Antibiotics for the common cold

Arroll B, Kenealy T


A substantive amendment to this systematic review was last made on 14 July 1998. Cochrane reviews are regularly checked and updated if necessary.

Background: The common cold is caused by viruses which cannot be helped by antibiotics.

Objectives: The objective of this review was to assess the effects of antibiotics for the common cold.

Search strategy: We searched the Cochrane Controlled Trials Register, MEDLINE, EMBASE, the Family Medicine Database, and reference lists of articles, and we contacted principal investigators. The most recent search was in December 1998.

Selection criteria: Randomised trials comparing any antibiotic therapy with placebo in acute upper respiratory tract infections.

Data collection and analysis: Both reviewers independently assessed trial quality and extracted data.

Main results: Seven trials involving 2056 people aged between six months and 49 years were included. The overall quality of the included trials was variable. People receiving antibiotics did not do better in terms of cure or improvement than those on placebo (odds ratio 0.95, 95% confidence interval 0.70 to 1.28 fixed effects model). One study found a significant benefit for antibiotics compared with placebo for runny nose (clear or purulent). The only other study to evaluate purulent nasal discharge found no significant benefit for antibiotics. Only one study reported work time lost with 22% of those on antibiotic treatment and 25% of those on placebo but this was not significant. Patients treated with antibiotics had a significant increase in side effects (odds ratio 2.72, 95% confidence interval 1.02 to 7.27, random effects model).

Reviewers' conclusions: Reviewers' conclusions: There is not enough evidence of important benefits from the treatment of upper respiratory tract infections with antibiotics and there is a significant increase in adverse effects associated with antibiotic use.

Background

There is evidence of high use of antibiotics for the common cold (viral upper respiratory tract infections) in spite of doubt about the efficacy of such therapy (McGregor 1995). In spite of the knowledge that viruses are the causative agent many patients presenting to their general practitioners receive antibiotics. In a New Zealand study computerised records of 100,222 consultations were examined from 17 general practices over one year by McGregor (McGregor 1995). Seventy eight percent of the patients received antibiotics. About one third of these medications were expensive broad spectrum antibiotics. There is also evidence from other studies that broad spectrum antibiotics are being used instead of narrow spectrum drugs (McCraig 1996; Waimedca study personal communication; McAvoy 1994). It has long been assumed that antibiotics have no place in the treatment of upper respiratory tract infections (Spector 1995). There are no published reviews of the topic of antibiotics as a treatment for upper respiratory tract infection. One review did examine the potential for
preventing pneumonia with antibiotics in patients with upper respiratory tract infection and included the Gadomski paper (Gadomski 1993). The results of that review found no benefit from giving antibiotics in terms of preventing giving antibiotics in terms of preventing pneumonia.

Upper respiratory tract infection (URTI) was the most common reason for new consultation in general practice and the second most common reason for the prescribing of an antibiotic in one study (McAvoy 1994). Because URTI are so common it is important to obtain an estimate of effectiveness. If ineffective, as has been long thought, there is concern that widespread use of antibiotics is not only a poor use of health funds but also a cause of morbidity (from adverse effects) as well as a source of the development of resistant strains (Fahey 1998; Verkatesum 1995).

Objectives

(1) To determine the efficacy of antibiotics in the treatment of acute upper respiratory tract infections in comparison with placebo in terms of cure or general improvement and improvement of nasopharyngeal symptoms.

(2) To determine whether there are significant adverse outcomes associated with antibiotic therapy for patients with a clinical diagnosis of acute upper respiratory tract infection.

Criteria for considering studies for this review

Types of studies

All trials in which patients with the diagnosis of acute upper respiratory tract infection were randomly assigned to treatment with an antibiotic or a placebo were included. Studies were excluded

(1) if they involved the use of an active substance instead of a placebo e.g aspirin as these substances may exert a beneficial effect thereby nullifying any beneficial effect of the antibiotic. Trials comparing one antibiotic with another or trials comparing the use of antibiotics versus other medications (such as cough mixtures or anti-pyretic/analgesics) were not included.

(2) if antibiotics were given prophylactically.

(3) if more than five percent of participants had throat swabs positive for beta haemolytic streptococcal infection. In the sore throat review by Del Mar the lowest percentage of streptococci on throat swab was 8% hence our choice of 5% (ICHPPC 1986). Two studies Hardy 1956 and Haight 1954 were excluded by this criterion. Neither had analyzable data.

