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Medical management of pulmonary disease caused by *Mycobacterium avium* complex

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The optimal drug therapy of pulmonary *Mycobacterium avium* complex (MAC) has not been determined. There are no clear-cut data demonstrating the benefit of treatment versus no treatment. We do not know the natural history of pulmonary MAC untreated; however, there is considerable clinical experience and inferential data that strongly suggest that drug therapy provides symptomatic relief and extended survival for cavitary, tuberculosis (TB)-like disease. Less well demonstrated are the benefits to those patients with the subtler, bronchiectatic variety of pulmonary disease; nonetheless, recent reports are beginning to define clinically beneficial treatment strategies.

Central issues reviewed in this chapter include the role of in vitro susceptibility testing in selecting drug regimens, preferred agents and regimens, the frequency of drug administration (daily or less frequent?), the duration of treatment, and the roles of adjunctive treatments.

The role of in vitro susceptibility testing

Unlike TB, in which there is a substantial body of science documenting a predictable relationship between in vitro susceptibility and clinical utility for medications, there is marginal evidence for the reliability of susceptibility testing for MAC therapy. The 1990 and 1997 American Thoracic Society (ATS) statements on therapy for MAC recommended standard empirical regimens [1,2]; susceptibility testing was advocated in 1997 only for clarithromycin (or azithromycin).

By contrast, at National Jewish Medical and Research Center, for the past 25 years we have employed in vitro testing to select drug regimens [3,4]. Our decision to use this system was based on analogy to other pulmonary mycobacterioses including TB and *M kansasii*, our clinical perceptions of utility, and mouse model studies [5,6] that showed consistent correlations between in vitro susceptibility and response to therapy.

A retrospective analysis of 75 patients with pulmonary MAC treated at National Jewish between 1976 and 1982 demonstrated a statistically significant relationship between response to treatment (consistently negative sputum culture for 3 or more consecutive months) and administration of drugs to which the strains had demonstrated susceptibility [4]. Fifty of the 75 patients were responders, and, as shown in Fig. 1, there was a progressive trend toward responsiveness associated administration of more drugs to which there was susceptibility. ''Susceptibility'' at that time was defined by the ''critical concentration'' technique, a method that we believe is less useful than our current minimal inhibitory concentration (MIC) method [7].

Similarly, Tsukamura in Japan studied 26 patients with pulmonary MAC [8]. He noted that among the seven nonresponders or failures, six had highly resistant strains; of the nine patients who were rendered consistently sputum culture negative, all had harbored strains that were relatively susceptible to the medications the patients had received.

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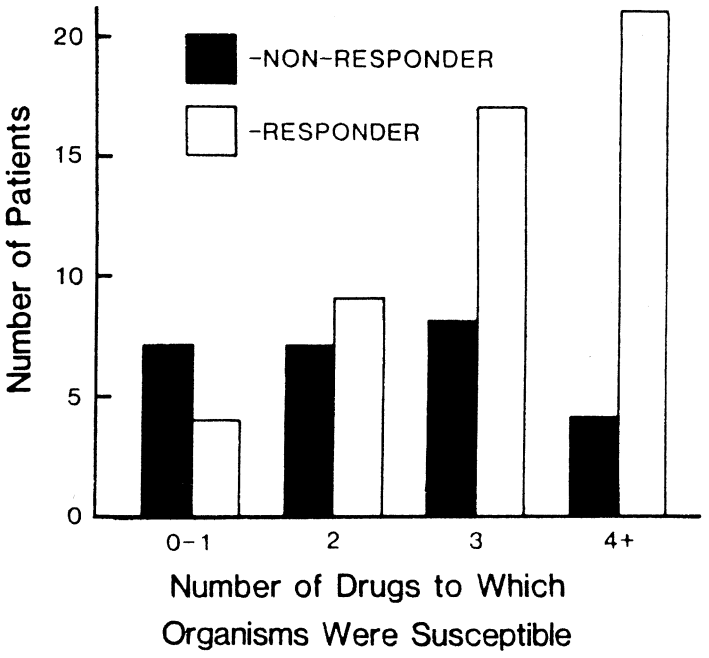

Fig. 1. Among a series of 75 consecutive patients treated for pulmonary MAC at National Jewish between 1976 and 1982, there was a clear association between response to chemotherapy and in vitro susceptibility to the agents used. (*From* Horsburgh CR Jr, Mason UG 3rd, Heifets LB, et al. Response to therapy of pulmonary mycobacterium avium-intracellulare infection correlates with results of in vitro susceptibility testing. Am Rev Respir Dis 1987;135(2):418–21; Official Journal of the American Thoracic Society © American Lung Association).

