

Nebulized Ipratropium Bromide in Acute Pediatric Asthma: Does It Reduce Hospital Admissions Among Children Presenting to the Emergency Department?

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CLINICAL SCENARIO

An 11-year old boy presents to the emergency department with shortness of breath and wheezing caused by acute asthma. He has a long history of asthma, usually exacerbated by a common cold. Three days before ED presentation, an upper respiratory tract infection developed and he experienced 24 hours of increasing cough, wheeze, shortness of breath, and chest tightness. There was no fever, and he described only occasional sputum production on coughing.

In the 24 hours before ED presentation, he admitted to taking 20 inhalations of his albuterol inhaler. In addition, he received 2 sidestream nebulizer treatments at home. Finally, he had been receiving long-term treatment with inhaled corticosteroids (budesonide; 200 µg/activation twice per day). His last hospital admission was 6 months ago, and he has been compliant with medications recently.

His respiratory rate (40 breaths/min) and pulse rate (120 beats/min) are increased, and saturation by pulse oximetry (SaO_2) is 83% on room air. The peak expiratory flow rate (PEFR) is less than 40% predicted for age, gender, and height. Diffuse wheezing in both lung fields, poor air entry, and use of accessory muscles of respiration are noted on physical examination. Treatment consists of nebulized albuterol every 20 minutes for 1 hour, oral corticosteroids (1 mg/kg prednisone), intravenous fluids, and oxygen. He is monitored for improvement. His condition improves but he remains hypoxic ($\text{SaO}_2 < 90\%$) and tachypneic after 30 minutes. The PEFR is approximately 50% predicted after 1 hour of treatment.

One of your colleagues suggests that nebulized ipratropium bromide may be beneficial in the care of this

child. Believing it unlikely to do harm, and observing the child's continued significant symptoms, you elect to administer nebulized ipratropium treatments. However, you are unsure about whether administration of ipratropium is justified for this patient, vaguely recalling several discussions of its efficacy at a recent conference you attended.^{1,2}

The remainder of this Evidence-Based Emergency Medicine installment will guide you through the process of formulating the question, searching for the best evidence, analyzing the evidence, and applying the evidence to future similar patients. You will also be shown how to critically appraise a systematic review.

FORMULATING THE QUESTION

The success of any evidence-based medicine (EBM) search is the development of a well-defined, clinically relevant, and succinct question.³ As previously discussed in this series,⁴ the question should include focused details on the population, intervention and comparison treatment, and outcomes associated with the clinical scenario. In this particular case, the issue involves a therapeutic or treatment intervention. As a clinician, you may also be interested in side effects (harm) and subgroups, which may specifically benefit from this treatment.

The clinical scenario involves a clear outline of the population (pediatric; <18 years of age), presenting for care in an emergency setting with acute asthma. Although subgroups within this population may be important (eg, very young, severe asthma, those taking inhaled corticosteroids), this broader approach is acceptable as a starting point.

Ipratropium is a quaternary ammonium compound, and along with atropine, is a member of the class of anticholinergics used in airway diseases such as asthma and chronic obstructive pulmonary disease. For this particular clinical scenario, you have chosen to compare treatment with "standard care," which implies that you are interested in the added benefit of this intervention. Whereas considerable practice variation exists with respect to the management of asthma,⁵⁻⁸ the use of repeated β_2 -agonists, corticosteroids,⁹ oxygen, and intravenous access are likely to be considered "standard" practice for a sick asthmatic child.^{5,6} Notwithstanding safety issues, you would also be interested in studies that involve multiple dosing of ipratropium, as opposed to a single nebulized dose.

Finally, outcome domains in acute asthma are highly variable and include administration of medications, pul-

monary function tests (PEFR and forced expiratory volumes in 1 second [FEV₁]), complications (pneumonia, intubation, and so on), as well as admissions to hospital and return visits after ED discharge. Although important results pertaining to any of these outcomes have potential clinical significance, you believe that decreasing the need for hospital admission would have the most direct effect on your patient. Your knowledge of the pathophysiology of asthma leads you to suspect that reduction of return visits is unlikely to result from the initial administration for a drug such as ipratropium. Outcome measures such as pulmonary function tests, vital signs, and oxygen saturation, although likely to be correlated with qualitative benefits, may not tell you what you really want to know about the therapeutic value of ipratropium. You decide to pay close attention to studies and reviews that report on the effect of multiple dose ipratropium administration in the ED on hospital admission rates.