(4) if antibiotics were given prophylactically.

(5) if more than five percent of participants had throat swabs positive for beta haemolytic streptococcal infection. In the sore throat review by Del Mar the lowest percentage of streptococci on throat swab was 8% hence our choice of 5% (ICHPPC 1986). Two studies Hardy 1956 and Haight 1954 were excluded by this criterion. Neither had analyzable data.

(5) if patients had past histories of serious illness.

(6) If the patients had been given the diagnosis of bronchitis (ICHPPC-2 definition is a definite cough with abnormal chest signs scattered or generalized coarse or moist sounds or wheeze).

(7) If the patients had purulent sputum or purulent nasal discharge. (this criterion would be challenged by Mainous et al (Mainous 1997) on the basis of one negative study (Todd) that purulent rhinitis is not of bacterial origin).

(8) If the patients had more than 6 days of symptoms at the time of study entry.

Types of participants

Patients of all ages who met the entry criterion.

Disease definition: The common cold or upper respiratory tract infection. The International Classification of Health Problems in Primary Care (ICHPPC-2) which defines a URTI as an illness with evidence of acute inflammation of nasal or pharyngeal mucosa and the absence of other specifically defined respiratory conditions.
e.g. streptococcal tonsillitis, laryngitis, bronchitis, pneumonia, asthma and hay fever (Arason 1996). This is commonly regarded as a self limiting viral illness that is experienced (usually) annually by the majority of the population. A practical definition is an acute illness with some of the following symptoms: rhinitis (not hay fever or allergic rhinitis), sore throat (not streptococcal pharyngitis), with or without fever, cough and/or productive sputum. Diseases diagnosed clinically such as pneumonia, bronchitis, sinusitis, otitis media and studies of patients with long standing symptoms were excluded. Lower respiratory tract signs were accepted in patients with the above symptoms so long as the majority of patients in the study did not have these signs and that pneumonia was ruled out. It was accepted by the reviewers that there would be some undetermined overlap with the alternative diagnoses of bronchitis, pneumonia and pharyngitis.

Types of intervention

All randomised controlled trials of any antibiotic therapy versus placebo used in the treatment of acute upper respiratory tract infections. Trials which allowed concurrent use of other medications were included if they allowed equal access for patients in both the antibiotic and placebo group.

Types of outcome measures

The outcome measures include resolution of symptoms of nasopharyngeal inflammation, global rating of health and adverse effects.

Search strategy for identification of studies

See: Collaborative Review Group search strategy
To identify trials of antibiotics as a therapy for upper respiratory tract infections - in terms of the above definition - from a (i) MEDLINE search from 1 January 1966 to January 1997 (ii) hand searched journals available to the Cochrane collaboration from the Cochrane Clinical trials register (iii) Family Medicine Database through the Canadian College of Family Physicians Library in London Ontario including a search on FAMLI Vol. 1, 1980 to Vol. 1, 1993 (this was discontinued in 1993) (iv) a search of the reference lists of relevant trials, review articles and textbook chapters (v) EMBASE (vi) Cochrane Central database.

All languages were included in the search strategy

Principal investigators were contacted to look for unpublished literature.

The search strategy for MEDLINE was: Papers found
1 expl antibiotics/ 283418
2 respiratory tract infections 15425
3 2 and upper.ti,ab,sh 1430
4 common cold/ 1334
5 pharyngitis/ 3256
6 3 or 4 or 5 5878
7 double blind method/ 45474
8 single blind method/ 2728
9 random allocation/ 34879
10 research design/ 18834
11 expl clinical trials/ 93448
12 (singl$ or doubl$ or trebl$).ti,ab,sh. 432064
13 (blind$ or mask$).ti,ab,sh. 83085
14 ((singl$ or doubl$ or trebl$ or tripl$) adj (blind$ or mask$)).ti,ab,sh. 44398
15 7 or 8 or 9 or 10 or 11 or 12 161628
16 volunteer$.tw. 47466
17 placebo$s.tw. 47466
A similar search strategy was used in EMBASE. A search was also done of the CENTRAL database via the Cochrane Centre in Baltimore. CENTRAL is "the central register of studies which may be relevant for inclusion in systematic reviews within the Cochrane Collaboration." Included in CENTRAL are both confirmed and unconfirmed reports of trials; the distinction between CENTRAL and the Cochrane Controlled Trials Register (CCTR) is that CCTR is made up of only the confirmed reports of trials in CENTRAL.

