Complementary/Alternative Medicine for Asthma

We Do Not Know What We Need To Know

Complementary/alternative medicine (CAM) has become an increasingly topical theme in respiratory medicine. It has been defined as "diagnosis, treatment and/or prevention which complements mainstream medicine by contributing to a common whole, by satisfying a demand not met by orthodoxy or by diversifying the conceptual frameworks of medicine." CAM comprises well over 100 different therapies, which have little in common. Each therapy proclaims to be a veritable panacea. Some of the most prevalent complementary treatments are acupuncture, aromatherapy, herbalism (phytotherapy), homoeopathy, reflexology, and spinal manipulation (chiropractic and osteopathy). For asthma, the most frequently tried therapies are breathing techniques (including yoga), herbalism, acupuncture, and homoeopathy, but the whole spectrum of CAM is also used.

CAM has become an important topic because it has grown immensely popular and increasingly profitable. In the United States, 40% of the general population is using some form of CAM. With asthma patients, the prevalence figures may be even higher. A recent survey by the United Kingdom National Asthma Campaign showed that only 41% of all 4,741 respondents had never tried any type of CAM, and 33% of all asthmatic children have experience with CAM. It is therefore timely to ask whether CAM is, at all, evidence based.

CAM is often perceived as effective by those who use it. For instance, in the above survey, 43% of asthma patients thought that breathing techniques were useful to "a great" or "some" extent. For acupuncture, this figure amounted to 44%, herbalism, 42%, and homoeopathy, 43%. Perceived effectiveness, however, is composed of specific and non-specific effectiveness, i.e., therapeutic success can be brought about by a specific mechanism of the given treatment (e.g., endorphin release after acupuncture, pharmacologic actions of herbal constituents), or by factors not directly related to the therapy (e.g., empathy, time spent with the patient, expectation, etc). Each of the two elements can vary in size from 0% to approximately 100% of the total therapeutic effect. It seems obvious that rigorous research should differentiate the nonspecific from the specific effects, because in the final analysis, this is in the interest of the asthma patient.

There are still too few investigations into the effectiveness of CAM for asthma. A systematic search of the available data revealed that randomized controlled trials existed only for acupuncture ($n = 13$), herbalism ($n = 2$), homoeopathy ($n = 2$), hypnosis ($n = 2$), spinal manipulation ($n = 1$), reflexology ($n = 1$), relaxation/meditation ($n = 9$), and yoga ($n = 3$). Studies of CAM also tend to be methodologically flawed, and the emerging evidence is usually contradictory. Therefore, systematic reviews could provide the best possible summary of the existing knowledge. (The selective citation of evidence fitting a particular hypothesis seems to be disappointingly prevalent in CAM, but it can be seriously misleading.) The conclusions of all systematic reviews of CAM include the following: (1) Breathing techniques: "Too few studies have been carried out to warrant firm judgments"; and (2) Acupuncture: "It is not yet possible to make any recommendations to patients, their physicians or acupuncturists about the practice of acupuncture in the treatment of asthma on the basis of the data currently reported."

As for homoeopathy and asthma, there were no positive results found by a thorough meta-analysis of all randomized or placebo-controlled trials. For the other above-named treatments, no systematic reviews in relation to asthma are available.

This disappointing state of affairs is difficult to reconcile with the success of CAM in everyday clinical practice. About 50% of all individuals (not just asthma sufferers) using CAM are satisfied with it. To a large extent, this could be due to the quality and character of care more than the specifics of the given therapy. For instance, a recent survey, showed that patients who use CAM and mainstream medicine in parallel (not for asthma), consistently rate the...
quality of the therapeutic relationship with CAM practitioners higher than that with conventional doctors.15 We should, however, remember that absence of evidence must never be confused with evidence of absence for efficacy (or safety).