In view of these considerations, it would seem appropriate to reformulate the question as follows: "In children under the age of 18 with acute asthma, does the addition of multiple doses of ipratropium bromide to a standard ED asthma regimen of inhaled β_2 -agonists and corticosteroids decrease the likelihood of hospital admission or result in other improvements in the course of the ED visit?"

SEARCHING FOR AND SELECTING THE BEST EVIDENCE

Armed with a well-developed question, the search strategy can quickly be developed. The efficiency of the search can be increased by seeking the highest level of evidence. For example, since this is a therapy question, the best level of evidence (Level I)^{3,10} includes results from large, randomized controlled trials or systematic reviews of randomized control trials. The next level of evidence (Level II) would be small, randomized clinical trials, that have insufficient numbers of patients to achieve statistically significant results. Finally, cohort (Level III), case control (Level IV), and case series (Level V) would be considered lower levels of evidence for treatment. It is therefore appropriate for a clinician to limit the initial search on a therapy question such as this one to randomized controlled trials or systematic reviews.

You conduct a search of MEDLINE (Internet Grateful Med) on an ED computer, using Medical Subject Headings (MeSH) for "asthma" (MeSH Major Topic) and "ipratropium" (MeSH Major Topic). You initially avoid further limits on your search because you are unsure of how much literature has been published on this topic. In

an attempt to examine the most recent acute asthma literature, you also start by searching between 1990 and 1999, knowing that you can easily extend the search to previous years if nothing is found initially. You find a total of 63 citations (Table 1).

The presence of so many published trials on a single computerized database should trigger the reader to think seriously about alternative strategies before proceeding. One option would be to further limit your search by publication type to either "clinical trial" (pt) or to "randomized controlled trials" and, by age group, to "child, pre-school" (mh) OR "child" (mh). This approach substantially reduces the number of articles you would need to review. However, the results of either search still indicate that many trials involving the use of ipratropium for pediatric asthma have been published.

It would be impractical for you to attempt to identify the ED-related trials and synthesize their results into an evidence-based clinical "bottom line" even if you had the time to evaluate them individually. As a clinician, you lack the expertise to do your own metaanalysis of individual studies. When many randomized controlled trials are published in a particular therapeutic area, a useful "best evidence" approach for the busy practitioner is to search for a systematic review on the topic. The most efficient approach to searching for systematic reviews on topics of therapy is to search the Cochrane Library's Database of Systematic Reviews (CDSR). The Cochrane collaboration is an international, collaborative, multidisciplinary organization whose mandate is to produce, update, and disseminate reviews on the effectiveness of medical therapy. These reviews are produced by researchers using standardized, validated review methods and Cochrane members take advantage of many resources not normally available to the authors of systematic reviews. The Cochrane Library contains the products of the Collaboration and is available by subscription in a CD-ROM version and on-line from Update Software (URL: <http://www.updateusa.com/cochrane.htm>). A limited version of the Cochrane Library can also be obtained from Ovid (URL: <http://www.ovid.com>).

Although systematic reviews completed by the members of the Cochrane Collaboration are occasionally published in traditional peer-reviewed journals, there are drawbacks to this format. For example, the publication of a systematic review in a standard journal is a "one-shot" event; the article's publication precludes systematic updates as new evidence from clinical trials appears. Furthermore, useful interactive features of the CDSR electronic format are lost in journal publications.

A simple, single term, search strategy may initially be an efficient option to searching the Cochrane Library. If this is unsuccessful or results in an untoward number of "hits," an "advanced search strategies" option is included in the Cochrane Library package. Another important option within the Cochrane Library, the Controlled Clinical Trials Register (CCTR), can simultaneously be used to locate individual trials of ipratropium for acute pediatric asthma.

You have heard about some of the unique qualities of Cochrane reviews and decide to start your search with this resource. Using the above techniques, in less than 1 minute, the Cochrane Library provides a full-text version of 1 relevant systematic review most recently updated in February 1997 and a summary of a review by Osmond and Klassen¹² published in 1995 in a peer-reviewed journal (Table 1). Although the Cochrane Collaboration review is also available in a journal format,¹³ for the reasons cited above, you elect to confine your attentions to the Cochrane Library's own version.

Examining the abstracts of the 2 reviews, you notice they arrive at somewhat different conclusions. A detailed perusal will be required to determine the basis for this apparent discrepancy.¹⁴ You elect to start by examining the CDSR review.^{11,15} For reasons that will become apparent, when a review is available on the CDSR, a time-consuming search of other sources should not be neces-

Table 1.

Search results from MEDLINE and from the Cochrane Library for the question pertaining to using ipratropium bromide in acute pediatric asthma ED presentations.