A citation is confirmed when it has both undergone review by Cochrane searchers and obtained approval from another body within Cochrane.

Using the names of the antibiotics listed below and terms relating to "upper respiratory infection", CENTRAL was searched (quotable definition above). The final search strategy is below:

#1 respiratory infection* or croup* or coryza* or common cold*
#2 1 not (cystic fibrosis).TI
#3 2 not (otiti*).TI
#4 3 not (asthma*).TI
#5 4 not (lower respiratory*).TI
#6 1 not 5
#7 6 not (upper and respiratory*)
#8 7 not (coryza*)
#9 8 not (common and cold*)
#10 6 not 9
#11 5 or 10
#12 antibiotic* or amoxicillin* or ampicillin* or penicillin* or tetracycline* or erythromycin* or oxytetracycline* or azithromycin* or amoxycillin* or ciprofloxacin* or pivampicillin* or cefuroxime* or augmentin* or co-trimoxazole* or cefoxitin* or ceftriaxone* or cefixime* or norfloxacine* or ceftazidime* or cefaclor* or ofloxacin*
#13 11 and 12

Methods of the review

One of the reviewers (BA) used the titles, abstracts and full articles to exclude trials which clearly did not meet the inclusion criteria of the review. The nine papers which passed the initial review were then assessed independently by the two reviewers. The methodologic quality of the trials was assessed using the scoring system described in the Cochrane handbook. Two papers were rejected at this stage as there was a concern about the method of randomisation (Ritchie 1958) and no placebo in the control group (Sutrisna 1991).

Scoring system

Selection
1. Randomisation reported but not specified, i.e. little effort to ensure proper randomisation
2. On site computer, random number tables.
3. Centralised or in pre-numbered/coded/identical boxes or containers.

Performance (co-interventions)
1. Allowed but not reported.
2. Allowed, reported.
3. Allowed, reported, analysed or not allowed.

Attrition (Losses to follow up)
1. < 80% overall or not reported.
2. ≥ 80%.
3. ITT, explicit and clear.

Detection bias (Blinding)
1. Not reported.
2. Reported but not fully blinded.
3. Outcome assessment fully blinded.

Disagreement among the reviewers regarding the quality of the articles was readily resolved by discussion and consensus.

Description of studies

Three of the trials in the review included only children (Lexomboon 1971; Gordon 1974; Taylor 1977). The remaining studies included adolescents and adults with no upper limit of age (Hoaglund 1950; Kaiser 1996; McKerrow 1961) and one study that stipulated males aged 20-49 (Howie 1970). Two studies examined only men (Hoaglund 1950 and Howie 1970). Only two of the studies had outcomes as measured by the effect of antibiotics on symptoms (Howie 1970 and Taylor 1977). Unfortunately the denominator for one of these (Howie 1970) was episodes of illness which did not enable the data to be added to the other studies. Side effects in the Howie study were based on individuals and hence side effects have been added to the side effects from other studies. In four studies a form of tetracycline was used (Hoaglund; Howie 1970; Gordon 1974; McKerrow 1961); penicillin, ampicillin and amoxycillin and amoxyccillin and clavulanic acid were used in four others (Lexomboon 1971; Gordon 1974; Taylor 1977; Kaiser 1996); erythromycin in one (Gordon 1974) and co-trimoxazole in one (Taylor 1977). In the study by Kaiser et al there was analysis by culture status of three naso-pharyngeal pathogens H Influenzae, M Catarrhalis and S Pneumoniae. The only trial to do throat swabs on almost all (88/89) participants was that by Gordon et al.

