Female	3325/4805 (69%)	4030/6088 (66%)	1282/1784 (72%)
Smoker	919/4774 (19%)	1395/6060 (23%)	327/1769 (18%)
Fever in past 24 h	2084/4414 (47%)	3965/5524 (72%)	873/1600 (55%)
Temperature (°C)	36·65 (0·61)	36·99 (0·74)	36·75 (0·60)
Pus on tonsils	329/4776 (7%)	3638/6052 (60%)	473/1779 (27%)
Severely inflamed tonsils	56/4486 (1%)	1334/5674 (24%)	101/1628 (6%)
Number of previous medical problems	0·24 (0·51)	0·24 (0·51)	0·24 (0·50)
Return within 4 weeks with new or worsening symptoms	764/4536 (17%)	846/5750 (15%)	177/1664 (11%)
Days delay for those receiving delayed antibiotics	..	..	3·52 (6·32)
Return within 4 weeks with complications	73/4536 (2%)	75/5750 (1%)	16/1664 (1%)
Individual complications			
Quinsy	11/4536 (0·24%)	30/5750 (0·52%)	4/1664 (0·24%)
Sinusitis	23/4536 (0·49%)	10/ 5750 (0·17%)	2/1664 (0·12%)
Otitis media	30/4536 (0·66%)	26/5750 (0·45%)	10/1664 (0·60%)
Cellulilitis or impetigo	10/4536 (0·22%)	9/5750 (0·16%)	0/1664 (0·00%)

Data are mean (SD) or number (%) of patients. Denominators vary owing to missing data.

Table 1: **Characteristics of patients**

	Complications (%)	Developed complication (%)	Univariate analysis		Multivariate analysis controlling for clustering and all covariates*		Multivariate analysis controlled for clustering and only significant covariates†		Multivariate analysis by stratified propensity score	
			Risk ratio (95% CI)	p value	Risk ratio (95% CI)	p value	Risk ratio (95% CI)	p value	Risk ratio (95% CI)	p value
No antibiotic	4463/11 786 (38%)	73/164 (45%)	1·00	..	1·00	..	1·00	..	1·00	..
Immediate	5675/11 786 (48%)	75/164 (46%)	0·81 (0·59–1·12)	0·198	0·64 (0·43–0·97)	0·034	0·62 (0·43–0·91)	0·015	0·66 (0·43–1·03)	0·068
Delayed	1648/11 786 (14%)	16/164 (10%)	0·60 (0·35–1·02)	0·060	0·58 (0·33–1·00)	0·051	0·58 (0·34–0·98)	0·040	0·61 (0·34–1·10)	0·093

*The full model has less power because of missing variables, and included the number of medical problems, previous duration of illness (<3 days), very inflamed tonsils, the absence of cough or coryza, age, cervical glands, severity of sore throat, pus, fever in the past 24 h, muscle aches, headache, sex, smoker, feeling generally unwell, diarrhoea, and disturbed sleep. †We used backward fitting of the regression model and retained all variables with a p value of 0·20 or lower. The final model included inflamed tonsils, fever in the past 24 h, generally unwell, and disturbed sleep.

Table 2: **Antibiotic prescription strategies and suppurative complications in the month after the index consultation**

	No new or worsening symptoms (%)	Developed new or worsening symptoms (%)	Univariate analysis		Multivariate analysis controlling for clustering and all covariates*		Multivariate analysis controlled for clustering and only significant covariates†		Multivariate analysis by stratified propensity score	
			Risk ratio (95% CI)	p value	Risk ratio (95% CI)	p value	Risk ratio (95% CI)	p value	Risk ratio (95% CI)	p value
No antibiotic	3722/10 163 (37%)	764/1787 (43%)	1·00		1·00		1·00		1·00	
Immediate antibiotics	4904/10 163 (48%)	846/1787 (47%)	0·87 (0·80–0·96)	0·003	0·76 (0·66–0·87)	<0·001	0·83 (0·73–0·94)	0·003	0·76 (0·67–0·86)	<0·001
Delayed antibiotic	1487/10 163 (15%)	177/1787 (10%)	0·63 (0·54–0·74)	<0·001	0·58 (0·47–0·70)	<0·001	0·61 (0·50–0·74)	<0·001	0·57 (0·47–0·68)	<0·001

