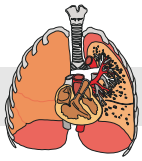

Community-Acquired Pneumonia

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Key words: pneumonia, *Pneumococcus*, antibiotic resistance, antibiotic therapy, hospital admission, empiric therapy

IMAJ 2003;5:133–138

Pneumonia is the sixth leading cause of death and the number one cause of death from infectious diseases in the United States [1]. In 1994, over 5.6 million people were diagnosed with community-acquired pneumonia in the U.S., but the majority, 4.6 million, was not treated in hospital. Although most patients with CAP are managed in the outpatient setting, most of the treatment costs (US$8.0 billion of the $8.4 billion spent on treatment) are focused on hospitalized patients, thus making the decision about who to hospitalize one of great economic impact [2]. The population of elderly patients is increasing in the U.S. and those over age 65 constitute about a third of all CAP patients, but this group accounts for more than half of the cost because elderly patients require hospitalization more often than younger patients and, when hospitalized, stay longer. Both of these findings are due to the fact that co-morbid illness is more common in elderly CAP patients than in younger CAP patients [2,3]. In the present update, several current management issues are discussed, including new information on the etiologic pathogens causing CAP, the use of prognostic scoring systems to triage patients, the controversies surrounding diagnostic testing, and an overview of the principles for effective antibiotic therapy.

Etiologic pathogens

Even with extensive diagnostic testing, an etiologic agent is defined in only about half of all patients with CAP, pointing out the limited value of diagnostic testing and the possibility that we do not know all the organisms that can cause CAP [1,3,4]. In the past three decades, a variety of new pathogens has been identified to cause CAP, including *Legionella pneumophila*, *Chlamydia pneumoniae*, and hantavirus. In addition, antibiotic-resistant variants of common pathogens such as *Streptococcus pneumoniae* have become increasingly common, with over 40% of these organisms being either intermediately or highly resistant to penicillin [5]. Current management guidelines recommend that all patients with CAP be treated for the possibility of atypical pathogen infection, either as a primary organism or as part of a mixed infection [1,6,7]. In addition, although the clinical impact of drug-resistant *Pneumococcus* is uncertain, all patients must be evaluated to define their risk for infection with this organism [1].

The most common pathogen for CAP in any patient population is *S. pneumoniae*. In one study, extensive testing with the use of genetic probes of material obtained from needle aspirates in the area of pneumonia revealed that this organism was often responsible for episodes of CAP that were undiagnosed by standard testing [8]. In the past, the therapy of pneumococcal pneumonia had been relatively simple, but over the past decade antibiotic resistance has become increasingly common, and penicillin resistance, along with resistance to other common antibiotics (macrolides, trimethoprim/sulfamethoxazole, selected cephalosporins), is present in over 40% of these organisms [5,9]. Fortunately, most penicillin resistance is of the "intermediate"-type (penicillin minimum inhibitory concentration 0.1–1.0 mg/L) and not of the high level type (penicillin MIC of 2.0 or more) [5]. In the 2001 American Thoracic Society guidelines for CAP, specific clinical conditions that increase the risk of infection with DRSP were defined and these were referred to as "modifying factors" (described below) [1]. It is difficult to show a clinical impact of *in vitro* resistance on outcomes such as mortality, but most experts believe that organisms with a penicillin minimum inhibitory concentration of $\geqslant$ 4 mg/L can lead to an increased risk of death [10–12]. Fortunately, very few organisms are currently at this level of resistance, but in order to prevent more organisms of this type from emerging, it may be necessary to identify patients with risk factors for resistance, and to target them with highly active anti-pneumococcal regimens when treating for CAP.