Methodological quality

The methodological scores ranged from 5 to 9 out of 12 but the reviewers did not feel that this was an accurate measure of study quality. All of the seven studies were double blind evaluations comparing antibiotic with a placebo. While no formal description of blinding was included in any of the studies it was assumed that this was satisfactory as the medication was given in a double blind manner and there was nothing reported in terms of unblinding of the patients. The method of randomisation was marginally satisfactory for some of the studies. In the study by Hoaglund et al all the pharmacist dispensed the medication in rotation while in the study by Lexomboon the allocation was determined by the selection of coloured strips and only the pharmacist knew selection of coloured strips and only the pharmacist knew the allocation. All of the studies had either an inclusion criteria that singled out cases of acute viral respiratory tract infection and/or had the term viral or minor respiratory infection or common cold in the title of the study. While there was some variation in the inclusion criteria (e.g. Gordon study had 13% of under 2 year olds and 16% of 2-4 year olds with clinical signs in the chest) the study groups generally included patients with acute upper respiratory tract infection. Loss to follow up was an issue for a number of the studies and none of them analysed the results on an
intention to treat basis.

Results

The same outcome measures were not reported in all the studies. However they all reported some general aspect of improvement. As stated above, theHoiglun study reported the outcome of treatment at 24 hours after medication was started. Although antibiotics are not thought to work so quickly it was decided to leave the findings in the analysis for the sake of being systematic. The study by McKerrow et al (1961) used 15 mg tablets three times daily for the three tetracycline groups in their study. This would be regarded today as sub-therapeutic but has also been included for the sake of being systematic.

Two of four studies reported adverse effects more commonly in the antibiotic group and at statistically significant levels (Howie and Kaiser). The McKerrow study did not distinguish between the pneumoconiosis group and the office group and is not included in the pooled analysis. The summary odds ratio, for adverse effects for all three studies, was increased significantly 2.58 (95% CI 0.71-3.89) (NNH number needed for harm =11). For this summary odds ratio there was significant heterogeneity (chi squared =7.4 p 0.05) and hence the odds ratio was re-calculated using a random effects model OR = 2.72 (95% CI 1.02-7.27). Three studies did not report side effects (Lexomboon; Hoaglund and Gordon). Analysis by type of antibiotic was not undertaken for any of the outcomes as there were only two studies in which the same antibiotic was used. i.e. penicillin was used in the studies by Lexomboon and Gordon and tetracycline in the Lexomboon and McKerrow studies. For the purposes of the analysis the results for different types of antibiotics were added together in situations where more than one antibiotic was used in a study.

The summary odds ratio for overall improvement was non-significant with an odds ratio of 0.95 (95% CI 0.70-1.28). The power calculation, assuming the variance will apply regardless of the true odds ratio, means that a true odds ratio of 0.65 would be detected with a significance level of 5% and a power of 80%. This included the proportion of patients who had returned to normal activity as a surrogate for general improvement or cure in the study by Taylor et al. The only study not to contribute to this analysis (other than Howie) was that by Gordon et al. Their results were expressed as p values with placebo being better at relief of symptoms than ampicillin p=0.05 and no significant difference for placebo Vs erythromycin and placebo Vs penicillin. Only two patients grew beta haemolytic strep in that study so it was decided to leave the study in the review. Only four of the seven reviewed studies were in adults which may explain why smoking was considered in only one of these (Howie). In this study (Howie) there was no significant difference between active and placebo treatments in terms of benefit in smokers or non smokers (p >0.05). The Howie study analysed antibiotic versus placebo by signs and symptoms (cough, purulent nasal discharge, spit and purulent spit) and found no significant differences. The only study to report work loss was that of Howie. The odds ratio for any work loss per episode of illness was 0.85 (95% CI 0.62-1.17). The only study to

The only study to report results relating to the specific symptom entry criteria in a form that could be analysed by the reviewers was that by Taylor et al. In this study there was faster relief from specific symptoms but this was not associated with a faster return to normal appetite and activity. The odds ratio for the return of appetite at day 7 was 0.99 (95% CI 0.45-2.18) (Work loss and return of appetite were not specified a priori as items warranting analysis). The return to normal activity had an odds ratio of 0.56 (95% CI 0.18-1.75) for antibiotic in relation to
placebo. Children in the antibiotic group had less nasal discharge at day 8 than those in the placebo group. The odds ratio for benefit of runny nose (clear) for antibiotic Vs placebo was 0.47 (95% CI 0.24-0.95) (NNT =7) and for runny nose (purulent) was 0.24 (95% CI 0.08-0.74) (NNT=5). It is worth noting that in the study by Howie there was no significant benefit from antibiotics in patients with purulent nasal discharge. A sensitivity analysis was undertaken by adding the findings of the study by Todd et al (1984) to that of Taylor et al (1977). The summary odds ratio for the two added together for purulent rhinitis was 0.64 (95% CI 0.28-1.47). The Todd study was excluded because of the purulent rhinitis. For patients with sore throat in the Taylor study the odds ratio was 0.91 (95% CI 0.22-3.84) for antibiotic vs placebo.