*The full model has less power because of missing variables, and included the number of medical problems, previous duration of illness (<3 days), very inflamed tonsils, the absence of cough or coryza, age, cervical glands, severity of sore throat, pus, fever in the past 24 h, muscle aches, headache, sex, smoker, feeling generally unwell, diarrhoea, and disturbed sleep. †We used backward fitting of the regression model and retained all variables with a p value of 0·20 or lower. The final model included number of medical problems, age, fever in the past 24 h, muscle aches, and sex.

Table 3: **Antibiotic prescribing strategies and reconsultation with new or non-resolving symptoms in the month after the index consultation**

complications due to antibiotics (0·65, 0·44–0·97) and also reduced the risk of reconsultation with non-resolving or new symptoms (0·71, 0·63–0·79).

For the main outcome measures and key covariate, the proportion of data missing was less than 5% for most variables (appendix), which would be expected to have little effect on the results. With a multiple imputed dataset, we recorded small changes in estimates and very few changes in inferences. The only changes of note were that the borderline significant results for delayed antibiotics in the multivariable and propensity score models for complications all become significant at the 5% level, so the primary analysis was conservative.

For subgroup analyses and individual complications, the power for this post-hoc analysis was low, with poor precision of the estimates (appendix). However, these analyses suggest that quinsy and cellulitis are probably prevented by both immediate and delayed antibiotics, and sinusitis most likely prevented by delayed antibiotics and possibly by immediate antibiotics. However, any benefit of antibiotics for the prevention of otitis media is less clear.

Discussion

The findings from this large prospective clinical cohort for acute sore throat, confirm that immediate antibiotic prescription or delayed antibiotic prescription are both likely to prevent complications and reconsultations. However, the protective effect of antibiotics recorded in this pragmatic observational study was lower than what has been found in randomised controlled trials (panel).

Some residual confounding is always possible in observational studies, but few variables predicted complications, which lessens any effect of confounding by indication. Furthermore, for delayed prescription, we recorded very little change in risks when a wide range of potential confounders were included in the models, which suggests that confounding was not a major issue for delayed prescription in this dataset. The use of stratified propensity scores did not change the estimates. The study was designed for easy recruitment to create little or no selection bias by using a simple clinical proforma to create a large generaliseable prospective cohort. Although few practices recruited patients for more intensive substudies (ie, diagnostic studies), patients could be enrolled in DESCARTE if they declined those studies, so barriers to recruitment were negligible. Patients were recruited at the times of year when sore throat is most common, and as with other studies of acute infection,[16,28] documentation of the details of patients not approached was poor because time pressure to recruit also meant pressure to document non-recruitment. Although the diagnosis of quinsy and cellulitis is more straightforward, what constitutes a clinical diagnosis of either otitis media[30] or sinusitis[31] is more variable, and variability in outcome ascertainment reduces the power to find associations. However, our findings showed that assessment of complications with a highly structured review of notes was reliable. Management strategy was not concealed from patients, so knowledge of the receipt of antibiotics might have changed their threshold for consultation. We recruited general practitioners who reported prescribing immediate antibiotics in less than 50% of cases, which resulted in a higher complication rate than for general practitioners who regularly prescribed more antibiotics. However, the complication rate we recorded was still low, and similar to rates from trials in the modern setting that did not use the Centor criteria[32] to establish inclusion.[7] For example, the complication rate was 1 in 400 for quinsy, and 0·8% including other suppurative complications in a previous UK pragmatic trial,[14,15] and 1 in 1000 for quinsy in routine observational studies.[1] These data support the likely generaliseability of the results, as does the wide range of general practitioners and practices included. The broader outcome of return to the surgery with non-resolving or new symptoms— which was a useful in a large international trial[28]—also showed similar estimates of the benefit of prescription strategies. Additionally, we did not measure longer-term reconsultation, although existing evidence suggests that delayed prescription does not encourage either short-term or long-term reattendance.[15,16,33]