I. MEDLINE (Internet Grateful Med, 1990-1999; 5 min):

Search strategy:

1. Asthma {MeSH Major Topic} [37,650] AND
2. Ipratropium {MeSH Major Topic} [793]
3. Restricted to English language AND human subjects

Search results:

- 63 citations
- More than 5 "reviews"

II. Cochrane Library (1999, issue 1) (30 sec):

Search strategy:

Ipratropium AND Asthma

Search results:

- The Cochrane Database of Systematic Reviews (CDSR): 12 hits, 1,014 total Complete reviews (4 hits, 522 total): 1 relevant to topic Protocols (8 hits, 492 total): 1 relevant to topic
- Database of Abstracts of Reviews of Effectiveness (DARE): 1 hit, 1,895 total Abstracts of quality assessed systematic reviews (1 hit, 727 total): 1 relevant to topic
- The Cochrane Controlled Trials Register (CCTR): 272 hits, 218,355 total References (272 hits, 218,352 total): many relevant to topic

sary.¹⁵ After taking note of 1 large trial cited in the CCTR,¹⁶ you decide to defer further examination of the results of your MEDLINE search until after you have evaluated the systematic reviews you have located. You can then reexamine the citation(s) you found in your MEDLINE search to determine whether any important recent studies were not included in the systematic reviews.

ANALYZING THE EVIDENCE

Clinicians may be unfamiliar with the nomenclature used in systematic reviews and uncomfortable evaluating their validity. However, given the exponential growth of the systematic review literature recently, it is important for emergency physicians to develop sound approaches to their appraisal. This will permit physicians to more rapidly identify the strengths and weaknesses of reviews and decide on their application to emergency care. A number of publications specifically address the evaluation of systematic reviews and metaanalyses. We have adopted the widely accepted JAMA “Users’ Guides to the Medical Literature”¹⁷ installment on systematic reviews which evaluates reviews on 3 key points: “Are the results valid?”, “What are the results?”, and “How will the results help me to care for my patient(s)?” We will start by examining the validity of the 2 reviews and their results.

The 2 reviews are summarized in Table 2. Assessment of a systematic review must be approached in much the same fashion as a high-quality individual controlled clinical trial.

Poorly formulated questions lead to poorly focused answers; the research question must be clearly defined and must fit with the clinical question. In the CDSR review, studies involving pediatric patients presenting to an ED with acute asthma treated with nebulized anticholinergic agents (ipratropium and atropine) were examined to determine the effect of treatment on hospital admission rate as the primary outcome. The review also examined pulmonary function, other physiologic measurements, interaction of treatment effect with steroid therapy, relapse rate, and adverse effects as secondary measurements. The authors started with a clear question that matched the clinical scenario previously discussed.

The journal review included studies from a mixture of ED and admitted patients with acute asthma.¹² The authors identified “any measured clinical or physiologic outcome” without prospectively distinguishing between qualitative and quantitative outcome measures as primary or secondary. Both reviews were restricted to randomized controlled trials, the highest quality level of evidence on therapeutic interventions.^{3,10} In general, the reviews were designed to answer the same question. Therefore differences between their results are not a result of a different question having been asked.

The thoroughness of the literature search done in conjunction with a systematic review is the most challenging and resource-consuming aspect of any review.^{17,20,21} The authors of a systematic review have no control over the

Table 2. Characteristics of 2 systematic reviews of ipratropium bromide in the treatment of acute asthma.

Characteristics	Plotnick & Ducharme ¹¹ /CDSR	Osmond & Klassen ¹² /MEDLINE
Year published	1997	1994
Years covered	1966-1997	1966-1992
No. of studies included	10	6
No. of patients included	836	285
Ages included	18 mo-17 y	<18 y
Population	ED	ED+Inpatient
Search methods	Multiple databases+Hand searches+Letters to investigators	MEDLINE+Science Citation Index+Letters to investigators
Language restriction	None	English
Unpublished data included	Yes	No
Independent study selection	Yes	Yes
Outcome measures	1st—Hospital admission 2nd—Pulmonary function	Any clinical or physiologic outcome
Duplicate data extraction	Yes	No
Measure of trial quality	Jadad scale	Authors’ own scale
Statistic*	WMD/OR	WMD/ES
Heterogeneity measured/reported	Yes	Yes

*WMD, Weighted mean difference; OR, odds ratio; ES, effect size.