Further evidence for the association between in vitro susceptibility and clinical responses was seen in a recent randomized trial of therapy for MAC, *M malmoense*, and *M xenopi* conducted by the British Thoracic Society [9]. Although the authors minimized the role of susceptibility testing, pooled data from the three groups found fewer failures or relapses among patients whose organisms were susceptible, not resistant, to rifampin (14% versus 21%) or susceptible, not resistant, to ethambutol (15% versus 24%).

We should be clear about the derivation of the definitions of "susceptible," "resistance," and "intermediate," which we use in our in vitro classification. Ideally there should be human clinical disease data that demonstrate that the drugs perform according to these classifications. Such data do not exist for pulmonary MAC. Heifets and I derived these descriptions based on relationships between pharmacokinetic information (the maximum concentrations, half-lives, areas-under-the-curve, etc) and minimal inhibitory concentrations and minimal bactericidal concentrations for the various drugs and comparison to activity versus *M tuberculosis* [10,11].

We do not dispute the general suitability of initiating therapy for a "new case" of pulmonary MAC with an empirical, standard three- or four-drug regimen as advocated by the 1997 ATS statement. Based on the prior probability of in vitro susceptibility to clarithromycin/azithromycin, rifampin, ethambutol, the rifampin-ethambutol combination or amikacin, such regimens are likely to be active. For patients who have received previous treatment, who are failing to respond to ongoing drug therapy, or who have had toxicity or intolerance to these standard agents, however, in vitro susceptibility testing is an important element of management.

Preferred agents and regimens

The drugs with the most predictable in vitro susceptibility and clinical utility versus pulmonary MAC are clarithromycin or azithromycin. Virtually all wild-strains of MAC are inhibited by these agents [12], and their clinical efficacy has been demonstrated in disseminated MAC in persons with AIDS [13,14] and pulmonary MAC in HIV-negative subjects [15]. In comparison trials conducted in Tyler, Texas, clarithromycin modestly outperformed azithromycin [16,17]. Both agents demonstrate a consistent additive

effect when combined with ethambutol (L. Heifets, personal communication, 1995). No information is available regarding the clinical efficacy of the newer ketolide agents against MAC.

Before the macrolides/azolides were available, rifampin was the central element of drug therapy. Although the MICs versus MAC for rifabutin are typically lower than for rifampin (0.25 to 16 μg/mL versus 0.063 to 2.0 μg/mL, respectively), maximum serum levels of rifampin are much higher than rifabutin (8 to 12 μg/mL versus 0.4 to 0.6 μg/mL) [18,19]. However, rifampin, by inducing the hepatic cytochrome P450 pathways, results in substantial reductions in the bioavailability of clarithromycin; data from Tyler, Texas and National Jewish document a very substantial reduction in the levels of clarithromycin and 14-hydroxy-clarithromycin, the active metabolite, when rifampin is co-administered [20,21]. Options in response to this factor include ignoring it, increasing the dosage of clarithromycin, using rifabutin (which has lesser effects on the cytochrome P450 pathways), or using azithromycin instead of clarithromycin. The problem with using the combination of clarithromycin and rifabutin is that the macrolide inhibits the hepatic elimination of rifabutin, which can result in toxic accumulations of rifabutin [22,23].

Ethambutol is the other agent that should be included in the standard management of pulmonary MAC. It has a predictable additive effect in vitro when combined with clarithromycin or azithromycin (L. Heifets, personal communication, 1995). When combined with the rifamycin, ethambutol has variably additive or synergistic effects in vitro [19,24]. Among a consecutive series of clinical isolates from pulmonary MAC cases, additive interaction (the fractional inhibitory concentrations of the two drugs was 1.0) was seen in 75% of the strains and synergistic (the FICs were 0.5 or lower) in 25% of strains [19]. Whereas there is no clinical evidence that this in vitro synergy translates to clinical efficacy, murine studies demonstrated enhanced clearance of MAC strains with such synergistic susceptibility when treated with the rifampin-ethambutol combination (P.R.J. Gangadharam, unpublished data).