Even if a given (complementary or orthodox) treatment were entirely devoid of specific effects, this would not necessarily mean that it is totally useless. There may be a case for “evidence-based placebo treatments” as an adjunct to conventional asthma treatment.16 Nonspecific effects can undoubtedly be an important part of the total therapeutic effect of any treatment, mainstream or complementary.6 This area is much neglected by present research. We need to understand the determinants of nonspecific effects better than we do at present.17 This type of inquiry is not aimed at denigrating CAM. Its objective is to determine how to optimize nonspecific effects and to find out how they can be used more widely to benefit the patient. Also, there may be important lessons to learn for mainstream respiratory medicine.

One essential precondition would, however, be the safety of the interventions in question. CAM is often promoted and perceived to be entirely riskfree. Yet, practitioners should know better, and patients should not be misled. Quite simply, there will never be a therapy that is totally devoid of risk. In conventional medicine, risks are routinely recognized, monitored, and quantified. This is necessary for balancing them against the potential benefit of a given treatment. We will employ a therapy only if the benefits outweigh the potential risks. What probably sounds like a platitude to respiratory physicians amounts to a veritable revolution for CAM where comparable risk benefit analyses are rarely possible. Not only are we uncertain about the benefits of most complementary therapies (see above), we also know far too little about the risks of CAM. All we do know is that complications, even serious ones, are on record,18 but we cannot even begin to estimate their frequency. Some of these risks include the following: (1) Acupuncture can cause trauma of vital tissue (eg, pneumothorax or cardiac tamponade); (2) Acupuncture can cause systemic infections (eg, hepatitis); (3) Some herbal remedies are hepatotoxic; (4) Some unregulated herbal remedies are adulterated (eg, with heavy metals or conventional drugs); and (5) Homoeopaths believe that their remedies cause (often severe) aggravation of symptoms in about 25% of all cases.

In addition to direct adverse effects, there is a further, even more neglected safety issue; even if a given form of CAM were entirely safe, the complementary practitioner who administers it may not be. Examples of this could be the overuse of radiographs by chiropractors19 or the advice against immunizations offered by some nonphysician homoeopaths and chiropractors.20

All experts agree that rigorous research must be conducted. As a first step, systematic reviews should establish what is already known and define specific research questions. Subsequently, these should be addressed with the most rigorous research design possible. It is true that in CAM some trials cannot be double-blind and placebo-controlled. Yet, there is no excuse for introducing double standards: randomized clinical trials are usually possible and always desirable.21 ‘Evidence-based CAM’ must no longer remain a contradiction in terms. We need to advise our patients responsibly about the risks and benefits of these treatments.22 Neglecting this challenge would be neglecting the best interests of our patients.

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REFERENCES
4 Ernst E. Use of complementary therapies in childhood asthma. Pediatric Asthma Allergy Immunol 1998; 12:29–32
5 Häusermann D. Wachsendes Vertrauen in Naturheilmittel. Dtsch Arzteblatt 1997; 94:1857–1858
6 Ernst E, Resch KL. The concept of the perceived and true placebo effect. BMJ 1995; 311:551–553
8 Borchgrevink CF. Forskning i alternativ medisin. Tidsskr Nor Legeforen 1997; 117:2469–2473
9 Crombie IK, McQuay HJ. The systematic review: a good guide rather than a guarantee. Pain 1998; 76:1–2
Steroids in COPD

The Nearly Eternal Question

Therapeutic trials of corticosteroids in stable COPD have been going on for 40 years, and the occasion for this editorial is another such trial in this issue of CHEST (see page 31), a good indication that the role of steroids in COPD is not yet settled. Why is this the case? First, steroids unquestionably work in asthma, and asthma has features in common with COPD, therefore, steroids “ought” to work in COPD. However, one could argue that the only trials that have shown unequivocally positive results were trials that did not exclude asthmatics. Second, many of the trials in patients fulfilling stringent criteria for COPD have shown substantial short-term benefit in some 15 to 30% of subjects; these benefits seemed too large to be accounted for by random variation, and were not predictable on the basis of the usual baseline characteristics, including those thought to relate to asthma. Third and finally, the advent of inhaled steroid preparations has substantially lowered the risk of steroid therapy, so that the size of a practically useful benefit has decreased. Indeed, in many areas of North America at least, the use of inhaled steroids in COPD has become widespread in the absence of clear evidence of benefit.