conduct of individual studies they select. However, they can reduce the biases associated with the selection of studies by attempting to include the entire population of eligible studies in their investigation.²¹ One of the Cochrane Collaboration's unique contributions to the methodology of systematic reviews has been to both demonstrate a methodology that addresses such a standard and to assemble the collective resources through a coordinated international volunteer effort that make such a methodology possible.²²

Search methods used in systematic reviews should be considered a form of detective work. Searches of MEDLINE alone, no matter how well planned and conducted, are insufficient to "find" all clinical trials relevant to a particular subject.²³ Moreover, simple searches of MEDLINE, which are not systematic, will not identify *all* clinical trials in a specific topic area.²⁴ Because of indexing issues, MEDLINE searches have been found to identify as few as 50% of all available randomized control trials in a topic area.^{23,24} The CDSR protocol uses a multiplicity of computerized and noncomputerized strategies designed to maximize the yield of all possibly relevant studies for a particular review.²¹

The CDSR review used search strategies that include computerized, standardized searches of the Cumulative Index of Nursing and Allied Health (CINAHL; 1982-1995) and Excerpta Medica (EMBASE; 1980-1995) databases in addition to MEDLINE (1966-1995). EMBASE is a European-based register of pharmacologic and biomedical literature whose journal indexing and inclusions are somewhat different from those of MEDLINE. CINAHL is a nursing and allied health database which may provide additional references in certain topic areas (eg, mental health, education). The CDSR searches were further updated for the 1997 review entry. The bibliographies of all studies found using these search strategies were reviewed independently by 2 reviewers. Finally, the Canadian headquarters of the manufacturer of ipratropium was contacted, and inquiries were made regarding researchers and research studies under their company's direction. The authors also made personal contacts with relevant trialists and colleagues in the field of pediatric asthma.

The CDSR search protocol takes advantage of a massive international volunteer hand searching effort, coordinated by the Cochrane Collaboration. Randomized controlled trials found through this effort are entered into the Cochrane Controlled Clinical Trials Register (CCTR; Table 1), which is routinely included in the CDSR search protocol and is available as part of the Cochrane Library.

Specific hand searching of 20 journals relevant to respiratory diseases and periodic review of relevant conference proceedings also contributed to the strength of the CDSR search protocols. Many airways reviews take advantage of this strategy through a central register maintained by the Cochrane Airways Group.

As is true of many published reviews, the literature search by Osmond and Klassen¹² was limited because of practicalities of context and resources. This is acknowledged by the authors. The review was limited to a single-strategy MEDLINE search of English-language publications between 1966 and 1992, supplemented by bibliographical and Science Citation searches. Written contact with principal investigators of studies identified through the search strategy was performed, but non-English and unpublished literature was not obtained.

Comparing the search results of the 2 systematic reviews, the review by Osmond and Klassen¹² included 6 studies between 1985 and 1988, all of which are included in the MEDLINE database and 2 of which involved patients studied in an inpatient setting. The CDSR review included 10 studies between 1985 and 1997. It included the 4 ED studies identified by Osmond and Klassen, as well as 3 studies not included in MEDLINE. Two of these were the direct result of searching for unpublished data. Finally, the publication of the earlier review in 1995 does not guarantee that it will be updated. The CDSR review will automatically incorporate new evidence as it arises.¹¹

The quality of the studies included in a review has implications with respect to the conclusions drawn. For example, a methodologically high-quality review, which includes low-quality primary studies (based on specific criteria), should lead the reader to interpret the results with caution. Researchers have demonstrated that weaker studies that obtain lower scores on quality assessment tend to overestimate the effect of treatment by approximately 34%.²⁵ Therefore the impact of trial quality is an important consideration when assessing a systematic review.²¹

Many quality scales and scoring systems are available.²⁵ The CDSR review used 2 simple scoring systems, 1 developed by the Cochrane Collaboration (based on concealment of allocation)^{21,26} and 1 developed by Jadad et al,²⁷ that demonstrate substantial reliability and validity. The scoring system developed by Jadad et al encompasses the 2 issues that have been empirically shown to affect study results: randomization²⁸ and double blinding.²⁶

The authors of the published review used a quality scale devised for use in their review; it included both methodologic and population criteria.¹² Although this

may be a valid approach, there was no justification for its use or proof of its performance characteristics provided. Despite the apparent methodologic rigor used in the CDSR review, there was no evidence in the analysis that study quality had any significant effect on the results. However, the authors did conclude that the overall quality of most included studies was “very good.”