Atypical pathogens, which include *C. pneumoniae*, *M. pneumoniae* and *L. pneumophila*, were originally believed to be of concern primarily in young and healthy patients with CAP. However, recent data show that these organisms are common in patients of all ages, and may be part of a mixed infection along with traditional bacterial pathogens [13–15]. Outbreaks of infection with organisms such as *C. pneumoniae* have even occurred in nursing homes [15]. The frequency of these agents can be as high as 60% in one Israeli series, with as many as 40% of all CAP patients having mixed

CAP = community-acquired pneumonia

MIC = minimum inhibitory concentration

DRSP = drug-resistant *Pneumococcus*

infection [13]. The data showing such a high incidence of these organisms were collected primarily with serologic testing, which is of uncertain accuracy, but the clinical relevance of these organisms is suggested by studies that show reduced mortality and length of stay when patients receive empiric therapy that provided antibiotic activity against these organisms, compared to regimens that do not cover these organisms [16,17]. In patients with severe CAP, atypicals are also common but may vary over the course of time and from one location to another, with regard to specific organisms. In fact, in one intensive care unit in Barcelona, atypical organisms accounted for approximately 20% of all severe CAP pathogens, but the dominant organism was *Legionella* in one observation period, while this organism was replaced by *M. pneumoniae* and *C. pneumoniae* in another time period [18].

The role of enteric gram-negatives in CAP is not known, but these organisms are generally uncommon, except in the setting of severe CAP, especially in the infirm elderly, including those with chronic cardiac or pulmonary disease. In these patients organisms such as *Eschericia coli* and *Klebsiella pneumoniae* can be found. *Pseudomonas aeruginosa* is an uncommon cause of CAP but can be isolated from patients with severe CAP and bronchiectasis, particularly in those over the age of 75 with impaired functional status [19].

Table 1 summarizes the common pathogens causing CAP in both outpatients and inpatients, as defined in the 2001 ATS guidelines. The classification is based on the presence of clinical risk factors for specific pathogens, referred to as "modifying factors" [1]. The modifying factors for DRSP are: age > 65 years, beta-lactam therapy within the past 3 months, alcoholism, immune suppressive illness (including therapy with corticosteroids), multiple medical co-morbidities, and exposure to a child in a day-care center. The modifying factors for enteric gram-negatives include: residence in a nursing home, underlying cardiopulmonary disease, multiple medical co-morbidities, and recent antibiotic therapy. The risk factors for *P. aeruginosa* infection are: structural lung disease (bronchiectasis), corticosteroid therapy (> 10 mg prednisone/day), broad-spectrum antibiotic therapy for more than 7 days in the past month, and malnutrition. In addition, there are certain clinical conditions that are associated with specific pathogens, and these associations should be considered in all patients when obtaining a history. These are outlined in more detail in the ATS guidelines, but include the association between: chronic obstructive pulmonary disease and *H. influenzae*, *M. catarrhalis* and *Pneumococcus*; poor dentition, or aspiration risks and anaerobes; exposure to farm animals and Q fever; post-influenza pneumonia and *S. aureus*, *Pneumococcus*, and *H. influenzae*; and exposure to bats and *H. capsulatum* [1].

Table 1. Common pathogens causing CAP

Outpatient, no cardiopulmonary disease or modifying factors
S. pneumoniae, M. pneumoniae, C. pneumoniae (alone or as mixed infection), *H. influenzae*, respiratory viruses, Others (*Legionella* sp, *M. tuberculosis*, endemic fungi)
Outpatient, with cardiopulmonary disease or modifying factors
All of the above plus: DRSP, enteric gram-negatives, and aspiration with anaerobes
Inpatient, with cardiopulmonary disease and/or modifying factors
S. pneumoniae (including DRSP), *H. influenzae, M. pneumoniae, C. pneumoniae*, mixed infection (bacteria plus atypical pathogen), enteric gram-negatives, aspiration (anaerobes), viruses, *Legionella* sp. Others (*M. tuberculosis*, endemic fungi, *Pneumocystis carinii*)
Inpatient, with no cardiopulmonary disease or modifying factors
All of the above, but DRSP and enteric gram-negatives are not likely
Severe CAP, with no risks for *P. aeruginosa*
S. pneumoniae (including DRSP), *Legionella* sp., *H. influenzae*, enteric gram-negative bacilli, *S. aureus, M. pneumoniae*, respiratory viruses, Others (*C. pneumoniae, M. tuberculosis* endemic fungi)
Severe CAP, with risks for *P. aeruginosa*
All of the pathogens above, plus *P. aeruginosa*.