The study from Kyoto by Nishimura and colleagues in this issue is reminiscent of the short-term, crossover, double-blind trials of the 1980s, the major difference being that high-dose inhaled beclomethasone dipropionate (BDP) was used as opposed to systemic agents. A well-characterized group of 34 stable patients with moderate to severe COPD were studied: the baseline FEV₁ ranged from 15 to 66% of predicted normal. BDP was given at a dose of 3 mg/d for 4 weeks and crossed over with placebo in double-blind fashion; there was apparently no washout period between treatments, but the authors sought to avoid carryover effects between treatments by collecting data during only the last 2 weeks of each treatment period. This was successful to the extent that there was no significant order effect observed in the results. The dose of BDP was deliberately set at the upper limits of those usually employed on the argument that the investigators were interested in the “maximum” benefit obtainable with inhaled therapy. This was certainly a very high dose. Outcomes were essentially spirometric measurements and diary data including peak expiratory flow (PEF) and symptom scores. The group as a whole showed better lung function on BDP than on placebo, but mean differences were small: FEV₁ differed by about 10% (0.1 L) and PEF by less. There was significantly less wheeze and dyspnea on BDP than on placebo, but not less cough and sputum. Patients preferred BDP to placebo, but this preference was better related to a decline in lung function during the placebo period than an improvement on BDP. The BDP-placebo difference in FEV₁ was greatly influenced by five patients who had increases of 0.24 to 0.51 L (mean, 0.34 L) on BDP; these increases were outside the 95% confidence limits of the responses to placebo. Nishimura et al describe these individuals as “steroid responders” and argue that steroid therapy should be limited to such responders. This argument is based upon the high price of inhaled steroids, by a significant association of BDP with adverse side effects including sore throat and hoarseness, and by the evidence of systemic effects of BDP.

How are we to interpret this interesting and carefully done study? It is supportive of current COPD guidelines which recommend use of steroids only in patients who show objective benefit during a steroid trial. Implicit in this rationale is that there are two kinds of patients with COPD: those who do respond to steroids and those who don’t. In other words, steroid response in COPD patients has a bimodal distribution. Some studies support this view, but others do not. Indeed, Nishimura and colleagues show their individual responses, and a bimodal distribution is not clearly evident. If steroid response is, in fact, normally distributed among patients with COPD, then “steroid responders” are simply individuals who fall at one end of the normal distribution. One then assumes that the people at the extreme(s) of the distribution are different from the others in the absence of any a priori reason to do so.
Under these circumstances, steroid therapy also assumes that these extreme responses are reproducible, something that has not, to my knowledge, been confirmed. Indeed, trials of steroids during exacerbations of COPD have yielded more impressive results than in stable disease, suggesting that steroid response in individual patients may vary with time and circumstance. On the other hand, one could argue that the most important finding of Nishimura et al is that steroids tended to increase FEV₁ slightly in most or all of the patients as compared to placebo. If this is true, then the question is whether the risk-benefit ratio of such a small increase is acceptable; in considering this, we must recognize that the local and systemic side effects observed by Nishimura and colleagues were related to their very high dose of BDP, and that similar benefits might be obtained at lower doses with less side effects.

We presently stand on the threshold of a considerable increase in data, and one hopes, knowledge, concerning inhaled steroids in COPD. A multinational study of the effects of 1 mg/d of inhaled fluticasone in COPD over 6 months has just been published. There was a suggestion that the frequency of severe exacerbations was decreased, but this is an extremely difficult end point to ascertain with certainty. There were also small improvements in lung function and decreases in complaints of cough and sputum, though not of dyspnea. Lung function changes were similar to the mean data of Nishimura and colleagues; on steroids, lung function improved some 10%, about what one would expect to see with bronchodilator therapy. The clinical significance and risk-benefit ratio of such a result is not clear to this reviewer. If this is true, then the question is whether the risk-benefit ratio of such a small increase is acceptable.