The study by Kaiser et al only found a significant benefit (cure) for antibiotics in the subset of patients who had positive nasopharyngeal aspirates for one of three respiratory pathogens. These were H Influenzae, M Catarrhalis and S Pneumoniae and they made up about 20% of the study participants. Open treatment was prescribed for 11 (39%) patients on placebo and three (10%) co-amoxiclav assigned patients odds ratio 5.8 (95% CI 1.2-31.1).

Summary of analyses

MetaView: Tables and Figures

Discussion

There is no gold standard definition for the common cold (upper respiratory tract infections) and the diagnosis has to be made on clinical grounds. Although the range of inclusion criteria appear wide the reviewers believe that the majority of patients in each study in this review were suffering from viral upper respiratory tract infections. Only two studies reported their findings in terms of the lower respiratory tract; Gordon reported 13% of under two year olds and 13% of those over 6 years to have lower respiratory tract signs and 43% (84/197) of participants in the study by Taylor had auscultatory evidence of more extensive peripheral airways disease. We assumed that this was mainly due to bronchospasm. We excluded studies with significant numbers of patients with streptococci found on throat swab; (see exclusion list for reference) Haight et al 1954 with 28.7% streptococci and Hardy et al 1956 at least 14% streptococci but kept the paper by Gordon et al which had 2 out of 89 (2%) patients with cultures of beta haemolytic streptococci. Other studies did not test for throat bacteria. The issue of bacterial involvement is a concern for reviews of bronchitis, sore throats and upper respiratory tract infections. There is no overlap of studies between our review and the Cochrane review of Bronchitis by Becker et al (http://som.flinders.edu.au/fusa/cochrane) and none with the bronchitis review by Fahey et al (Unpublished). The review by Del Mar on managing Sore throat included one study that is in our review and that is the study by Taylor et al (1977) (ICHPPC 1986). Clearly the larger the proportion of illnesses caused by bacteria that exist among the cases of viral illness the more likely the findings are to show a benefit for antibiotics. There is no other way of defining the disease of interest other than perhaps doing nasopharyngeal aspirations as done in the study by Kaiser et al and throat cultures on all patients. This is not current clinical practice and the purpose of our review is to be relevant to clinical practice.

The a priori outcomes for analysis include resolution of symptoms of nasopharyngeal inflammation, global rating of health and adverse effects. The summary odds ratio for general improvement or cure was 0.95 (95% CI 0.70-1.25). In contrast with the Cochrane review by Becker et al there was no over reporting of significant findings. Indeed there was a tendency to under-report findings and hence less
likelihood of a Type 1 statistical error. In spite of three studies not reporting adverse effects the summary odds ratio for adverse effects from the three that had analyzable data was 2.72 (95% CI 1.02-7.27); two of the studies were statistically significant. The majority of adverse effects were gastrointestinal which is consistent with clinical anecdote. The symptoms of nasopharyngeal inflammation chosen for analysis were sore throat and runny nose, either purulent or clear. The only studies to provide outcome data on this were the studies by Howie and Taylor. The Howie data was not in a form that could be used in this review but reported no benefit from antibiotics for purulent nasal discharge. This was in contrast with the results from the Taylor et al study where antibiotic was significantly better than placebo for runny nose (clear) and runny nose (purulent) at day 8 of treatment. The faster relief of these symptoms in the study was not matched by the return to normal activity and normal appetite both of which were non-significant. There is differing collateral information about this in the literature. In a (acute bronchitis) study by Stott and West (1976) there was a lower incidence of runny nose at day 7 in the doxycycline group than in the placebo group p < 0.01 (Stott 1976). This is not confirmed by the finding from another study which found no effect of antibiotics on purulent rhinitis although the sample size was small (24 -29 participants) which may have resulted in a type two statistical error (Todd 1984). The sensitivity analysis adding the Todd results to the Taylor results produced a non-significant odds ratio. The study by Stott and West did not report analyzable data. The Todd study did not provide analyzable data for the cure or improvement outcome. Our review cannot resolve this issue and it may be necessary for a Cochrane review of studies with an outcome of rhinitis for antibiotics versus placebo.