Other medications that are potentially active versus pulmonary MAC include aminoglycosides, fluoroquinolones, cycloserine, clofazimine, ethionamide, or isoniazid. Amikacin has the most favorable profile of activity among the aminoglycosides; the MIC_{50} was 2.65 μg/mL, and the MIC_{90} was 6.75 μg/mL [25]. When giving amikacin twice- or thrice-weekly, we usually employ doses in the range of 15 to 20 mg/kg body weight, assuming normal renal function and hearing. Such doses typically result in maximum serum concentrations in the range of 45 to 55 μg/mL, a C_{max}-to-MIC ratio of 10- to 20-fold in most cases. Amikacin is most often given intravenously, generally through an indwelling peripheral venous catheter and less frequently through a central venous access device. For some patients with pre-existing hearing impairment, we have delivered amikacin by inhalation, particularly for airway-centered, bronchiectatic disease (see Appendix for inhalation method).

Among the first- and second-generation fluoroquinolones, ciprofloxacin was the most active in vitro; 28% of clinical isolates at NJC had MICs V 2 μg/mL, 33% had 4 μg/mL, and the remainder >4 μg/mL [26]. Because the usual maximum concentration following a dose of 750 mg of ciprofloxacin is in the range of 4 to 6 μg/mL, this did not result in a favorable C_{max} to MIC ratio in most cases. Moxifloxacin is more active in vitro [27], but we should offer a cautionary note: Although the safety profile for moxifloxacin given for shorter durations for community-acquired pneumonia is encouraging, there is little information about its safety or tolerability in long-term use typical of mycobacterial therapy.

Cycloserine was a mainstay of MAC therapy at NJC for many years [3,4]. During the period when susceptibility was determined by solid-medium critical concentration technique, 65% of isolates were deemed susceptible [4]. By contrast, when we switched to the liquid medium minimal inhibitory concentration technique, significantly fewer clinical strains appeared susceptible [28]. In general, we reserve the use of this agent for patients who have failed conventional therapy or who have toxicity/intolerance to standard agents and for cases in which the in vitro activity of the drug is encouraging.

Clofazimine (Lamprene) has been used for the past quarter century in the treatment of leprosy. Based on reports of efficacy in the mouse model, including synergistic action with rifabutin [29,30] and favorable in vitro susceptibility data [4], we have used it in pulmonary MAC therapy since the late 1970s. Although we have perceived it to be useful and generally well tolerated, we were unable to prove its efficacy because of the number of variables involved; however, in therapy trials of disseminated MAC in persons with AIDS, initial data suggested that clofazimine was not effective [31] or that it might have a slight negative impact [32]. At this time, it is not possible to definitively describe the role of clofazimine. We generally use it in cases in where there has been intolerance or toxicity from standard medications.

Ethionamide is an old, second-line anti-TB agent. Based on in vitro activity, we used it extensively in the

1970s and 1980s [4]; however, because of its formidable side-effect/toxicity profile, we have largely retired this agent. Similarly, a related compound (thiacetazone), although active in vitro [33], has been found to be poorly tolerated and, therefore, of limited clinical utility.

Isoniazid (INH) is a puzzling issue in the modern therapy of MAC. Because it was so active versus TB, INH was routinely used in MAC therapy despite very limited in vitro activity. A series of 46 pulmonary MAC patients treated in Texas with a regimen of INH, rifampin, and ethambutol for up to 24 months including an initial 6-month course of twice-weekly streptomycin resulted in a 91% "cure" rate [34]; this led to the 1990 ATS advocacy of this as the standard regimen [1]. However, these 46 patients were chosen from a very large cohort in whom treatment outcomes were not described.

Nonetheless, based on a very low likelihood of in vitro activity [4,11], minimal evidence of in vitro synergy with other medications [35], we and others began removing INH from MAC therapy in the 1990s. However, the British Thoracic Society study included some interesting observations regarding INH [9]. The trial compared a three-drug combination (INH, rifampin, and ethambutol) with a two-drug combination (rifampin and ethambutol) in adult patients with pulmonary disease caused by MAC, *M xenopi*, or *M malmoense*. Among the MAC patients receiving INH, the numbers of failures (4 of 38) and relapses (2 of 34) were slightly but not significantly lower than those who did not receive INH (failures in 7 of 37 and relapses in 8 of 30). Mycobacterial mortality for patients with all three organisms was greater in patients receiving INH (9 of 111) than those taking only rifampin/ethambutol (1 of 112). These data suggest that the activity of this drug versus MAC should be reconsidered. In this light, previous reports of synergistic effects of INH with other agents should be re-examined [24,36]

Preferred regimens and schedules

Based on the published experience of the Tyler, Texas program and our clinical observations, the following treatment options appear appropriate.

