

Nebulized Bronchodilator Formulations: Unit-Dose or Multi-Dose?

Joseph L Rau PhD RRT FAARC and Ruben D Restrepo MD RRT

BACKGROUND: Nosocomial infections linked to the use of multi-dose bronchodilator nebulizer formulations have been reported in the literature. **OBJECTIVE:** Survey American hospital respiratory therapy services to determine practice patterns, opinions, and awareness regarding unit-dose and multi-dose bronchodilator formulations. **METHODS:** A quota sample targeted 4 hospital size categories (0–100 beds, 101–200 beds, 201–400 beds, and > 400 beds) using a listing of general medical/surgical hospitals from the American Hospital Association. Hospitals were contacted via telephone to identify the director of respiratory therapy services, who was invited to complete a 29-item Web-based survey of their hospital practices and their opinions about and knowledge of issues with multi-dose and unit-dose bronchodilator formulations. **RESULTS:** One thousand forty-seven hospitals were recruited and 409 valid surveys were completed (completion rate 39%). The reported mean \pm SD percentage of unit-dose nebulizer treatments was $80.2 \pm 26.2\%$. Seventy-two percent (296) of respondents indicated having a policy and procedure manual that deals specifically with nebulized bronchodilator solutions, but only 107 reported having internal monitoring guidelines for compliance with those policies and procedures. Multi-dose bottles of bronchodilator concentrate were used with multiple patients in 77% of cases, and on average 9.7 ± 8.5 patients were treated with the same multi-dose bottle. Eighty-one percent of respondents reported that treatments from multi-dose bottles are prepared at the bedside. The length of time a multi-dose bottle was kept (after being opened) ranged from 24 hours (8%) to 1 month (11%), and only 3% of respondents reported following manufacturers' recommendations. In the respondents' opinion the chief advantage of multi-dose was cost per dose (84%), and the chief advantage of unit-dose was less risk of contamination (92%). With other factors (therapist time, cost of saline diluent for multi-dose concentrate, dose-error, and contamination) considered, 73% thought that unit-dose vials were more cost-effective. Three hundred thirty-six respondents (82%) thought that a sterile, low-volume (0.5 mL) unit-dose vial of bronchodilator concentrate would be useful, and 249 (74%) of those 336 respondents indicated that such a formulation would replace multi-dose bottles. Only 56% of respondents knew about the evidence regarding the risk of contamination with multi-dose bottles. **CONCLUSIONS:** Multi-dose bottles of bronchodilator solution are used in approximately 20% of nebulizer treatments, and without strict adherence to infection control procedures they are a potential source of nosocomial infection. A sterile, low-volume unit-dose vial of bronchodilator concentrate would be a useful alternative to multi-dose concentrate for modifying doses or mixing drugs in nebulizer therapy. *Key words:* nebulizer, bronchodilator, albuterol, unit-dose, multi-dose, infection control. [Respir Care 2003;48(10):926–939. © 2003 Daedalus Enterprises]

Joseph L Rau PhD RRT FAARC and Ruben D Restrepo MD RRT are affiliated with Cardiopulmonary Care Sciences, Georgia State University, Atlanta, Georgia.

This study was supported by a grant from the American Respiratory Care Foundation and funding from Sepracor Incorporated, Marlborough, Massachusetts. The authors have no financial interest in any of the products surveyed.

Correspondence: Joseph L Rau PhD RRT FAARC, Cardiopulmonary Care Sciences, MSC 8R0319, Georgia State University, 33 Gilmer Street SE, Unit 8, Atlanta GA 30303-3088. E-mail: resjlr@langate.gsu.edu.

Introduction

Aerosolized β_2 agonist bronchodilators are one of the most commonly used inhaled medications for respiratory disease and are frequently administered as a nebulized solution in the acute care setting. Nebulizer solutions of bronchodilators such as albuterol or metaproterenol are available in premixed unit-dose vials (drug plus saline diluent) and as multi-dose bottles (drug only), which can be used with more than one patient in the hospital setting.