Editorials

Causes of Chronic Airway Disease

Chronic airway disease is a major cost to the community and, as a matter of some urgency, the causes of this group of conditions need to be defined. Most physicians would be able to point to a multifactorial situation with airway inflammation, loss of pulmonary elastic supporting tissue, bronchial muscular dysfunction, and accumulation of secretions due to mucociliary impairment all...
having the potential to explain the pathogenesis. The further superimposition of variables such as the hypoxic polycythemic response, central sensitivity to carbon dioxide, and hypoxic pulmonary vasoconstriction add to the spectrum of clinical syndromes. As to the reason why an individual develops chronic airway disease, current thinking would suggest that this is the tobacco-smoking-induced illness par excellence. Yet, this is too simplistic. All physicians will have seen elderly patients with impeccable pulmonary function who have been heavy cigarette smokers for their entire adult lives and, perhaps more unusually, lifetime nonsmokers with chronic airflow disease. Early studies examining tobacco smoking and ventilatory capacity suggested that there was more to it than simply the amount of tobacco consumed, and the operation of some other risk factor was suggested.1 About 25% of male cigarette smokers proceed to develop significant airway abnormality2 and the role of nonspecific bronchial reactivity in defining this subgroup at special risk has been examined but remains inconclusive.3,4 Variation between individuals in the efficiency of protective mechanisms such as the antielastase systems may also be a factor determining the likelihood for emphysema.

Epidemiological studies can contribute to an unraveling of etiological factors, provided that sufficiently heterogeneous populations can be studied. It is sobering to realize that if cigarette smoking were a universal habit, recognition of the role it plays in the incidence of lung cancer would have been long delayed. To quote Geoffrey Rose, “the cause that is universally present has no influence at all on the distribution of disease, and it may be quite unfindable by the traditional methods of clinical impression and case-control and cohort studies; for all of these depend on heterogeneity of exposure.”5

With this background, the article by Berglund and colleagues in this issue of CHEST (see page 49) is of considerable interest. The group from Loma Linda University has had the opportunity to study over 1,300 subjects as part of the Adventist Health Study of Smog. These subjects were a geographically stable, nonsmoking population whose general exposure to particulate air pollution was reasonably documented over 20 years. Respiratory-orientated questionnaires were completed on four occasions over 16 years. At the end of the observational period, spirometry with bronchodilator reversibility was performed in 98% of subjects. Categorization into diagnostic subgroups (asthma, chronic bronchitis, emphysema) was based on patient-reported symptoms and a history of diagnosis by a physician. The study was designed to weigh the importance of factors other than direct cigarette smoking in the genesis of chronic airway disease.

What were the findings? Significant airflow obstruction was demonstrated in 10.6% and chronic airflow disease in 15% of the population. The prevalence was higher in males and increased with advancing age, past smoking history, parental airway disease, environmental tobacco smoke exposure, and a history of childhood respiratory illness. Interestingly, ambient dust exposure was a barely significant risk factor in males only. An earlier study from this group in a larger cohort of similar subjects and using estimates of levels of mean particle size of < 10 mg indirect (PM10) from total suspended particulate measurements suggested a relative risk of 1.17 for developing symptoms of airway obstruction if ambient PM10 levels exceeded 100 µg/m3 for 1,000 h/yr.

Comparing the spirometric data with symptoms reported with the questionnaire established some important points. Spirometric airflow obstruction (FEV1/vital capacity < 65%) was present in 7.5% of asymptomatic subjects. Subjects with definite symptoms showed obstructive spirometry in 25% of cases, although chronic cough alone (unlike cough with sputum) was not significantly associated with airflow obstruction. Patients considered to have asthma on the questionnaire reassuringly showed greater acute reversibility on spirometry.

Does this study have clinical messages? It confirms previous findings, which indicate that respiratory illness in early life is a determinant of airway disease in adulthood. It suggests that tobacco smoke, even in nonsmokers, appears as a risk factor in terms of past smoking and environmental tobacco smoke exposure. Ambient dust exposure (in contrast to occupational exposure)7,8 seems of minor importance, highlighting the need for further studies on the role of fine particulate inhalation in producing increased general mortality.9,10 In terms of the possible use of questionnaires to screen adult populations considered at risk of developing significant chronic airway disease, it suggests that productive cough and breathlessness are robust but late markers and that an asymptomatic population will still require objective testing for detection. Finally, the study emphasizes the large amount of subject cooperation, data collection, and collaborative multidisciplinary skill required in respiratory epidemiology.