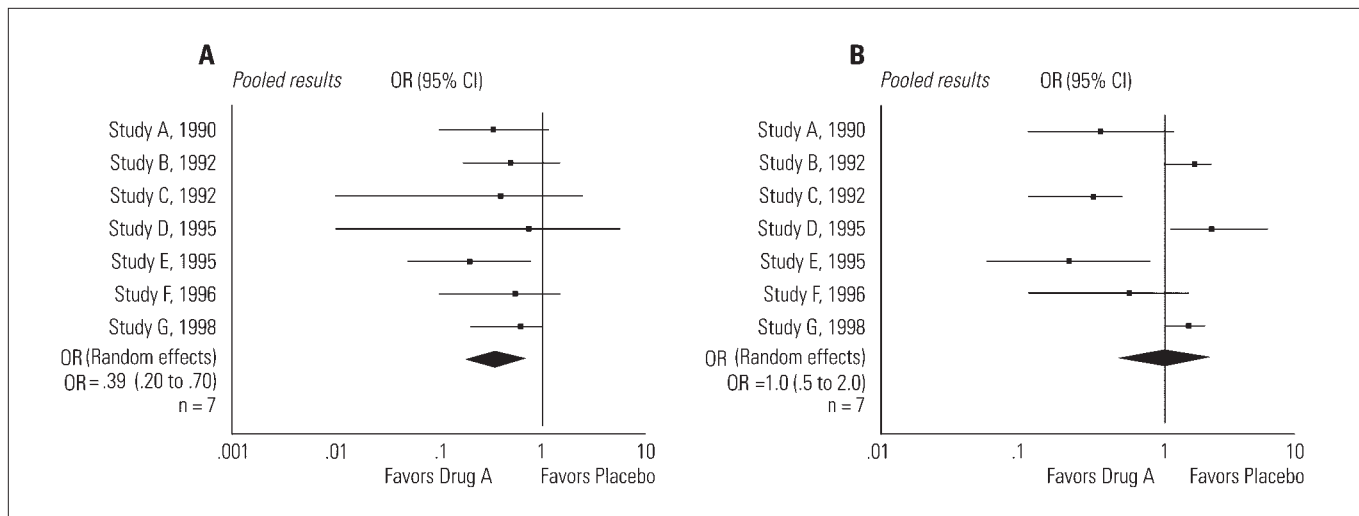
Systematic reviews ideally involve collaboration between members of a research team. The reader should search for evidence that a single author’s own bias(es) did not influence either the inclusion of trials in the systematic review or the assessment of trial quality. The most valid method to ensure that this bias does not exist is to have a blinded, independent comparison of the relevant and included studies and quality scores for studies by 2 or more assessors using scoring criteria described a priori. Both reviews under discussion describe independent application of the selection and quality rating of included studies and resolution of differences by consensus. There is no evidence that bias materially affected

either the selection or evaluation of individual studies in either review.

One of the most common questions about systematic reviews is whether differences between studies have been accounted for and analyzed. This particular aspect of systematic reviews is called *heterogeneity*, a term that refers to the degree to which studies differ within a metaanalysis.^{21,29} Hypothetical examples of homogeneity and heterogeneity in results are shown in the Figure, parts A and B, respectively. High-quality systematic reviews describe a priori approaches to dealing with heterogeneity. The main methodologic concern for the reader at this point is whether it is appropriate to pool the studies. Primary studies must be similar in design, population, intervention, and outcome to justify pooling in a statistical manner. When differences between studies appear sufficiently extreme, either by visual inspection or statistical testing, the authors may elect not to pool their results but rather to review the studies individually.²¹

Figure.

Homogeneity of pooled analyses of Drug A versus placebo for the treatment of asthma in the ED: analysis of admission rates. In this hypothetical example of a metaanalysis, the results of 7 fictitious studies on efficacy of Drug A for asthma are displayed. Each study is represented by the point estimate for the outcome in question and by CIs on either side of that value. The vertical line corresponds to an OR of 1.0. **A**, In all 7 trials, the point estimate lies to the left of the vertical line, indicating benefit of Drug A for the outcome measure in question. Furthermore, all of the point estimates are close together and the CIs all overlap. The large horizontal diamond at the bottom of the figure corresponded to the pooled results of the individual studies. In this case, the studies are homogeneous and pooling is appropriate. **B**, Among the 7 trials, the point estimates lie variously to the left or to the right of the vertical line. The results of the former studies imply benefit of Drug A; those of the latter studies imply that Drug A does harm with respect to the outcome measure in question. Furthermore, all of the point estimates vary widely and some CIs do not overlap. The large horizontal diamond at the bottom of the figure corresponded to the pooled results of the individual studies. In this case, the studies are heterogeneous. Pooling of the results may not be appropriate.