For therapy of previously untreated cavitary, TB-like disease, a regimen of clarithromycin or azithromycin, rifampin, ethambutol, and amikacin should be potent and reasonably well tolerated. Clarithromycin was modestly more effective than azithromycin, even in doses up to 600 mg/day, in comparative trials in Texas and should probably be the primary agent. If intolerance evolves (typically profound dysgeusia with anorexia), azithromycin may be substituted. The adverse drug reactions for this agent increased as the dosage was increased [37]. The amikacin should be given for the initial 2 to 3 months of treatment depending upon tolerance and response. In general, to lessen intolerance to medications, it is advantageous to introduce the drugs one by one, giving each agent for a few days before adding the next.

One of the major innovations in MAC treatment is the observation by the Tyler, Texas group that thrice-weekly treatment for pulmonary MAC seems to be of comparable efficacy to daily therapy [38,39]. This has the advantages of lessened side effects, curtailed expenses, and reduced toxicity. The potential drawback is that patients are more likely to become confused over intermittent schedules and miss some of their doses; this poses the risk of weakening the regimen's effectiveness.

For patients who have failed therapy or experienced a relapse after prior treatment, one should obtain in vitro susceptibility testing and amend treatment in accordance with these results. For patients with non-cavitary, bronchiectatic pulmonary MAC, I would use the standard regimen described above. In elderly patients with impaired hearing or diminished renal function, amikacin may be omitted. For some patients, the side effects of the three oral drug regimen may be quite disruptive. In elderly patients with limited life-expectancy (in whom acquired drug resistance seems less likely and of lesser import), a simple suppressive regimen of clarithromycin or azithromycin coupled with ethambutol may be more suitable.

Duration of therapy

Historically, we have advocated 24 months as the usual duration of pulmonary MAC drug therapy [4]. This was based on observations that treatment delivered for 12 months was apparently associated with an increased risk for relapse [3]. We still use this as a standard, but the benefits of the extended treatment have not been clearly proven. Practically, if I am treating a patient who has responded nicely to treatment, who is tolerating therapy well, and who wishes to minimize the risk of relapse, I encourage the 2-year treatment. By contrast, for patients who struggle with the side-effects of treatment or who do not manifest clear improvement after 6 or more months of treatment, it may be appropriate to stop medical therapy and observe.

For patients with clear-cut disease but modest or minimal symptoms, we may employ a 2- to 3-month

"therapeutic trial." We ask the patient to carefully note whether their symptoms or overall health status is "improved" with treatment or whether the side-effects or perceived onus of treatment exceeds their sense of benefit. In the cases where treatment is abandoned, it is important that the patient receive periodic follow-up, lest the MAC progress substantially while off therapy.

Adjunctive therapy

The most commonly overlooked element of management for patients with the bronchiectatic variety of MAC is bronchial hygiene. Inhaled beta-agonists, mucus-clearing devices such as Flutter or Pep valves, and periodic antibiotic treatment directed against Gram-negative rod superinfections may be highly beneficial.

We have used resectional surgery for patients with extensive damage to lobes or lungs, which, we believe, predisposes patients to NTM treatment failure or chronic superinfection with other microbes. Because we have not randomized these patients, we cannot state with certainty the benefits of this approach. We note that resection of bronchiectatic/atelectatic right middle lobes or lingulae seems to be efficacious and well tolerated [40]. Pneumonectomies, particularly right sided, entail significant risks of postoperative bronchial dehiscence with bronchopleural fistulae. Such surgery is highly demanding and should be performed only in specialized centers.

There currently is a trial examining the role of inhaled interferon-gamma in the management of pulmonary MAC (Intermune Company, Brisbane, California). Preliminary experience with inhaled interferon in multi-drug resistant (MDR)-TB and pulmonary MAC was encouraging.

Summary

Medical therapy for pulmonary MAC disease is a complex issue. Empiric regimens for previously untreated cases appear appropriate. For patients who have been previously treated or who manifest intolerance or toxicity with initial regimens, in vitro susceptibility testing seems to be advantageous in selecting alternative agents. Thrice-weekly regimens are comparable in efficacy to daily therapy and lessen costs and side effects. Adjunctive treatment including bronchial hygiene, periodic therapy of Gram-negative rod superinfections, and surgical resection of destroyed lung tissue may be useful, particularly in those patients suffering mainly from bronchiectatic disease.