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Full Polysomnography in the Home

Has It Come of Age?

Over the last decade, there has been more evidence that sleep disorders, such as obstructive sleep apnea, are extremely prevalent in the population. There has been a raging debate between proponents of home studies and proponents of in-laboratory full polysomnography with each side proposing that its technology represents “the best test.” Proponents for home studies have claimed that these studies provide a greater amount of information. In addition, they allow a comfortable setting at a potentially reduced cost.

Advocates of in-laboratory full polysomnography have claimed that these studies provide a greater amount of information. In addition, they allow a technician to be available to adjust signals, potentially start nasal continuous positive airway pressure if the patient meets the criteria for a split night study, and intervene if the patient has a medical problem.

Part of the problem in this debate is that there is probably no single “best text.” In fact, the best test really depends on what clinical question is being addressed. Choosing the best test should be based on pretest clinical suspicion for disease.

For example, if one is evaluating a patient with a high clinical suspicion for obstructive sleep apnea, there may be several alternatives for testing. The patient with a high clinical suspicion for sleep apnea typically complains of extremely loud snoring (frequently in any position), observed apneas or choking arousals during sleep, and excessive daytime sleepiness, and has upper body obesity, and associated hypertension. In this type of patient, the diagnosis of obstructive sleep apnea can probably be made either with full polysomnography or in the home setting using even a four-channel cardiorespiratory recorder. The clinical suspicion for these patients is so high that one would have trouble accepting a normal sleep study. In fact, data are available to show that negative findings on polysomnographic evaluations in the laboratory setting in these patients warrant a second study. Negative results from a home study would also necessitate a repeat evaluation.

It becomes more difficult if the pretest clinical suspicion for obstructive sleep apnea is lower as with patients with mild sleep apnea or with the “upper airway resistance syndrome.” Sleep centers are seeing more and more of these patients as public awareness of sleep disorders increases. These patients have been shown to require greater technological assessment. Full sleep stage monitoring is essential to detect EEG arousals. Qualitative respiratory inductive plethysmography or nasal pressure transducers are being used more frequently to assess hypopneas and sensitive changes in upper airway resistance. Some sleep centers also use esophageal balloons, although this is not universally practical.

Though pulmonologists tend to focus on obstructive sleep apnea, there are a large number of sleepy patients in whom snoring is not a major issue. Though a large component of these patients will be suffering from insufficient sleep, others will have organic sleep disorders warranting testing. These include patients with periodic limb movements during sleep, narcolepsy, or idiopathic CNS hypersomnia. Clearly, these patients need in-laboratory full polysomnography. These patients would require sensitive respiratory monitoring because they might have very subtle obstructive sleep apnea. They also would frequently require multiple sleep latency test-

REFERENCES

1 Read J, Selby T. Tobacco smoking and ventilatory function of the lungs. BMJ 1961; 2:1104–1108
3 Taylor RG, Joyce H, Gross E, et al. Bronchial reactivity to inhaled histamine and annual rate of decline in FEV1 in male smokers and ex-smokers. Thorax 1985; 40:9–16
ing the next day to assess the degree of sleepiness and to help exclude narcolepsy.

The other part of the problem with the in-home vs laboratory debate is that in the past, proponents have been comparing “apples” to “oranges.” This is because the technology that has been used in the two settings has been very different. The typical home study was performed with a four-channel cardiorespiratory recorder measuring heart rate, respiratory effort, airflow, and pulse oximetry. Although a popular new piece of equipment has added qualitative sleep monitoring and measurement of periodic limb movements, it suffers from an inability to detect actual arousals on EEG recording. This makes it difficult to detect subtle respiratory events and determine whether periodic limb movements have any clinical relevance.