The “bottom line” for the clinician when reading a systematic review is that heterogeneity should be discussed, examined in an a priori fashion, and explained by the authors if it is either visually or statistically present. Both Osmond and Klassen¹² and Plotnick and Ducharme¹¹ describe the statistical methods used to evaluate heterogeneity, as well as their findings in this regard. In the CDSR review,¹¹ the authors found significant heterogeneity only with respect to trials that involved single-dose treatment with ipratropium. They elected to pool the results with some adjustment for the heterogeneity in that case.

On a 4-point categorical scale of “weak, fair, very good, excellent,” you assess the CDSR review to merit an “excellent” rating. You also note that the limitations of the study by Osmond and Klassen¹² primarily involve the potential for bias resulting from a failure to locate relevant unpublished data and more recently published studies. This is commonly referred to as “publication bias.” Secondly, the less-focused a priori definition of the outcomes and population is of some concern. As a result of this, the results of the CDSR review emerge as the most relevant to your clinical question.

CDSR reviews characteristically present their results with exhaustive completeness, looking at all primary and secondary outcomes. Although this approach contributes to the usefulness of CDSR reviews, it poses a special challenge to clinicians who may not have defined in advance what specific results are relevant to their own clinical question. Consequently, a clinician should decide which outcomes are important to patient management, and focus specifically on these.

You have decided in advance to look for results involving multiple doses of ipratropium combined with standard use of β_2 -agonists and corticosteroids from the standpoint of the efficacy of ipratropium in reducing the likelihood of hospital admission. Your own “review methodology” helps to simplify your scanning of the results of the CDSR review.

Many clinicians are also unfamiliar with the statistical methods applied to systematic reviews. Obviously, there is reason to be concerned, because statistics can be used inappropriately. However, if the review has been of high quality to this point, it is unlikely to fail on the basis of the statistical tests applied. For the clinician in search of an answer, it is sufficient to know that, irrespective of the mathematical technique for pooling data chosen by the authors, those studies with the largest sample sizes and the least variation of outcome measurements within the study populations will proportionally contribute more to the pooled estimate.

A reader contemplating research or an original review in the topic area of a CDSR review will find it useful to examine the full scope of results as reported and tabulated by the authors. A unique program feature of the CDSR reporting format, taking full advantage of the electronic publication framework, is called MetaView. The MetaView display provides a graphic presentation of the results, with favorable treatment effects displayed to the left of the neutral line, and unfavorable treatment effects displayed to the right of the line (Figure A). The reader can quickly obtain an overview of the effect of treatment by looking at the trends for all outcomes or examine each individual outcome more closely.

The authors of metaanalyses often provide a single, pooled estimation of effect from the individual studies. These can be presented as “odds ratios” (ORs) for dichotomous variables (yes/no response such as admission) or as weighted mean differences (WMD) for continuous variables (such as PEFR). ORs reflect the ratio of the odds of a patient experiencing an outcome (in this case admission) in the intervention group compared with the odds in the control group.²¹ For example, if 20 of 100 patients in the treatment group experience an outcome, the odds are $20/80 = .25$. If in the control group, 40 of 100 experience the outcome (odds $40/60 = .66$), the $OR = .38$ ($.25/.66$). An OR of 1.0 suggests no difference between the intervention and the control group. For adverse outcomes such as admission, ORs less than 1.0 reflect a benefit of experimental treatment. ORs greater than 1.0 reflect better outcomes in the control group, implying that the treatment might cause harm.

CI s are usually reported in association with all outcomes, and these reflect the precision of the results.³⁰ Wide CI s suggest an imprecise estimate; narrow CI s reflect precision. Finally, CI s also indicate statistical significance.³⁰ CI s that cross the neutral line of 1.0 are not considered statistically significant, and CI s that do not cross 1.0 are considered significant.

Five studies that reported the effect of multiple doses of ipratropium combined with standard therapy on hospital admissions were included in the CDSR review. A 38% reduction in hospital admissions was demonstrated with the multiple-dose ipratropium protocols ($OR .62$; 95% $CI .39$ to $.98$). These results, presented as conventional metaanalysis ORs, can be converted to a more clinically relevant outcome measure, such as the number of patients needed to treat (NNT) to prevent 1 unwanted outcome.^{3,31,32} In their review, Plotnick and Ducharme^{11,13} report the NNT for a strict multiple-dose protocol as 11; the CI s for a combined NNT are wide

(95% CI 2 to 446). In addition, a significant difference was observed between the groups for percent change in FEV₁. For example, on average, patients receiving multiple doses of ipratropium recorded 10% higher FEV₁ results (95% CI 4 to 15) at 60 minutes. Pulmonary function test changes of this magnitude are thought to represent a clinically important and detectable difference.⁶ From the CDSR review, no statistically significant increase in side effects (vomiting, nausea, tremor) were observed with the use of anticholinergics.