Assessment of severity of illness

In the initial evaluation of a patient with CAP, it is important to define severity of illness to guide decisions about the site of care and to decide whether the patient should be treated out of the hospital or in the hospital, and if admitted, whether ICU care is needed. While a number of prediction models have been developed to guide the admission decision, no rule is absolute and the decision to admit a patient should be based on social as well as medical considerations, and remains an "art of medicine" determination. The Infectious Disease Society of America has developed CAP guidelines that endorse the use of the Prognostic Scoring Index to guide the admission decision, while the ATS guidelines are less emphatic on endorsing a specific rule and view the PSI as a decision support tool [1,6,20]. In general, the hospital should be used to observe patients who have multiple risk factors for a poor outcome, those who have decompensation of a chronic illness, and those who require interventions not easily administered at home (oxygen, intravenous fluids, cardiac monitoring).

The PSI was developed by the investigators in the Pneumonia Outcomes Research Team (PORT) study, and uses a scoring system that classifies patients into one of five groups (classes I–V), each with a different risk for death [20]. As mentioned, although this is a mortality prediction model, some CAP guidelines have used this risk score to guide the admission decision [6]. In the IDSA guidelines, admission was recommended for patients in classes IV and V, with a predicted mortality risk of 8.2–9.3% and 27–31.1%, respectively, while outpatient care was recommended for patients in classes I and II, with mortality risk of 0.1–0.4% and 0.6–0.7%, respectively [6,20]. Patients in class III had an intermediate risk of death, 0.9–2.8%, and the recommendation was that the admission decision be individualized for these patients. The use of this scoring system is complex, and points are calculated based on such factors as age, gender, the presence of co-morbid medical disease, certain physical findings, and certain laboratory data [20].

ATS = American Thoracic Society

ICU = intensive care unit
PSI = Prognostic Scoring Index
IDSA = Infectious Disease Society of America

There are now several prospective studies on the accuracy of the model for the admission decision. In general these studies have shown that the use of the PSI can reduce the number of low risk patients being admitted to the hospital, but even in the hands of experts, 30–43% of low risk patients are still admitted, overriding the rule and reflecting the fact that the rule is not absolute and must be subject to clinical judgment [21,22]. In the ATS CAP guidelines, some of the limitations of the PSI to guide the admission decision were identified, including the fact that age, male gender, and co-morbid illness are heavily-weighted variables for defining mortality risk [1,20]. Thus, an elderly male with any chronic illness will have enough points to fall into a high risk category and to possibly be admitted to the hospital, regardless of the severity of his pneumonic process. On the other hand, a young patient with multilobar pneumonia may never be considered for admission using the PSI, unless certain vital sign thresholds are reached (heart rate > 125/min, respiratory rate > 30/min, and systolic blood pressure < 90 mmHg). One factor that can add to the admission decision process is an assessment for hypoxemia, admitting all patients who have oxygen saturation < 90% on room air, provided they are not chronically on oxygen therapy.

One prediction rule that can help identify CAP patients with a high risk of death is the British Thoracic Society's rule, which is simple and includes only four variables: respiratory rate $\geqslant$ 30/min, diastolic blood pressure $\geqslant$ 60 mmHg, blood urea nitrogen > 19.6 mg/dl, and confusion. The rule states that patients have a 9 to 21-fold increased risk of death if they have at least two of these four criteria [23,24]. Although this rule may be simple and useful, its value may be limited in the elderly, reflecting the altered clinical presentations of pneumonia in this population [25,26]. In one study, the rule had a 66% sensitivity and a 73% specificity for predicting mortality in a population that included 48% who were at least 75 years of age [25,26]. Interestingly, although the British Thoracic Society rule was not optimal in an elderly population and did not work as well as it did in other populations, it had a higher sensitivity for predicting mortality than the PSI derived from the PORT study [25].

There is no specific rule for who should be admitted to the ICU, but in general the ICU is used for approximately 10% of all CAP patients, and this population has a mortality rate of at least 30% [27]. There is some debate about the benefit of ICU care for patients with CAP, but the benefit seems most certain if patients are admitted early in the course of severe illness [1,28]. Criteria for ICU admission, in addition to the need for mechanical ventilation and septic shock, are the presence of at least two of the following: PaO_2/FiO_2 ratio < 250, multilobar infiltrates, and systolic blood pressure $\leqslant$ 90 mmHg [29].