The debate would obviously make more sense if the technology in the home environment and in the laboratory were equivalent. The paper by Mykytyn and colleagues that appears in this issue of CHEST (see page 114) tries to compare “apples” to “apples.” They compare portable full polysomnography and in-laboratory full polysomnography simultaneously. These studies were done in the laboratory, and to try to simulate the home environment, the authors ignored the portable polysomnographic measuring equipment in half of the studies. Although the study has weaknesses, including the small sample size, no actual in-home evaluation, and failure of both electromyographic and oximetry signals, it does begin to support the authors’ conclusion that portable polysomnography may be a viable alternative to in-laboratory polysomnography.

A recent article by Fry et al supports this notion. This study also compared simultaneous recording of portable full polysomnography with standard full polysomnography in the laboratory. In addition, these authors performed full polysomnography in the home 1 to 2 weeks after in-laboratory evaluation in 77 patients. Similar results were obtained from both methods. Interestingly, patients preferred the in-laboratory study over the home evaluation (63.6% compared to 33.5%). They felt the equipment was less cumbersome in the laboratory, and they felt they could actually sleep better in the laboratory which obviously is counter to popular belief. With the type of equipment being tested, the patients had to have the sensors applied in the laboratory first, and several patients complained of the travel time and the fact that they had to take too much equipment home.

Obviously there has to be improvement in technology and convenience for full polysomnography to be performed in the home setting with any frequency. Practitioners of sleep medicine have to be confident that the technology answers the clinical questions being posed. One has to be sensitive to the pretest clinical suspicion of disease. In addition, studies need to assess whether home technology actually allows for the assessment of a greater number of patients at a reduced cost. Specifically, we need to assess not only the cost of a single test, but whether there is any additional cost incurred because of equipment failure or because the initial study failed to answer the underlying clinical question.

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References

Circulating Natriuretic Peptides
A Biologic Marker of Tissue Injury?

The family of natriuretic peptides comprises five structurally-related 22-53-amino acid peptides, atrial natriuretic peptide (ANP), brain natriuretic peptide (BNP), two C-type natriuretic peptides (CNP), and dendroaspis natriuretic peptide (DNP). They express broad and disparate effects in the cardiovascular system, including natriuresis, diuresis, vasodilation, and inhibition of the renin-angiotensin system, sympathetic outflow, and vascular smooth muscle and endothelial cell proliferation.

The salutary cardiovascular effects of natriuretic peptides suggest that they could play a pivotal role in mitigating the deleterious effects of phlogistic mediators elaborated during the host inflammatory response to injury, including cardiovascular surgery. However, data compiled from large-
scale clinical trials seem to indicate that an increase in circulating levels of natriuretic peptides and their degradation products during the early phase after myocardial infarction is an independent predictor of left ventricular dysfunction and death.\(^5\)–\(^7\)

Although the mechanisms underlying this process are uncertain, they may be related, in part, to increased production and/or decreased degradation and inactivation of these peptides in inflamed tissues.\(^1\) Nonetheless, Amano and colleagues\(^8\) showed that unilateral pulmonary artery occlusion in patients with lung cancer is associated with a significant decrease in ANP level in the coronary sinus which is reversed by atropine. These data imply that ANP secretion is modulated, in part, by the parasympathetic nervous system.

To this end, Berkenstadt and colleagues in this issue of CHEST (see page 130), found that circulating ANP levels are increased during and after short-term balloon occlusion of the thoracic aorta in patients with inoperable intraabdominal malignancy undergoing vascular bed-selective high dose chemotherapy. They suggested that circulating ANP level is determined, in part, by factors other than arterial wall stretch and transmural pressure. However, they did not report on circulating BNP levels nor correlated ANP levels with survival.

Circulating ANP levels are also increased in patients undergoing elective cardiac surgery.\(^2\)–\(^4\)

However, only a small number of patients were studied, and no correlation between ANP level and short- and long-term outcome was sought. Importantly, circulating BNP level, which correlates better with left ventricular dysfunction and survival than ANP in patients with MI,\(^7\) was not determined.

On balance, these data suggest that tissue-specific natriuretic peptides are elaborated early in the course of inflammation and may serve as a simple and reliable biologic marker of its progression and patient’s survival. However, the sensitivity and specificity of this response, as assessed by circulating natriuretic peptides levels, should be determined in large scale, prospective multicenter studies.