A sensitivity analysis adding the Ackerman (1968) study to the five others found a summary odds ratio of 0.95 (95% CI 0.71-1.26). Although Robitussin may have no effect on the outcome of the common cold this cannot be assumed a priori. Consequently this paper has been left out of the final analysis.

The role of bacteria in upper respiratory tract infections either as a causal factor or a complication is highlighted in the study by Kaiser et al (1996). They make a convincing argument for the role of three types of bacteria (H Influenzae, M Catarrhalis and S Pneumoniae) and it would be helpful to see this work repeated in another centre.

Although only two of the studies were conducted in general practice (Howie and Taylor) the other studies were either at a military base (Hoaglund), Office staff (McKerrow), casualty clinic (Gordon; Kaiser) or hospital outpatients (Lexomboon) and seem to represent a cross section of patients in primary care settings. If the assumption is made that patients can self refer to these secondary care settings and use them as primary care providers then our results are generalizable to the wider primary care setting.

Reviewers' conclusions

Implications for practice

Antibiotics appear to have no benefit in the treatment of acute upper respiratory tract infections. The implications for practice are that prescription of antibiotics should not be given in the first instance as they will not improve the symptoms and some patients will get adverse effects.

Implications for research

The issue of the effect of antibiotics on nasal discharge either purulent or clear requires further research. A systematic review
is probably needed to resolve the question of any benefit of antibiotics in purulent or clear rhinitis. The clinical implications of this may indicate the use of antibiotics for persisting nasal discharge. Further research is needed on the role of pathogenic nasopharyngeal bacteria and their presence in upper respiratory tract infections.

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Characteristics of included studies

Table: Characteristics of included studies

Characteristics of excluded studies

Study : Ackerman

Exclude as had active control i.e. robirussin. Result. No difference in shortening the median duration of illness or in preventing secondary complications using penicillin V 100,000 units 4 times daily for 10 days and tetracycline 50 mg 4 times daily for 10 days and Robitussin

Study : Banks

Uses ascorbic acid as control group. No difference between tetracycline spiramycin and ascorbic acid.

Study : Bateson

Not randomised nor controlled.

Study : Burke
Burke JB. Prophylactic sulphadimidine in children subject to recurrent infections of upper respiratory tract. BMJ 1956; March 10: 539-41.

Excluded as antibiotics given prophylactically. Results. In children awaiting tonsillectomy antibiotics were associated with 25 colds compared with 60 on calcium tablets p <0.01. The antibiotic group had 30 weeks school absence while the group on calcium tablets had 80 weeks school absence p <0.001. P> Study : Cronk

Excluded as control group had salicylamide in its medication. Results. Better response to aspirin than to penicillin.

Study : Darelid
Excluded as study subjects had cough for 10 days minimum. Results. Moraxella Catarrhalis in 75% of children. An open study with control group untreated. 88% better in erythromycin group versus 36% in untreated group p <0.0001. P> Study : Fraser Fraser PK, Hatch LA, Hughes KEA. A comparison between aspirin and antibiotics in the treatment of minor respiratory infections. Lancet 1962;1:614-7.

Excluded as used aspirin in control patients. Results. Phenoxymentpenicillin and oxytetracycline were no better than aspirin.

Study : Gottfarb

Excluded as study subjects had cough for 10 days minimum. 71% improved on antibiotic while 22% improved on placebo.

Study : Gupta
Gupta S, Bhumus V, Srivastava G. Therapeutic trial of chloramphenicol, Eskaycillin (ampicillin) and co-trimoxazole in respiratory tract infection of childhood. Indian Pediatrics 1977;14:391-3.

Excluded as had no placebo control group

Study : Haight

Exclude as 28.7% have group A Beta haemolytic strep. Results. In non bacterial group there was no difference between non bacterial group there was no difference between erythromicin and penicillin and placebo.

Study : Hardy

Not randomised into treatment groups. i.e supposedly rotated medication but left with unequal numbers in each of 4 groups. The authors of the paper expressed their concern over the adequacy of randomisation. Exclude as at least 14% have Group A Beta Hemolytic Streptococci. Results. No benefit from antibiotics.