Diagnostic testing

The presence of pneumonia is best confirmed by careful physical examination and a chest radiograph. Although some patients may have clinical findings of pneumonia (focal crackles, bronchial breath sounds) and a negative chest radiograph, the need for antibiotic therapy for CAP has been established in patients with a radiographic infiltrate, and thus the suspicion of pneumonia should be confirmed radiographically. A routine chest radiograph is the preferred tool, although computed tomography scanning may demonstrate infiltrates not seen in CAP patients with a routine radiograph [30]. In some patients, such as the elderly and chronically ill, the clinical diagnosis of CAP is difficult since these patients can present with non-respiratory findings such as confusion, falling, and worsening of an underlying illness. For these individuals, a chest radiograph is essential to define the presence of respiratory infection [3]. Although a radiograph is recommended in all outpatients and inpatients, it may be impractical in some settings outside of the hospital. A chest radiograph not only confirms the presence of pneumonia, but can be used to identify complicated illness and to grade severity of disease by noting such findings as pleural effusion and multilobar illness. There is no specific radiographic pattern that can be used to define the etiologic pathogen of CAP, but certain findings can suggest specific organisms, such as anaerobes if a cavitary infiltrate is found, or tuberculosis if a posterior upper lobe infiltrate is present [1].

Most recent studies have emphasized the mortality benefit of prompt administration of effective antibiotic therapy, with a reduced mortality if hospitalized patients are treated within 8 hours of arrival at the hospital [31]. Thus, therapy should never be delayed for the purpose of diagnostic testing, and the diagnostic workup should be streamlined, with all patients receiving empiric therapy based on algorithms, as defined below. With such empiric regimens, as many as 90% of admitted patients will have a prompt response to therapy [32].

Recommended testing for outpatients is limited to a chest radiograph and pulse oximetry, if available, with sputum culture only in patients suspected of having an unusual or drug-resistant pathogen. For admitted patients, diagnostic testing should include a chest radiograph, assessment of oxygenation (pulse oximetry or blood gas, the latter if retention of carbon dioxide is suspected), routine admission blood work and two sets of blood cultures. If the patient has a pleural effusion, this should be tapped and the fluid sent for culture and biochemical analysis. Although blood cultures are positive in only about 10% of CAP patients, they can be used to define a specific diagnosis and to define the presence of drug-resistant pneumococci [7]. Sputum culture should be restricted to patients suspected of infection with a drug-resistant or unusual pathogen, and Gram's stain of sputum should be used to guide interpretation of sputum culture but not to focus initial antibiotic therapy. However, Gram's stain can be used to broaden initial empiric therapy by enhancing the suspicion for organisms that are not covered in routine empiric therapy (such as *S. aureus,* being suggested by the presence of clusters of gram-positive cocci, especially during an epidemic influenza). In a recent study, the practical limitations of the test were clear: of 116 patients with CAP, only 42 could produce a sputum sample of which 23 were valid, and only 10 samples were diagnostic, with antibiotics directed to the diagnostic result in only 1 patient [33]. Even if Gram's stain findings were used to focus antibiotic therapy, this would not allow for empiric coverage of atypical pathogens, which might be present with *Pneumococcus* as part of a mixed infection. Routine serologic

testing is not recommended. However, in patients with severe illness, the diagnosis of *Legionella* can be made by urinary antigen testing, a test most likely to be positive at the time of admission, but a test that is specific only for serogroup I infection [34].

Therapy for CAP

The goal of empiric therapy in patients with CAP is to target the likely etiologic pathogens by categorizing patients on the basis of place of therapy, severity of illness, and the presence or absence of cardiopulmonary disease or modifying factors. A list of likely pathogens can be predicted for each patient [Table 1], and this information can be used to guide initial empiric therapy. If a specific pathogen is subsequently identified by diagnostic testing, then therapy can be focused.

In choosing empiric therapy for CAP, certain principles should be followed, as outlined in Table 2 [35]. Empiric therapy for outpatients with no cardiopulmonary disease or modifying factors should be a new macrolide (azithromycin or clarithromycin) or a tetracycline. Erythromycin has limited value for these patients because of its lack of coverage of *H. influenzae* and the higher frequency of intestinal complications (nausea, vomiting) than the newer macrolides. Therapy with an anti-pneumococcal quinolone is not necessary in these uncomplicated outpatients. However, outpatients with cardiopulmonary disease and/or modifying factors should not receive macrolide monotherapy, which has been occasionally associated with therapeutic failure [36]. These patients are at risk for infection with DRSP or enteric gram-negatives and should receive either a selected oral beta-lactam [Table 2] with a macrolide or tetracycline; or an oral anti-pneumococcal quinolone (gatifloxacin, levofloxacin, moxifloxacin) alone. Quinolone monotherapy may be easier and less costly than a beta-lactam/macrolide combination for these complex outpatients.