In April 2002 the United States Food and Drug Administration notified health professionals of two hospital outbreaks of *Burkholderia cepacia* (formerly known as

Pseudomonas cepacia) lower respiratory tract infections, which were traced to contamination of multi-dose albuterol bottles.¹ Adverse outcomes included prolonged hospital stay, complications, and even death.¹ An investigation published in 2001 reported an outbreak of *B cepacia* lower respiratory tract infection in 9 mechanically ventilated patients, which was linked to extrinsically contaminated multi-dose albuterol bottles.² Other reports of nosocomial infection from contaminated multi-dose albuterol bottles have also appeared in the literature over the last decade.³⁻⁵ A letter to the editor of *The Annals of Internal Medicine* in January 1996 noted that similar nosocomial infections were associated with nebulized bronchodilator therapy as far back as 1967 and led manufacturers to develop single-dose vials of bronchodilator solution.⁶⁻⁷

Although unit-dose formulations reduce the probability of cross-contamination between patients, unit-dose medications are usually more expensive than their multi-dose equivalents. In an atmosphere of hospital cost-containment the perceived higher cost of unit-dose formulations is a disincentive to their use, especially in a setting with a high volume of nebulizer bronchodilator treatments. Additionally, if unit-dose vials are mixed, excessive volume and prolonged treatment times result. It is not clear what the prevailing practice is in acute care hospitals with regard to use of multi-dose versus unit-dose formulations, what infection control practices or training are in place, or what respiratory care department managers' knowledge and perceptions are with regard to advantages and disadvantages of unit-dose versus multi-dose formulations.

The purpose of this study was to determine practice patterns, opinions, and awareness among hospital respiratory therapy services regarding unit-dose and multi-dose bronchodilator solutions.

Methods

Population and Sample

The population of interest was defined as directors/managers of respiratory therapy departments and services in general medical/surgical hospitals in the 48 contiguous United States. Hospitals considered rehabilitation facilities, specialty hospitals, or skilled nursing facilities were excluded, as were military and Veterans Affairs hospitals. To qualify for inclusion, respiratory therapy departments had to provide nebulizer treatments using bronchodilator solutions, and the director/manager must have been in his or her position for at least 1 year.

A list of general medical/surgical hospitals was obtained from the American Hospital Association 2002 database (American Hospital Association Resource Center, Chicago, Illinois) together with a database that lists the volume of nebulizer prescriptions (IMS-Exponent, Plymouth Meet-

ing, Pennsylvania). To provide sufficient representation and a large enough sample for statistical comparison, non-random-quota sampling targeted 100 valid survey responses from hospitals that have ≤ 100 beds, 101–200 beds, and 201–400 beds, and 25 responses from hospitals that have > 400 beds. The small number of responses sought from hospitals with > 400 beds simply reflects the relatively small number of very large hospitals in the United States.

A marketing analysis firm (NFO WorldGroup, Greenwich, Connecticut) was subcontracted to convert the completed survey to a computer-assisted, Web-based survey instrument, recruit directors of respiratory therapy services, administer the survey, and compile the responses. An executive summary of the study results was offered to all directors who agreed to participate in the survey. We obtained the e-mail addresses of those directors willing to participate, and respondents were directed to a secure Web site with the required password to complete the survey items.

Measurement

A survey instrument (see Appendix) of 29 items was constructed by a group that included representatives from medical administration, the American Association for Respiratory Care, the pharmaceutical industry, and the respiratory therapy education sector. The final instrument incorporated revisions from pilot testing. Institutional review board approval was obtained for exempt status prior to sample recruitment.

Data Analysis

Frequency distributions of responses to multiple-choice questions were compiled. Means, medians, and standard deviations were calculated for items in which a number was requested. Comparisons among categories of hospital size were performed using a modified Student's *t* test. Differences were considered statistically significant when $p < 0.05$. Key descriptors and phrases were compiled for the open-ended question on nebulizer infection control guidelines.

Results

One thousand forty-seven hospital respiratory therapy directors were contacted, resulting in 502 total survey log-ins (48%), from which 409 valid surveys were collected, for an overall response rate of 39%. Reasons for rejecting 93 of the 502 responders were: the respondent did not qualify as a director of respiratory services; the quota for that hospital size category had already been reached; or the survey was exited before completion. Table 1 describes the hospitals that responded. Survey results are reported

NEBULIZED BRONCHODILATOR FORMULATIONS: UNIT-DOSE OR MULTI-DOSE?