The authors of the CDSR review did not thoroughly examine the benefit of ipratropium in moderate-severe acute asthma because of the small number of studies reporting these subgroups and the small number of patients. However, they did examine the issue of counterintervention with inhaled corticosteroids and concluded that the effect of ipratropium was enhanced by coadministration of steroids.

The results of the review by Plotnick and Ducharme¹³ suggest a clear benefit of ipratropium administered in multiple doses in combination with β_2 -agonists and corticosteroids in reducing hospital admissions of children presenting to the ED with acute asthma. Your original MEDLINE search identified a recent large study of ipratropium use in children that emphasized hospital admissions in the title.¹⁶ You noticed from the abstract that the 434 patients included in this study constitute a larger number of patients than included in the pooled results of the review by Plotnick and Ducharme¹³ for this outcome and are curious about whether the results of this study agree with those of the review.

A quick review of study by Qureshi et al¹⁶ reveals that it is of high methodologic quality (5/5) according to the criteria of Jadad et al.¹⁵ The population studied, children between the ages 2 and 18 years presenting to a pediatric ED with acute asthma, corresponds closely to your own clinical scenario. All patients were treated with albuterol and corticosteroids, and then were randomly assigned to receive 2 doses of either ipratropium or an identical-appearing placebo in a double-blind fashion. Although negligible differences are reported between the study groups in the secondary outcome measures such as pulmonary function tests, the authors report a virtually identical benefit of ipratropium with respect to hospital admissions (NNT=11, 95% CI 6 to 269). Moreover, the effect was most pronounced in the most severe cases of asthma (NNT=6). Again, no clinically significant adverse effects of ipratropium were reported.

You are impressed with the agreement between the metaanalysis¹¹ and the large trial.¹⁶ Agreements between

results from reviews and large clinical trials are reassuring and common with Cochrane reviews¹⁶ but are observed less often with other types of systematic reviews.^{14,33} Although the wide CIs around the NNT of 11 reported in both studies indicate that there is a statistical chance that the benefit of ipratropium could be less impressive, you anticipate that the incorporation of the results of the trial by Qureshi et al¹⁶ into an updated version of the Cochrane review will substantially narrow the CI around the outcome in question. This and the agreement between the studies persuade you that the true benefit is very likely to be clinically significant.

APPLYING THE EVIDENCE

Having searched for and reviewed what you consider the best and most relevant evidence, you now apply the evidence to this or future similar patients in your ED. To do this you must translate the evidence to your own practice setting and patient population. Despite the apparent relevance of a particular review, it may be difficult for clinicians to use the results in caring for the patients in their setting. Examination of the populations of the trials in the review by Plotnick and Ducharme¹³ reveals that a large number of trials (10) recruited patients with variable ages, baseline severity, and sample sizes. These observations suggest that the results are based on typical patients from the ED setting. Examination of the treatments of the trials in the CDSR review reveals the dose of ipratropium used varied from 250 μ g to 500 μ g per dose, and most patients received this by means of a nebulizer system. This delivery approach for ipratropium would be similar to most busy EDs in the United States and Canada using this agent.⁷ Repeated doses were usually given as 250 μ g/dose every 20 to 60 minutes for a total of 2 to 6 doses. Finally, counterinterventions such as regular inhaled β_2 -agonists were used in all and many used systemic corticosteroids.

An important consideration in applying the evidence is the question of whether all of the important outcomes were considered. A focused question often includes 1 specific outcome measure. However, the reader may also be interested in secondary outcomes, side effects, and patient preferences. Although patient preferences are often not reported in clinical trials and therefore systematic reviews, side effects and secondary outcomes are commonly encountered. The importance of secondary outcomes is that, if their pooled results are concordant with that of the primary outcome, this adds corroborating evidence to the conclusions. In addition, side effect pro-

files provide the clinician with the opportunity to evaluate the risks associated with the treatment.