Study : Jones

Excluded as used acetylsalicylic acid in control patients. Results. No benefit from antibiotics

Study : Knox

Excluded as used acetylsalicylic acid in control patients. Results. No difference between antibiotics and aspirin. Results. No difference between antibiotics and aspirin.

Study : Kuh

Excluded as antibiotics given prophylactically.
Study: Lapin

Excluded as antibiotics given prophylactically. Penicillin group experienced a lower rate of upper respiratory tract infections and a reduction in number of febrile days compared with the no prophylaxis group.

Study: Lockhart

Not randomised or controlled. Results. Not able to assess any benefit.

Study: Marlow

Excluded as did not meet the entry criteria for URTI i.e. no rhinitis. Results. Statistically significant improvement in sickness but not in soreness of throat.

Study: Mclane

Excluded as control group received APC (acetylsalicylic acid, phenacetin and caffeine) and/or antihistamine. Results. APC and antihistamine and procaine penicillin were more effective at relieving nasopharyngeal symptoms and preventing secondary complications than APC alone or with antihistamine.

Study: Reinert

Excluded because antibiotic combined with topical cortisone. Results. The tixocortol neomycin combination was more effective at controlling symptoms at 7 days than the placebo.

Study: Ritchie
Ritchie JM. antibiotics in small doses for the common cold Lancet 1958;i:618-21.

Corrupted randomisation. Results. The proportion of participants who had full colds was consistently lower in the antibiotic group than in the control group.

Study: Seal

Excluded as antibiotics given prophylactically and focus on streptococcal tonsillitis. Results. Both penicillin and chlortetracycline were effective in the prevention of streptococcal infections during the period of administration.

Study: Sutrisna
There was no placebo group as a control group. Results antibiotic no better than control group.

Study: Todd

Excluded as the study inclusion criterion required the patients to have purulent nasopharyngeal discharge thereby possibly making it more likely for bacteria to be involved. Results. No benefit from antibiotics.

Study: Townsend

Excluded as used prophylactic antibiotics. Results. No benefit from antibiotics.

Study: Townsend 1962

Delete as control group not obtained by randomisation. Results no benefits from antibiotics.

Study: Traisman

Not randomised - simply divided in to 4 groups. Results. No benefit from antibiotics.

Study: Walker

Excluded as was using antibiotic prophylactically. Results. No Benefit from antibiotics.

Study: Wynn-williams

Exclude as patients have complicated past histories for inclusion. Results. 58% reduction in bronchitis in tetracycline group and 49% reduction in the placebo group. The average durations of time off school were 1.9 days and 2.9 days respectively. No statistical testing was reported.

References

References to studies included in this review

Gordon 1974 (published data only)

Hoaglund 1950 (published data only)

Howie 1970 (published data only)

Kaiser 1996 {published data only}

Lexomboon 1971 {published data only}

McKerrow 1961 {published data only}

Taylor 1977 {published data only}

* indicates the major publication for
* indicates the major publication for the study

References to studies excluded from this review

Ackerman
Banks
Bateson
Burke
Cronk
Darelid
Fraser
Gottfarb
Gupta
Haight
Hardy
Jones
Knox
Kuh
Lapin
Lockhart
Marlow
Additional references

Arason 1996

Del Mar 1992

Fahey 1998

Gadomski 1993

ICHPPC 1986

Mainous 1997

McAvoy 1994

McCrae 1996
McGregor 1995

Reynolds 1996

Spector 1995

Stott 1976

Todd 1984

Verkatesum 1995

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Arroll B, Kenealy T
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Contact address :
Dr Bruce Arroll
Associate Professor
General Practice
University of Auckland
Private Bag 92019
Auckland
NEW ZEALAND
Telephone: 64-9-3737599 extension: 6978
Facsimile: 64-9-3737006
E-mail: b.arroll@auckland.ac.nz

For information on the editorial group see: Cochrane Acute Respiratory Infections Review Group
Extramural sources of support to the review
No sources of support supplied
Intramural sources of support to the review
No sources of support supplied
Synopsis

Comments and criticisms

Antibiotics versus placebo for the common cold

Summary of comments and criticisms

METHODS and METHODOLOGICAL QUALITIES OF INCLUDED STUDIES

1. The reviewers use a scoring system for methodological quality, whereby each trial is given a numerical score on a scale of 1 to 12 points. The reviewers then say that they do not think that these scores are an accurate measure of study quality. Furthermore, trial quality is not incorporated into interpretation of the results.