Table 1. Characteristics of Hospitals That Responded to the Survey on the Use of Multi-Dose Versus Unit-Dose Bronchodilator Nebulizer Solutions*

	Number of Hospital-Beds			
	0–100	101–200	201–400	> 400
Number of beds (mean \pm SD)	55.1 \pm 25.8	152.6 \pm 29.4	291.8 \pm 54.7	634.5 \pm 187.1
Valid surveys (<i>n</i>)	124	113	136	36
Percent of total sample	30	28	33	9
<u>Region (<i>n</i> and %)</u>				
Northeast	16 (13)	15 (13)	23 (17)	9 (25)
Midwest	39 (31)	33 (29)	36 (26)	11 (31)
South	45 (36)	48 (42)	49 (36)	13 (36)
West	24 (19)	17 (15)	28 (21)	3 (8)
<u>Type of Hospital (<i>n</i> and %)</u>				
Government	46 (37)	15 (13)	12 (9)	5 (14)
Church (not for profit)	7 (6)	14 (12)	23 (17)	5 (14)
Investor-owned (for profit)	8 (6)	16 (14)	14 (10)	4 (11)
Not for profit (non-government, non-church)	63 (51)	68 (60)	87 (64)	22 (61)
<u>Type of Nebulizer Solution (mean % \pm SD)</u>				
Unit-dose	79.7 \pm 26.2	80.8 \pm 25.4	79.3 \pm 28.0	83.4 \pm 21.6
Multi-dose	20.3 \pm 26.2	19.2 \pm 25.4	20.7 \pm 28.0	16.6 \pm 21.6
<u>Treatment Ratio[†] (<i>n</i> and %)</u>				
Low (> 2.0)	28 (23)	20 (18)	49 (36)	17 (47)
Medium (1–2)	48 (39)	45 (40)	64 (47)	13 (36)
High (0–1)	48 (39)	48 (42)	23 (17)	6 (17)

*The percentage of valid surveys in each number-of-beds category are based on the total of 409 hospitals. For region, type of hospital, and treatment ratio, percentages are based on the total for the number-of-beds category. Hospital type is based on American Hospital Association listing as reported by the hospitals.

[†]Treatment ratio = number of beds per number of treatments.

Percentages may not total 100, because of rounding.

for the 3 survey sections on practices, opinions, and awareness of contamination issues.

Practices

The overall mean \pm SD percentage of treatments given with unit-dose bronchodilator formulations was 80.2 \pm 26.2%. Only 6 hospitals (1%) indicated that they did not use unit-dose vials, and 76 hospitals (19%) indicated that they did not use multi-dose bottles. Most hospitals use a mix of the 2 formulations for nebulizer treatments. The respiratory therapy department directors were the primary determiners of which type of dose formulation to use (Fig. 1), although budget responsibility for nebulizer solutions was more equally divided between respiratory therapy departments and pharmacies (55% vs 50%).

The majority of respiratory therapy departments (296 of 409) indicated that they had an infection control policy and procedure manual that deals specifically with the use of nebulized bronchodilators (Fig. 2), but only 107 of those 296 stated that they have internal monitoring guidelines for compliance with infection control policies for nebulized bronchodilator solutions. Table 2 summarizes the responses to the open-ended question about monitoring guidelines.

Although only about 20% of nebulized bronchodilator treatments were reported as coming from multi-dose bottles, there were large differences in how long the bottle was kept (once opened) before discarding it (Figure 3).

At 84% of respondent institutions the multi-dose bottles are initialed and dated by those who open them. One multi-dose bottle was assigned to multiple patients in 77% of cases. Across all hospital responses an average \pm SD of 9.7 \pm 8.5 patients were estimated to be treated with the same multi-dose bottle. Figure 4 shows estimates of the average number of patients treated with the same multi-dose bottle.

Most hospitals (269 of 334, 81%) reported that doses from multi-dose bottles are prepared at the patient's bedside. Table 3 shows the frequencies of methods for dose preparation. The addition of diluent when using a multi-dose bottle is by means of unit-dose saline in the majority of such treatment formulations (309 of 334, 93%) among the hospitals that use multi-dose bottles. Other methods of adding diluent (\leq 4% in all cases) included multi-dose bottles of saline, pressurized saline canisters, or another medication mixed with the bronchodilator from the multi-dose bottle. Figure 5 shows the estimated average percentage of multi-dose bottles that are discarded with some bronchodilator remaining. For all hospitals, the mean per-

NEBULIZED BRONCHODILATOR FORMULATIONS: UNIT-DOSE OR MULTI-DOSE?