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References


Antimicrobial Therapy of Ventilator-Associated Pneumonia

How To Select an Appropriate Drug Regimen

V

enilator-associated pneumonia (VAP) refers to nosocomial pneumonia developing in a patient receiving mechanical ventilation. VAP is recognized as being one of the leading causes of death from hospital-acquired infections in the ICU setting.\(^1\)\(^2\)

The estimated prevalence of VAP ranges from 10 to 65% with case fatality rates of 13 to 55%.\(^3\)\(^4\)

Additionally, several clinical studies have demonstrated an attributable mortality associated with VAP that is independent of patients’ underlying diagnoses and severity of illness at the time of ICU admission.\(^5\)\(^6\)

The occurrence of VAP also increases the costs associated with hospitalization. Several economic analyses estimate the excess medical costs attributed to an episode of VAP to be $5,000 with prolongation of the hospital stay from 6 to ≥30 days.\(^7\)\(^9\)

Recently, the importance of providing early effective antimicrobial therapy for patients with VAP has been highlighted by several clinical investigations.\(^10\)\(^–\)\(^13\)

Once VAP develops, treatment is usually support-
ive along with the administration of antibiotics. The selection of antimicrobial agents for the initial empiric treatment of VAP appears to be an important determinant of clinical outcomes, especially hospital mortality. Luna and colleagues examined patients requiring mechanical ventilation with clinically suspected VAP. A total of 50 patients with positive BAL cultures received empiric antibiotic therapy prior to obtaining the BAL culture results. Patients who received adequate antibiotic therapy (n = 16), as defined by the BAL culture results, had a significantly lower mortality rate compared with patients receiving inadequate antibiotic therapy (n = 34) (37.5% vs 91.2%; p < 0.001). Alvarez-Lerma evaluated the appropriateness of antimicrobial therapy in 430 patients with VAP receiving antibiotic treatment. The attributable mortality from VAP was significantly greater among patients receiving inadequate initial antimicrobial therapy compared with patients receiving adequate initial therapy (24.7% vs 16.2%; p < 0.039). Similarly, Rello et al found that patients with VAP who received adequate initial antibiotic therapy had significantly greater crude mortality rates (63.0% vs 41.5%; p = 0.06) and VAP attributable mortality rates (37.0% vs 15.6%; p < 0.05) compared with patients receiving adequate initial antibiotic therapy. Lastly, our own group confirmed these findings in a study employing mini-BAL to obtain lower respiratory tract cultures in patients with suspected VAP.

Table 1 summarizes the pathogens associated with inadequate initial empiric antimicrobial treatment of culture-positive VAP in the four clinical studies noted above. Most episodes of inadequate antimicrobial treatment were attributed to Gram-negative bacteria, with Pseudomonas aeruginosa, Acinetobacter species, Klebsiella pneumoniae, and Enterobacter species accounting for most cases. These same species of Gram-negative bacteria are often associated with antibiotic resistance and worse patient outcomes compared with more antibiotic susceptible strains of Gram-negative bacteria (eg, Haemophilus influenzae, Escherichia coli). Methicillin-resistant Staphylococcus aureus (MRSA) was the next most common pathogen associated with the administration of inadequate antimicrobial treatment. Interestingly, only one of these four studies reported using specific methods for the isolation of anaerobic bacteria. This probably accounts for the lack of identified anaerobic bacteria in the lower airway cultures from these studies.