2. It is not clear how concealment of allocation in each trial was assessed. The trials Howie 1970, Kaiser 1996 and Taylor 1977 are reported as having adequate concealment of allocation (A) yet there is no description of how this was achieved. In the trials Hoaglund 1950 and Lexomboom 1971, allocation concealment is reported as unclear (B) yet, according to the Table of characteristics of included studies, in the latter only the pharmacist knew of allocation. Also, why have the reviewers use the option (D) not to assign a score for allocation concealment to the trial Sutrisna 1991? The reader can not find any information in the review about adequacy of allocation concealment for the trial Gordon 1974.

3. The statement that "Loss to follow-up was an issue for a number of studies..." needs to be expanded and loss to follow-up in each trial should be documented in the table of characteristics of included studies. How might loss to follow-up have affected the findings in the review (worst case and best case scenario)?

RESULTS

4. In the meta-analysis of General improvement, it would be better to present the Hoaglund study separately if, as the reviewers say, there is good biological reason why measuring this outcome at 24 hours does not make sense.

5. It is questionable to calculate numbers needed to treat and numbers needed to harm from pooled data without qualification of the conditions to which they apply, and they should not be reported without confidence intervals.

6. There are several inconsistencies in the numerical data reported in the text compared with the graphs.

CONCLUSIONS

7. The statement, in Implications for practice, that "many patients will get adverse effects" from antibiotics is not supported by evidence presented in the review.

REFERENCES

8. The references should be listed in the appropriate reference sections rather than included as text at the end of the conclusions.

CONFLICT OF INTEREST: None.

Reviewer's reply

I thought the comments made were very helpful to us. I have been struggling with the numbers needed to treat information and the
recent BMJ article and some stuff from the EBM mailbase has been useful. I can see the advantages of an electronic database where changes can be continuously made.

METHODS and METODOLOGICAL QUALITIES OF INCLUDED STUDIES

1. The two papers which did not contribute to the review for benefit were the two high scoring studies, Howie with a score of 9 and Gordon with a score of 8. The others either had a 6 or a 7 and we did not feel that there was any face validity in using such a small score difference to meta-analyse the others (referring to the Cochrane library 1999 issue two -the commentator may be referring to the original review which was in fact a draft and put on the Cochrane database by mistake).

2. We assumed that if the authors said they randomised the study then there was adequate concealment of allocation. The study by Sutrisna has been eliminated from the final review as it did not have a placebo control group.

3. The worst case scenario found that the adverse effects became statistically significant when added to the adverse effects of antibiotics but did not change the findings when added to placebo. There was no change for treatment or control when the missing patients were added for general improvement.

RESULTS

4. Removing the Hoaglund study did not alter the results nor did removing the McKerrow study where very low doses of tetracycline (15mg) were used (these would be considered to be sub-therapeutic today).

5. We agree with this comment and quote Smeeth et al BMJ 1999;318:1548-51 that it is best not to use NNT derived from meta-analyses as there are differences in baseline risk. In the next update there are no statistically significant findings apart from runny nose (both purulent and clear in one study). Hence there will be no NNT or NNH. The adverse effects findings have changed as there were 5 patients in the trial by Howie who had side effects on more than one occasion and hence contributed more to the adverse effects. With those 5 patients removed the adverse effects confidence interval now includes one.

6. There were two typographical errors in translating the tables to the data form. Correction of this did not alter the findings.

CONCLUSIONS

7. The commentator may be looking at the original version of the review which as explained above was a draft version. The current version has "there is a significant increase in adverse effects associated with antibiotic use. OR = 2.72 (95% CI 1.02-7.27). This is consistent with findings of other meta-analyses of antibiotics versus placebo e.g. Del Mar C, Glaziou P, Hayem M. Are antibiotics indicated as initial treatment for children with acute otitis media? A meta-analysis. BMJ 1997;314:1526-9. In the next version of the review we have removed 5 patients from the adverse effect intervention group. This makes the adverse event findings non-significant and hence our conclusions will need to note that they are not significant but are very similar to those in other meta-analyses of antibiotic versus placebo which were significant.

8. This will be added to the next version.

Contributors to comment

Heather McIntosh

Keywords