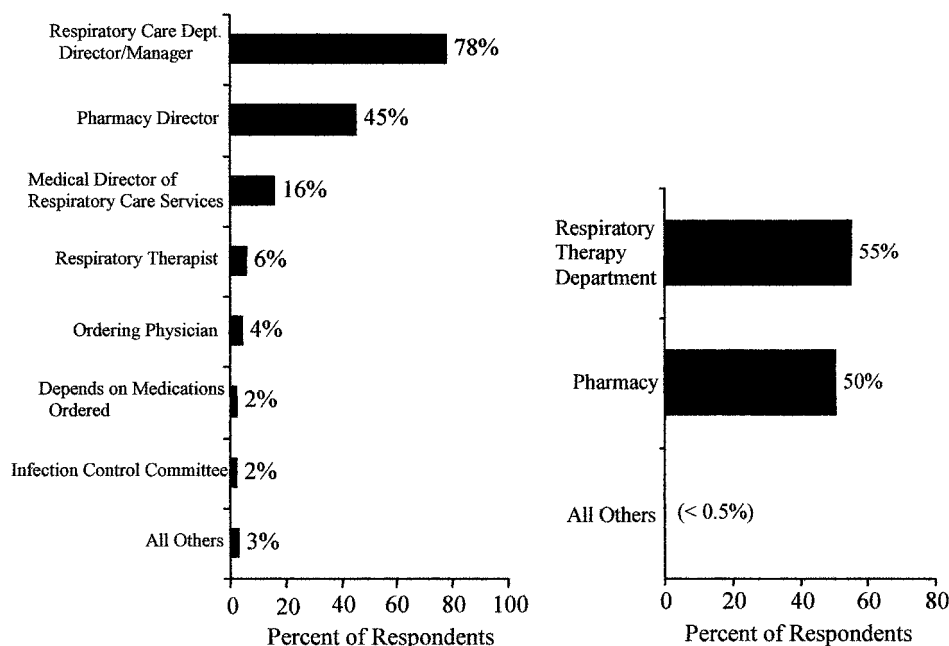


Fig. 1. Left: Responsibility for choice of nebulized bronchodilator formulation (multi-dose bottle or unit-dose vial). There were 409 survey respondents. More than 1 response was possible. Right: Department or unit budget responsible for the cost of nebulized drug solutions. There were 409 survey respondents. More than 1 response was possible.

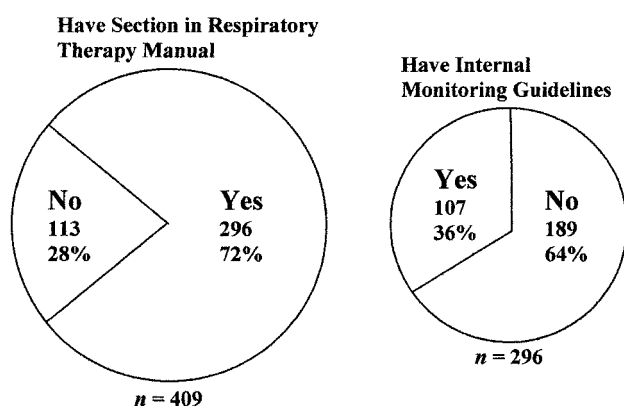


Fig. 2. Responses regarding policy and procedure manual and internal monitoring guidelines. There were 409 survey respondents, of which 296 indicated that they have a policy and procedure manual that deals specifically with nebulized bronchodilator solutions. Of the 296 that have policy and procedure manuals 107 (36%) indicated they had internal monitoring guidelines for compliance with the policies and procedures.

percentage of discarded non-empty bottles was 35% (SD = 35%), the median percentage was 20%, and the median ranged from a low of 11% (in hospitals with < 100 beds) to a high of 45% (in hospitals with > 400 beds). The reasons for wasted medication were: simply discarding solution (36%), throwing out expired drug (34%), loss or misplacement (11%), patient discharge or discontinuation

(6%), spills (3%), contamination of bottle (4%), too empty to use (1%), bottle not dated when opened (2%), and "all others" (3%).