Appendix

Below is described the policy and procedures by which we deliver inhaled amikacin at the National Jewish Medical and Research Center. Although we have used this system with general safety, we cannot and do not vouch for its freedom from complications. Please note that there are predictable side effects and that monitoring patients for renal-or ototoxicity is advised.

Policy statement

The purpose of inhaled antibiotics is to provide delivery of antibiotics to the respiratory tract by aerosol form for local delivery. Patients requiring this type of therapy will have initial instruction from a respiratory care practitioner. This is to establish patient assessment and monitor adverse reactions and response to therapy. The physician order will include drug, dose, diluent, and frequency of therapy.

Scope

All patients requiring this therapy.

Indications

1. The need to deliver a topical antibiotic in aerosol form that has its site of action in the lung.
2. Reduce the toxicity of these drugs to the patient.
3. Specific conditions:
   a. Cystic fibrosis
   b. Nontuberculous mycobacteria (NTM)
   c. *Pseudomonas* and other gram-negative bacterial infections

Contraindications

1. Contraindications related to substances being delivered may exist (consult the package insert for product-specific contraindications to medication).
2. Allergy to specific antibiotic.

Adverse effects

1. Complications related to specific pharmacologic agents.
2. Bronchospasm or irritation of the airway
3. Pharyngitis
4. Laryngitis
5. Dyspnea
6. Rhinitis
7. Ototoxicity (hearing loss and vestibular changes)
8. Renal toxicity
9. Exposure to aerosolized medications may be hazardous to clinicians.
   a. Drug exposure
   b. Increased risk of infection

Procedure

Inhaled antibiotics will be delivered according to the physician's written order. This medication will be delivered with an appropriate small-volume nebulizer designed for this purpose, currently either the Pari LC set or Pari LC Star with an expiratory filter/valve set attached.

Obtain the proper equipment

A. PARI LC Jet or PARI Star nebulizer with an expiratory filter/valve set (#41F05) (may not substitute other nebulizers)
   Oxygen tubing
   Solid mouthpiece
   Interruptor
   Medication ordered by physician
   Pulmo-Aide or compressor
   Pulse oximeter
   Kleenex
   Noseclips (if applicable)
   Filter pads
B. Goggles, gloves, and gowns should be used as splatter shields and to reduce exposure to medications and body substances as indicated.
C. Assemble equipment using diagram in Fig. 2.
D. Procedural steps:
   1. Check physician's order.
   2. Review patient's chart.
   3. Administration of all first doses of inhaled antibiotics will be administered and observed by respiratory therapy staff.
   4. Assemble equipment appropriately.

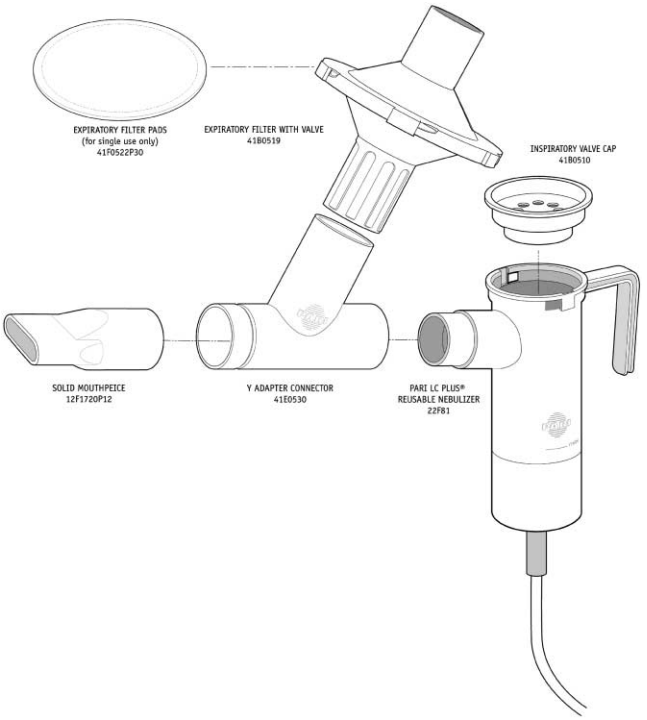

Fig. 2. Assembly diagram of small-volume nebulizer. (Courtesy of PARI Respirator Equipment, Inc, Monterey, CA.)