Only 1·4% of patients developed complications overall. No non-suppurative complications of post streptococcal glomerulonephritis or rheumatic fever were recorded, and many of the complications were minor and self-limiting (eg, otitis media and rhinosinusitis). Although suppurative complications were uncommon, our results show that immediate antibiotic prescription could reduce the risk of complications by roughly a third, equivalent to an NNT of nearly 200. However, any action would need to be balanced against the danger of antibiotic prescription driving antibiotic resistance.[3,34] Additionally, our findings contrast with those from systematic reviews of trials, which show a larger effect size for all complications.[7] This larger effect in the trial data might be due to residual confounding by indication in our dataset, but could also be indicative of selection or spectrum bias in the trial data because much of the systematic review evidence does not relate to primary-care settings, and the estimates for complications are dominated by older trials in which complications were more common and the health of participants poorer.[7,35] The differences might also be due to the fact that in trials, patients are more likely to adhere to drug use than in routine practice in which adherence to antibiotic use is poor.[19] Delayed prescription was no less effective than an immediate antibiotic prescription in reducing complications (in fact a little more effective), and reduced the risk of complications compared with no antibiotic prescription by more than 40%. To our knowledge, this is the first time delayed antibiotic prescription has been shown to have clear benefit in reducing complications and reconsultations (ie, a no antibiotic prescribing strategy and a delayed prescription strategy are not equivalent), and to provide similar benefits to immediate antibiotic

Panel: **Research in context**

Systematic review

Authors of a Cochrane Review of antibiotics for sore throat searched the Central Register of Controlled Trials (Central) 2013, issue 6, Medline (Jan 1966 to July week 1, 2013), and Embase for randomised controlled trials (RCTs) or quasi-RCTs of antibiotics versus control assessing typical sore throat symptoms or complications. Selection criteria taken from abstract: RCTs or quasi-RCTs of antibiotics versus control assessing typical sore throat symptoms or complications. Antibiotics reduced all complications by more than 50% (acute rheumatic fever RR 0·27; acute otitis media RR 0·30; acute sinusitis RR 0·48; and quinsy RR 0·15). The authors searched Central (Cochrane Library 2013, issue 2), which includes the Acute Respiratory Infection Group's Specialised Register; Ovid Medline (January 1966, to February, week 3, 2013); Ovid Medline in-process and other non-indexed citations (Feb 28, 2013); Embase (1990–2013 week 8); Science Citation Index - Web of Science (2007–May 2012), and EBSCO CINAHL (1982–Feb 28, 2013) for RCTs involving participants of all ages defined as having an acute respiratory tract infection, where delayed antibiotics were compared with antibiotics used immediately or no antibiotics. The authors concluded no significant differences in complication rates, but few data were available for complications, and had low power. The review provided no comparison of reconsultation rates for immediate or delayed prescription strategies with a no prescription strategy.

Interpretation

The effect of immediate antibiotic prescription is lower than the previous trial evidence suggests. Previous systematic reviews of delayed prescription concluded there was no advantage to using a delayed prescription compared with no offer of a prescription. However, the previous reviews were not adequately powered to assess reconsultation and the prevention of complications. Findings from this study show that delayed prescription and no prescription are not equivalent, that delayed prescription prevents complications as effectively as immediate antibiotics, and that delayed prescription is more effective than immediate antibiotics at reducing reconsultations.

prescription for preventing complications (because the present systematic reviews of randomised trials of delayed prescription are underpowered).[17]

Similarly, although antibiotic prescription reduces reconsultations with new or non-resolving symptoms compared with a no antibiotic strategy, the reduction can be achieved more effectively with a delayed rather than an immediate prescription. A delayed prescription of antibiotic had a larger estimated effect on reconsultation (RR 0·61, 39% reduction) than did immediate antibiotics (RR 0·83, 17% reduction), and the CIs exclude the estimate for immediate antibiotics. Because a delayed prescription is more likely to result in more than a 50% reduction in antibiotic use than is an immediate prescription,[17] when physicians are unsure about prescribing an antibiotic because of concerns about poor outcome (eg, for individuals who might be at high risk such as male patients and middle-aged smokers with severe tonsillar inflammation[36]), a delayed rather than an immediate prescription could be issued. The assumptions about reconsultations and complications underlying the NICE economic model, which suggested that delayed prescribing was probably a more efficient strategy than was either immediate prescription or no prescription, are also supported by our data.[10] Complications are a major issue in the decision to prescribe,[6] but clinicians will still need to balance patients' concerns about control of symptoms, expectations for antibiotics, patients' satisfaction, maintenance of the relationship between doctor and patient, and the threat of antibiotic resistance. However, most of these competing desires can be successfully met with a no prescription or delayed prescription approach.[6,10]