Opinions

Figures 6 and 7 show the responses regarding advantages and disadvantages of multi-dose and unit-dose bronchodilator formulations.

Table 4 summarizes the responses regarding contamination sources. The most often picked source of contamination was the act of touching the nebulizer with the multi-dose dropper when adding medication. Figure 8 shows the distribution of opinions regarding the risk of contamination, cost-effectiveness, preference of formulation, and predicted use in the coming year. Three hundred thirty-six respondents (82%) thought that a sterile, low-volume (0.5 mL) unit-dose vial of concentrated bronchodilator solution would be useful, and 249 (74%) of those 336 respondents indicated that such a formulation would replace the use of multi-dose bronchodilator solutions.

Awareness

Fifty-six percent of respondents indicated they knew about the recent reports in the literature regarding contamination with multi-dose bronchodilator solutions. Ta-

NEBULIZED BRONCHODILATOR FORMULATIONS: UNIT-DOSE OR MULTI-DOSE?

Table 2. Sorted Responses to Open-Ended Question on Internal Monitoring Guidelines for Infection Control Policies and Procedures When Using Nebulized Bronchodilator Solutions*

	Number of Hospital-Beds				Total
	0–100	101–200	201–400	> 400	
Aseptic/sterile technique, infection control	6	3	6	1	16
Bottles labeled, date/time checked routinely	5	2	5	1	13
Not to touch inside nebulizer with dropper	2	1	0	0	3
Use unit-dose vials, not multi-dose bottles	5	1	5	1	12
Patient is assessed for complications	0	0	1	0	1
Policy and procedures manual	3	0	1	1	5
Single-patient use; discard when patient is discharged	10	2	3	3	18
Unit is changed routinely every 24 h, 7 d/wk	13	2	7	0	22
Universal formulary	2	3	1	0	6
All others	19	7	22	5	53
Don't known or no answer	2	4	0	1	7

*107 departments had internal monitoring guidelines. More than one response was possible from a single department. Values represent number of responses.

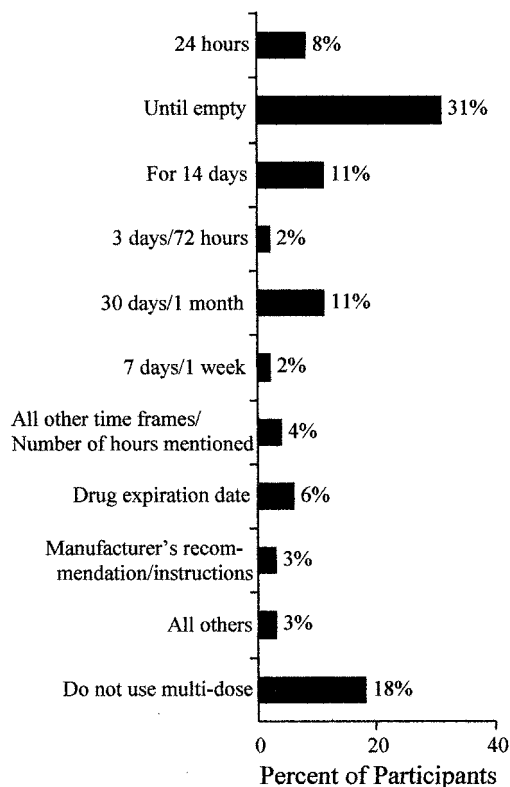


Fig. 3. Length of time that a multi-dose bottle of bronchodilator concentrate is kept, after opening, based on department policy and procedure ($n = 334$).

ble 5 lists the survey respondents' reported sources of information on contamination issues with nebulizer solutions.