The clinical importance of not specifically treating anaerobic bacteria in patients with suspected VAP is unknown. In this issue of CHEST Marik and Careau describe their experience with 185 episodes of suspected VAP or aspiration pneumonia (AP) in 143 patients. Despite using specific methods to isolate anaerobic bacteria, only one anaerobic microorganism was isolated from 75 episodes classified as either VAP or AP. These results differ somewhat from those of Dore’ and coworkers who examined 130 patients with microbiologically docu-

| Pathogens Associated With Inadequate Initial Empiric Antimicrobial Treatment of VAP |
|----------------------------------|----------------------------------|----------------|----------------|
| Alvarez-Lerma11                  | Kollef and Ward13                 | Luna et al10   | Rello et al12  |
| Culture-positive patients, No.   | 430                              | 60             | 65             | 100            |
| Patients receiving inadequate initial treatment, No. (%) | 146 (34)                        | 44 (73)        | 34 (52)        | 27 (27)        |
| Pathogens associated with inadequate treatment, No. | | | | |
| P aeruginosa                     | 64                               | 19             | 7              | 20             |
| S aureus                        | 30                               | 12*            | 25†            | 3‡             |
| Acinetobacter species           | 28                               | 3              | 27             | 0              |
| K pneumoniae                    | 2                                | 1              | 13             | 0              |
| Streptococcus pneumoniae        | 3                                | 0              | 0              | 0              |
| H influenzae                    | 1                                | 0              | 0              | 1              |
| E coli                          | 4                                | 0              | 0              | 2              |
| Enterobacter species            | 8                                | 4              | 0              | 0              |
| Proteus mirabilis               | 4                                | 0              | 1              | 0              |
| Serratia marcescens             | 5                                | 3              | 0              | 0              |
| Stenotrophomonas maltophilia    | 0                                | 5              | 0              | 0              |
| Moraxella nonognii              | 0                                | 0              | 0              | 1              |
| Candida species                 | 0                                | 2              | 3              | 0              |
| Viral species                   | 0                                | 3              | 0              | 0              |
| Streptococcus viridans          | 0                                | 0              | 2              | 0              |
*All resistant to methicillin.
†Predominantly resistant to methicillin.
‡One of three resistant to methicillin.
mented VAP using protected specimen brush (PSB) cultures and rigorous anaerobic culturing techniques. Among these patients, 100 (77%) had only aerobic bacterial strains isolated from PSB cultures. In 30 (23%) patients, PSB cultures resulted in anaerobic strains. Aerobic strains were associated with anaerobic strains in 26 patients, whereas 4 patients had only anaerobic strains isolated from PSB cultures. The 3-month mortality rates were reported to be similar for patients with and without anaerobic strains isolated (31% vs 36%). However, the influence of the adequacy of the initially prescribed antimicrobial treatment, for both aerobic and anaerobic bacterial strains isolated from the PSB cultures, on patient outcomes was not described in this investigation.

To date, and to our knowledge, no convincing clinical data are available supporting the hypothesis that routine treatment for anaerobic bacteria will improve the outcomes of patients with suspected VAP. Alternatively, several investigations have highlighted the problems associated with the overuse of anaerobic antibiotics, particularly clindamycin, in the hospital setting. These problems include antibiotic-associated diarrhea or colitis due to *Clostridium difficile* infection, direct end-organ drug toxicity, and unnecessary increases in medical care costs.17,18

What appears to be currently needed are well-performed outcome studies aimed at determining the most effective, least toxic, and most cost-efficient approaches for the initial empiric treatment of suspected VAP. Included within such studies could be an evaluation of the routine administration of specific antimicrobial agents directed against anaerobic bacterial strains. However, as noted by the experience in patients with VAP described above,10–13 developing new strategies aimed at providing improved initial antimicrobial coverage for potentially antibiotic-resistant Gram-negative bacteria and MRSA may yield greater clinical benefits.

At the present time, clinicians should be aware of the most common bacterial pathogens, and their antimicrobial resistance patterns, accounting for VAP at the hospitals where they practice. Prescribing an initial broad-spectrum antibiotic regimen to cover all likely pathogens will help to reduce the occurrence of inadequate treatment and may result in improved clinical outcomes. Initial combination antimicrobial therapy, particularly aimed against antibiotic-resistant Gram-negative bacteria (*eg*, *P. aeruginosa*, Acinetobacter species) and MRSA, offers the greatest likelihood of providing adequate initial treatment. However, such broad-spectrum treatment should not be unnecessarily prolonged unless supported by appropriate culture data in order to avoid the emergence of antibiotic-resistant infec-

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**REFERENCES**


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