Conclusion

Most suppurative complications are uncommon in primary care, and most are not serious. The risks of suppurative complications or reconsultation with non-resolving or new symptoms in adults are reduced by antibiotics, but the effect of immediate antibiotic prescription for complications is less than trial evidence suggests, with very high NNT. Although in most cases an antibiotic is not needed, delayed antibiotic prescription and no antibiotic prescription do not have equivalent outcomes. If an antibiotic prescription is being considered, a delayed antibiotic prescription strategy is likely to provide a similar reduction in complications to an immediate antibiotic prescription, and with reduced reconsultations.

Conflicts of interest

We declare that we have no conflicts of interest.

Contributors

DESCARTE Investigators: CB developed the protocol for funding, supervised the running of the study in the Cardiff Network and contributed to the drafting of the paper, PB and SB developed the protocol, provided day to day overall management of the study, coordinated recruitment in the lead study centre and coordination of other centres, commented on drafts of the paper. JC developed the protocol for funding, led the running of the study in the Exeter Network and contributed to the drafting of the paper. BD developed the protocol for funding, coordinated the development and management of the web resource, and contributed to drafting of the paper. HE developed the protocol, with SB led the reliability study, supervised data collection for the reliability study, contributed to analysis and contributed to drafting the paper. AH developed the protocol for funding, led the Bristol study centre and contributed to the analysis and the drafting of the paper. FDRH developed the protocol for funding, led the Birmingham study centre and contributed to the drafting of the paper. PL had the original idea for the protocol, led protocol development and the funding application, supervised the running of the lead study centre and coordination of centres, contributed to the analysis, led the drafting of the paper. DM developed the protocol for funding, supervised the running of clinical studies in the Oxford centre and contributed to the analysis and the drafting of the paper. MiM (GP and Reader in Primary Care, University of Southampton), developed the protocol for funding, contributed to the management of the study, and contributed to the drafting of the paper. MaM (study Statistician, Director Research Design Service, University of Southampton) developed the protocol for funding, contributed to study management, supervised data management, shared the quantitative analysis with BS and PL and contributed to the drafting of the paper. BS (study statistician, University of Southampton) developed the protocol, and led the quantitative analysis with MM and PL, and with PL drafted the initial versions of the paper. IW (GP and Senior Lecturer in Primary Care, University of Southampton), developed the protocol for funding, contributed to the management of the study and drafting of the paper. KH (Director of South East Wales Trials Unit, Cardiff University) contributed to protocol development, supervised the running of the study in the Cardiff Network, and contributed to the drafting of the report.

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Antibiotic prescription for sore throat or the legacy of Mr X[2]

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See **Articles** page 213

In his 1945 Nobel lecture, Sir Alexander Fleming described a hypothetical "Mr. X, [who] has a sore throat…buys some penicillin and gives himself, not enough to kill the streptococci but enough to educate them to resist penicillin".[1] Ironically, this eminent scientist selected group A streptococci for his example—the leading cause of bacterial pharyngitis and almost the sole organism that remains universally susceptible to penicillin in an era of multidrug-resistant bacteria.[2] However, more generally, Fleming was prescient; antibiotic misuse drives antimicrobial resistance and pharyngitis—mainly caused by respiratory viruses—is a cornerstone of antibiotic overuse in the community. Findings of a recent analysis[3] of US outpatient data between 1997 and 2010 showed that antibiotics—often macrolides instead of penicillins—were prescribed to 60% of patients who visited the clinic or emergency department because of sore throat. Although most guidelines concur that penicillins should be first-line in the antibiotic treatment, marked heterogeneity exists as to when that treatment should be deployed to prevent complications.[4-6] For a complaint as common as sore throat, the scarcity of observational data for the occurrence of complications in patients treated with or without antibiotics is therefore surprising.