In the end, a clinician must decide whether the benefits of treatment are worth the costs and harms associated with the care. This is often a difficult task; however, it is made less difficult by comprehensive reporting of all outcomes. In this particular case, ipratropium is not particularly expensive and can be used in a variety of doses. Patients experience few side effects. Furthermore, it appears to be effective, particularly for the selected asthmatic in the ED and in multiple doses. Consequently, it would appear that the benefits of ipratropium outweigh the costs and harm associated with its use.

The CDSR review,¹¹ in agreement with the more recent large randomized controlled trial,¹⁶ identifies the beneficial effect of ipratropium in the patient from our original scenario. This review represents a comprehensive, unbiased, pooled analysis of available literature and would suggest that our patient would benefit, at least with multiple-dose ipratropium, in the ED (see critically appraised topic summary³⁴).

Given this evidence, using input from the patient/guardian (preference) and physician experience, there are a variety of potential applications of the systematic review results. First, in a patient with mild asthma whose condition is improving, a clinician who is experienced with treating asthma and has provided best evidence care in other areas (eg, provision of repeated β_2 -agonist care, use of systemic corticosteroids) could safely manage the patient without ipratropium treatment. This would be particularly true if the patient had experienced adverse effects previously with ipratropium treatment or was reluctant to try a new agent for his or her disease.

However, for the patient with more severe asthma or one who had received evidence-based care and still required aggressive management, additional treatment with ipratropium would seem to be justified. The patient presented in the Clinical Scenario (or future similar patients) should be considered an ideal candidate for multidose ipratropium therapy.

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Critically Appraised Topic (CAT):

Nebulized Ipratropium Bromide in Acute Pediatric Asthma: Does It Reduce Hospital Admissions Among Children Presenting to the Emergency Department?

Title	Nebulized ipratropium bromide in acute pediatric asthma
Reviewed by	Rowe BH, Travers AH, Holroyd BR, Kelly KD, and Bota GW
Date	December 1998
Expiration date	December 1999
Question	In children under the age of 18 with acute asthma, does the addition of multiple doses of ipratropium bromide to a standard ED asthma regimen of β_2 -agonists and corticosteroids decrease the likelihood of admission to hospital or result in other improvements in the course of an ED visit?
Clinical bottom line	These results are based on a metaanalysis of 10 trials, and 1 large trial in which children with acute asthma were administered anticholinergic agents (250 to 500 μg per dose of ipratropium in multiple-dose fashion). In repeated doses, ipratropium also reduced hospital admissions (NNT=11). Ipratropium appears to be safe and well-tolerated by patients from 2 to 17 years of age.
Search strategy	"Asthma" AND "Ipratropium." Search applied to 1999 Cochrane Database of Systematic Reviews (CDSR) on the Cochrane Library and Internet Grateful Med.
Citations	Primary Plotnick LH, Ducharme FM: Combined inhaled anticholinergics and β_2 -agonists for initial treatment of acute paediatric asthma [Cochrane Review]. In: The Cochrane Library, issue 1. Oxford: Update Software, 1999. Supportive Qureshi F, Pestian J, Davis BA, et al: Effect of nebulized ipratropium on the hospitalization rates of children with asthma. <i>N Engl J Med</i> 1998;339:1030-1035.
Critical appraisal of primary citation	Population Children with presentations of acute asthma to the ED Interventions Single (5 studies) and multiple-dose (5 studies) wet nebulization of ipratropium (9 studies) or atropine (1 study) Outcomes Admissions, pulmonary functions, and complications Design Systematic review of randomized controlled trials
	The systematic review controlled for publication and selection bias to identify all relevant studies for the review. In addition, the a priori protocol and the methods of relevance, inclusion, and quality assessment were independent and valid. Finally, data extraction was verified and the data were pooled appropriately with no heterogeneity. These results were confirmed by the results of the supportive citation, a recently published similar large, high-quality randomized controlled trial.
The evidence	For multiple-dose ipratropium bromide treatments Primary citation Admission OR: .62 (95% CI .38 to .99); NNT: 11 (95% CI 2 to 446; assuming a control admission rate of 34%); increased percent predicted FEV ₁ by 10% (60 minutes) Supportive citation Admission OR: .65 (95% CI .43 to .98); NNT: 11 (95% CI 6 to 269)
Recommendations	Multiple doses of ipratropium bromide can be safely administered over the first hour of ED treatment for acute asthma, and this treatment is effective in the treatment of asthma. Ipratropium bromide should be provided to children with acute asthma.

NNT, Number of patients needed to treat to prevent one hospital admission; **FEV₁**, forced expiratory volume in 1 second;

OR, odds ratio: an OR<1 indicates benefit of the therapy; **CI**, confidence interval.