Discussion

Burkholderia cepacia is a multidrug-resistant, Gram-negative bacillus that has been implicated as a cause of numerous outbreaks of nosocomial infection.^{2,3,8} Since 1995 there have been 3 peer-reviewed published reports of lower respiratory tract colonization and infection with *B cepacia* linked to extrinsically contaminated multi-dose bottles of albuterol sulfate.^{2–4} More recently a Public Health Advisory from the Food and Drug Administration Center for Drug Evaluation and Research noted that “the Agency has become aware of 2 recent hospital outbreaks” of similar infections linked to contaminated multi-dose bottles of albuterol sulfate.¹ In 1996 Pegues et al reported nosocomial *B cepacia* respiratory tract infection associated with receipt of nebulized medications, of which the most common was multi-dose albuterol.⁹ In light of those data, our survey finding that the majority of nebulized bronchodilator treatments are from unit-dose vials is reassuring. At the same time, the persistence of reports of nosocomial infections linked to contaminated multi-dose bottles is disturbing and raises a question of risk versus value with multi-dose formulations. The exact prevalence of nosocomial infections caused by contaminated multi-dose bronchodilator formulations is not known. The Public Health Advisory from the Center for Drug Evaluation and Research noted “2 recent hospital outbreaks” but gave no patient numbers. In the 3 studies mentioned above^{2–4} and in the Pegues et al study⁹ there were 165 total patients involved. Though that may be a low number as a percentage of all multi-dose bronchodilator treatments in hospitals, it is a large number of patients for an adverse effect that could be prevented by “careful attention to proper aseptic technique each time a multi-dose bottle for nebulization is opened and used.”¹ It is not known how many

NEBULIZED BRONCHODILATOR FORMULATIONS: UNIT-DOSE OR MULTI-DOSE?

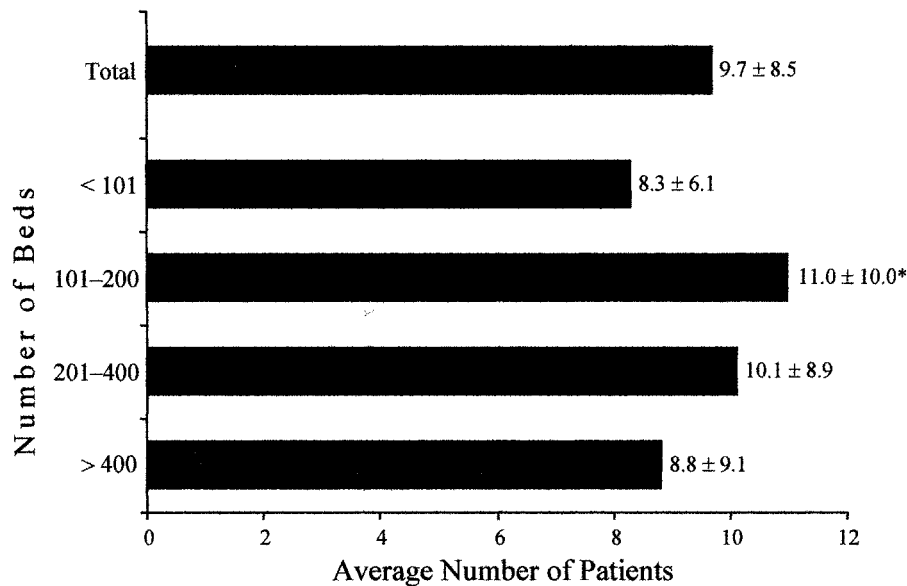


Fig. 4. Average number of patients treated with the same multi-dose bottle of bronchodilator solution, for each hospital size category and as a total across all hospital sizes ($n = 334$). * The average is significantly higher in the 101–200 beds category than in the ≤ 100 beds category ($p < 0.05$).

Table 3. Methods of Preparing a Dose From a Multi-Dose Bottle of Bronchodilator Solution*

	Number of Hospital-Beds				Total
	0–100	101–200	201–400	> 400	
Number of respondents	104	94	104	32	334
Method of Preparing Dose					
At the patient's bedside (%)	78	82	85	72	81
At the nursing station (%)	13	6	13	31†	13
In the respiratory therapy department (%)	14	20	19	22	18
In the medication/drug/pharmacy room (%)	6	2	1	6	3
Outside the patient room (%)	2	0	0	3	1
All others (%)	1	1	1	3	1

*Percentages are based on number of respondents in each category. More than one choice could be selected for the survey item.

Total = percentage of selection by all respondents.

†Significantly higher than other number-of-beds categories ($p < 0.05$).

instances of nosocomial infection from contaminated multi-dose solutions occur without identification of the cause.