For the non-ICU inpatient, therapy can be an intravenous macrolide (azithromycin) alone, provided that the patient has no underlying cardiopulmonary disease and no risk factors for infection with DRSP, enteric gram-negatives or anaerobes. Although very few patients of this type are admitted, macrolide monotherapy has been documented to be effective in this population [37]. The majority of admitted patients will have cardiopulmonary disease and/or modifying factors and they can be treated with either a selected [Table 2] intravenous beta-lactam combined with a macrolide, or with a monotherapy regimen using an intravenous anti-pneumococcal quinolone (gatifloxacin, levofloxacin, moxifloxacin). Either of these regimens is effective and it may be useful to use these two types of therapies interchangeably, striving for "antibiotic heterogeneity" in the hospital so that one regimen is not used exclusively in all patients, thereby minimizing the selection pressure for antibiotic resistance. In choosing between these options, a guiding principle should be to use a different agent than the patient has received in the recent past, since recent therapy with macrolides, beta-lactams and quinolones can predispose to resistance to these same agents during a subsequent course of therapy [1,36,38]. Although oral quinolones may be as effective as intravenous quinolones, the ATS guidelines recommend that all admitted patients receive initial therapy intravenously to ensure that the therapy has been absorbed. Once the patient shows a good clinical response (defined below), oral therapy can be started. Selected inpatients with mild to moderate disease can initially be treated with the combination of an intravenous beta-lactam and an oral macrolide, switching to exclusively oral therapy once the patient shows a good clinical response.

Table 2. Principles for antibiotic therapy of CAP

- All hospitalized patients should receive initial antibiotic therapy intravenously, and the first dose of therapy should be within 8 hours of arrival at the hospital.
- All patient populations should be treated for the possibility of infection with "atypical pathogens" and *Pneumococcus*, as well as other organisms (depending on modifying factors) in selected individuals.
- Monotherapy with a macrolide can be administered to outpatients or inpatients with no underlying cardiopulmonary disease and no risks for DRSP, enteric gram-negatives or aspiration.
- For outpatients and inpatients with risk factors for DRSP and gram-negatives, therapy can be with either a beta-lactam/macrolide combination or monotherapy with an anti-pneumococcal quinolone (gatifloxacin, levofloxacin, or moxifloxacin). Choice between these regimens should be guided by a history of recent antibiotic therapy, choosing an agent that the patient has not recently received.
- For outpatients with clinical risks for DRSP, therapy can be with a beta-lactam/macrolide combination or an anti-pneumococcal quinolone. Acceptable oral beta-lactams include: cefpodoxime, cefuroxime, high dose amoxicillin, amoxicillin/clavulanate.
- For inpatients with clinical risks for DRSP, therapy can be with an intravenous anti-pneumococcal quinolone or a selected beta-lactam combined with a macrolide. Acceptable intravenous beta-lactams include: cefotaxime, ceftriaxone, ampicillin/sulbactam, or high dose ampicillin.
- Empiric anti-pseudomonal therapy should be limited to patients with identified risk factors for *P. aeruginosa*. Anti-pseudomonal agents include: cefepime, imipenem, meropenem, piperacillin/tazobactam, ciprofloxacin and the aminoglycosides.
- Vancomycin should not be used in the empiric therapy of CAP unless the patient is severely ill and is also suspected to have pneumococcal meningitis.

For ICU-admitted CAP, all individuals should be treated for DRSP and atypical pathogens, but only those with appropriate risk factors (above) should also have coverage for *P. aeruginosa*. Since the efficacy, dosage and safety of quinolone monotherapy have not been established for ICU CAP patients, the therapy for such patients, in the absence of pseudomonal risk factors, should be a selected intravenous beta-lactam combined with either an intravenous macrolide or an intravenous quinolone [1]. For patients with pseudomonal risk factors, therapy can be a two-drug regimen using an anti-pseudomonal beta-lactam (cefepime, imipenem, meropenem, piperacillin/tazobactam) plus ciprofloxacin (the only anti-pseudomonal quinolone); or alternatively a three-drug regimen using an anti-pseudomonal beta-lactam plus an aminoglycoside plus either an intravenous non-pseudomonal quinolone or macrolide.