In this issue, Paul Little and colleagues[7] partly fill this knowledge gap by reporting the results of DESCARTE, a pragmatic observational cohort study analysing the effect of three different antibiotic-prescribing strategies (no antibiotics, delayed antibiotics, and immediate antibiotics) on suppurative complications in nearly 13 000 adult patients with pharyngitis consulting general practices in England and Wales between 2006 and 2009. 1·4% of patients had complications (mostly otitis media or sinusitis). After adjusting for potential confounders, antibiotic prescription (both immediate and delayed) was associated with fewer complications and reconsultations than no antibiotic prescription. This prospective study is remarkable for its size; a recently updated Cochrane review[8] on the same topic yielded roughly the same total number of patients after including 27 randomised controlled trials (RCTs) and quasi-RCTs, many of them done in the 1950s. Another strength of this study is the thorough statistical analysis, which confirmed that the estimated effects of antibiotic prescription were robust using different models.

How should one interpret the findings of this study? First, findings confirm that, independent of antibiotic prescription, pharyngitis complications are rare and mostly minor, important information for risk-adverse physicians and patients (a separately published analysis[9] also showed that these complications are difficult to predict). Although antibiotics (both immediate and delayed) reduced suppurative complications, the recorded reduction in risk was lower than in the Cochrane review.[8] In the present study, the estimated number needed to treat to prevent one complication was 193 for immediate and 174 for delayed antibiotics.

Second, antibiotic prescription for sore throat remains disturbingly common. Roughly 50% of patients received immediate antibiotics despite England's long history of antibiotic awareness campaigns and availability of guidelines that both recommended no antibiotics or delayed treatment in most patients with sore throat.[10]

Third, compared with immediate antibiotics, the delayed antibiotics strategy was as effective at reduction of complications and resulted in fewer reconsultations. Although the delayed antibiotic strategy reduces antibiotic use (compared with immediate prescription), the approach is criticised as being unclear and unfairly shifting responsibility to patients. These criticisms might explain why the strategy has not been widely accepted outside the UK.[11,12]

As with any observational study, this report has limitations that complicate the interpretation of its findings. DESCARTE is vulnerable to the effect of residual unmeasured confounding. In particular, factors affecting both the treatment strategy and the propensity to re-consult (and thus also the likelihood to detect complications) cannot be excluded. We are also not provided with information on what percentage of patients with delayed and immediate antibiotics actually took the antibiotics, what percentage of prescriptions arose in patients with three or four Centor criteria[13] (criteria used to predict the likelihood of group A streptococcal pharyngitis in adult patients with sore throat), what antibiotics were prescribed, how prescription strategies varied among physicians, whether adjunctive treatment was given, or whether differences in antibiotic-related side-effects were recorded.

Of note and consistent with NICE guidelines, microbiological tests to differentiate group A streptococci pharyngitis from other causes of sore throat were not routinely done in the present study. In view of many other guidelines including such tests in their algorithms, this limits the generalisability of the findings.[5] On the other hand, a parallel RCT done by the same group of researchers failed to show an advantage of a clinical score over a rapid streptococcal antigen-based algorithm with regard to reduction of antibiotic prescription or time to symptomatic improvement.[14] This failure might be explained by streptococci other than group A streptococci being a more frequent cause of pharyngitis than previously thought; in the PRISM diagnostic substudy[15] about a third of isolated streptococci were non-group A streptococci. Whether this explanation is also true for other settings will need to be confirmed.

If Mr X were to present to a practice instead of self-medicating, how should a doctor manage his sore throat? The optimum strategy is still unknown, but this study has provided further evidence that indiscriminate immediate prescription of antibiotics is the worst approach. And if you use antibiotics, it should be good old penicillin.

Benedikt Huttner
Infection Control Programme, Geneva University Hospitals and Geneva University Faculty of Medicine, Geneva CH-1205, Switzerland
benedikt.huttner@hcuge.ch

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