5. The inhaled medication dispensed will be clearly marked by pharmacy as "for inhalation only."
6. Observe standard precautions.
7. Introduce self; explain procedure to patient.
8. Provide written education material on chosen antibiotic, pre-dose bronchodilator (ie, albuterol), nebulizer care, setup.
9. Assess patient, including:
   a. Heart rate
   b. Respiratory rate
   c. Breath sounds
   d. Oxygen saturation
   e. Prepare the patient (patient should be sitting upright).
10. Pretreat patient with a rapid-onset bronchodilator (ie, albuterol, levalbuterol) 15 to 20 minutes before inhaled antbiotic; this should be ordered when there is an order for antibiotic aerosol therapy.
11. Connect one end of the oxygen tubing to the Pulmoaide compressor and the other end to the gas source inlet on the nebulizer.
12. Place medication in nebulizer; turn compressor on.
13. Have patient, inhale using solid mouthpiece. Observe if patient is nose breathing; if so, use noseclips.
14. Instruct patient to depress interruptor button during inhalation; take finger off button during exhalation and when taking mouthpiece out of the patient's mouth.
15. Reassess patient; monitor SpO_2 as needed.
16. Encourage patient to perform effective breathing technique while receiving treatment.
17. Stop treatment if patient's condition deteriorates; perform necessary steps to stabilize the patient.
18. Dispose of filter in appropriate container daily.

Note: Antibiotics should be phenol free and the pH of the final solution should be 6.8–7.0.

Pre-treatment bronchodilator therapy should ideally consist of a rapid-onset bronchodilator such as albuterol or levalbuterol. If the patient does not tolerate a rapid onset bronchodilator, a long-acting bronchodilator may be used (eg, Serevent or Foradil), but patient must wait an appropriate time period for onset of action. Pre-treatment may be provided by either a metered dose inhaler or nebulization.

The antibiotic dose to be administered depends on the chosen antibiotic. For example, a standard TOBI® dose is 300 mg. Dosages of amikacin, streptomycin and kanamycin are 5–10 mg/kg lean body weight rounded off to the nearest 50 mg; for example, 63 kg × 10 mg/kg = 630 mg should be ordered as 650 mg total dose. Frequency of administration of all of these may vary (see physician order). Doses should be mixed with normal saline to total volume of 5 to 10 cc.

Documentation

1. Medications given and dosage
2. Breath sounds before, during, and after
3. Heart rate before, during, and after
4. SpO_2
5. Compliance with treatment
6. Any adverse reactions
7. Note character of patient's coughing and mucus production, if any

Infection control

1. Caregiver should exercise standard precautions for body substance isolation and follow CDC recommendations for control of exposure to droplet nuclei, if applicable.
2. The recommended Nebulizer system is assigned for single patient use that patient may reuse these nebulizers for 6 months to a year, according to the manufacturers instructions.
3. All medications should be handled aseptically.
4. Clean and dry nebulizer per National Jewish policy.

Exposure controls

The Centers for Disease Control and Prevention recommend addressing exposure control be 1) Administrative policy 2) Engineering controls.

Administrative controls

Administrative controls should include warning signs to apprise all who enter a treatment area of potential hazards of exposure. Accidental exposures should be documented and reported according to accepted standards.

Measures to reduce aerosol contamination of room air include:

1. Discontinuing nebulization of medication while patient is not breathing the aerosol.
2. Ensuring that staff who administer medications understand risks inherent with the medication and procedures for safely disposing of hazardous wastes.

3. Screening of staff for adverse effects of exposure to aerosol medication.
4. Providing alternative assignments for those staff who are at high risk of adverse from exposure (eg, pregnant women and those with demonstrated sensitivity to the specific agent).
5. Health care workers should be periodically screened for tuberculosis or other illnesses that could be attributed to occupational exposure risks.

Engineering controls needed, if applicable

1. Filters or filtered scavenger systems to remove aerosols that cannot be contained.
2. Frequent air exchanges to dilute concentration of aerosol in room to eliminate 99% of aerosol before the next patient enters and receives treatment in the area.
3. If applicable to the situation, handling and filters, nebulizers, and other contaminated components of the aerosol delivery system used with suspect agents should be handled as hazardous waste.

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