The anti-pneumococcal quinolones are commonly used to treat CAP because, as a single drug given once daily, they can cover *Pneumococcus* (including DRSP), gram-negatives, and atypical pathogens. Quinolones penetrate well into respiratory secretions

and are highly bioavailable, achieving the same serum levels with oral or intravenous therapy, thereby allowing moderately ill outpatients to be managed effectively with oral antibiotics. Although all the anti-pneumococcal quinolones are available orally and intravenously, and all have been effective for the therapy of CAP, there are differences among the available agents in their intrinsic activity against *Pneumococcus*. On an MIC basis, these agents can be ranked from most to least active as: moxifloxacin, gatifloxacin and levofloxacin [1,35]. Some data suggest a lower likelihood of both clinical failures and the induction of pneumococcal resistance to quinolones if the more active agents are used in place of the less active agents [38,39]. In addition, there are now reports of failures of levofloxain in pneumococcal CAP, and risk factors for resistance to levofloxacin include recent quinolone therapy and the presence of chronic obstructive pulmonary disease [38].

Evaluation of response to therapy

The majority of outpatients and inpatients will have a rapid clinical response to the empiric therapy regimens suggested above, usually within 24–72 hours [1]. Clinical response in inpatients is defined as improvement in symptoms of cough, sputum production, and dyspnea, along with the ability to take medications by mouth, decreasing white blood cell count, and an afebrile status on at least two occasions 8 hours apart. When a patient meets these criteria, if he or she is otherwise medically and socially stable, it is appropriate to switch to an oral therapy regimen and to discharge the patient; and it is not necessary to observe the patient in the hospital on oral therapy [40]. Radiographic improvement lags behind clinical improvement, and in a responding patient a chest radiograph is not necessary until 2–4 weeks after starting therapy.

If the patient fails to respond to therapy in the expected time, then it is necessary to consider infection with a drug-resistant or unusual pathogen (tuberculosis, anthrax, *C. burnetii*, *Burkholderia pseudomallei*, *C. psittaci*, *Pasteurella multocida*, endemic fungi or hantavirus); a pneumonic complication (lung abscess, endocarditis, empyema); or a non-infectious process that mimics pneumonia (bronchiolitis obliterans with organizing pneumonia, hypersensitivity pneumonitis, pulmonary vasculitis, bronchoalveolar cell carcinoma, lymphoma, pulmonary embolus). The evaluation of the non-responding patient should be individualized but may include CT scanning of the chest, pulmonary angiography, bronchoscopy, and occasionally open lung biopsy [1].

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Human nature, essentially changeable, unstable as the dust, can endure no restraint; if it binds itself it soon begins to tear madly at its bonds, until it rends everything asunder, the wall, the bonds and its very self.

Franz Kafka (1883-1924), Czech author, whose vision of the world, the original "Kafkaesque" nightmare, is that of man overwhelmed by incomprehensible labyrinths of totalitarian bureaucracy

Capsule

Production of nerves in pregnancy

Changes in the numbers of olfactory neurons or in neuroblast migration to the olfactory bulb can affect abilities to discriminate odors or establish new odor-related memories. Studying female mice, Shingo and co-workers show that the hormone prolactin induces increased production of olfactory cell precursors. The prolactin-induced changes were apparent during pregnancy and also just after mating. Odor discrimination contributes to recognition of mates and offspring.

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Capsule

Male contraception

van der Spoel et al. report that oral delivery of a sugar molecule called NB-DNJ (for N-butyldeoxynojirimycin) causes sterility in male mice that is fully reversible after withdrawal of the drug. Although NB-DNJ did not affect sperm counts, the epididymal spermatozoa in the treated mice showed morphologic abnormalities and severely impaired motility. These effects may relate to the drug's ability to inhibit synthesis of certain glucosphingolipids that are required for spermatogenesis. NB-DNJ is a particularly promising lead in the search for a male pill, since it has already been evaluated in clinical trials for other indications and is known to be well tolerated by humans.

Proc Natl Acad Sci USA 2002;99:17173