An overall picture emerged in our survey that cost is a primary disadvantage of unit-dose vials. The cost of unit-dose bronchodilator formulations is higher, on a dose-for-dose basis. Based on average wholesale prices in early 2003 (Cardinal Health, Pharmaceutical Division, McDonough, Georgia), the multi-dose-bottle cost per dose was 37 cents, compared to \$1.21 for the unit-dose formulation. If we assume 25% wastage with multi-dose bottles and unit-dose saline diluent at 23 cents each, the cost of multi-dose climbs to 73 cents per dose. The risk of contamination and nosocomial infection must also be factored into the cost of multi-dose bottles. In their 1996 report of an outbreak of *B*

cepacia linked to extrinsically contaminated albuterol solution, Reboli et al pointed out that single-dose vials of albuterol would have cost \$33,800 more per year than multi-dose bottles, but antibiotic charges and infectious disease consultation alone added \$52,400 to the cost of patient care.³ The \$33,800 estimate (in 1996 dollars) may well be inflated if the cost of saline diluent, wasted medication in discarded bottles, and therapist time was not factored into the estimate. It should be noted that malpractice awards for preventable in-patient adverse drug events averaged \$376,500 in 2002 for a single patient/event.¹⁰ Cross-contamination among multiple patients caused by poor aseptic technique when using the same multi-dose bottle of bronchodilator solution must be categorized as such a preventable event.

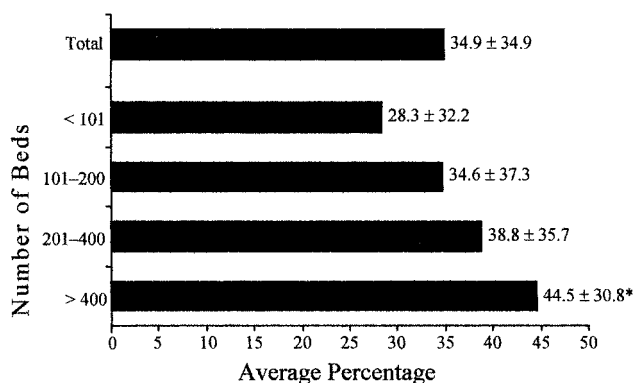


Fig. 5. Average percentages of multi-dose bottles that are discarded with some volume of drug remaining in the bottle, for each hospital size category and as a total across all hospital sizes, for those hospitals that use multi-dose bronchodilator formulation ($n = 334$). * The average is significantly higher in the > 401 bed category than in the other categories ($p < 0.05$).

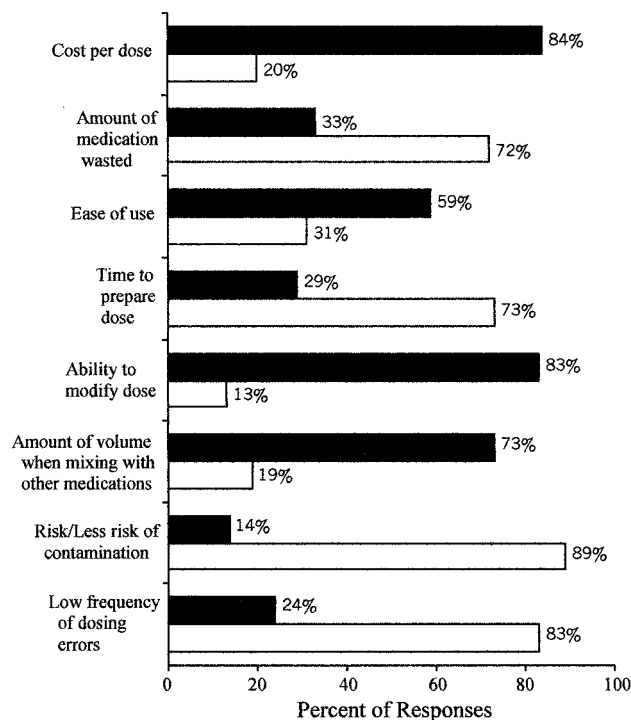


Fig. 6. Responses regarding advantages (black bars) and disadvantages (white bars) of multi-dose bottles. The bars represent the percentages of respondents who selected a given choice ($n = 409$). More than 1 choice could be selected.

Respondents noted that a major inconvenience with unit-dose bronchodilator vials is the inability to mix several unit-dose medications without causing an unacceptably large volume in the nebulizer. A sterile, low-volume (0.5 mL) unit-dose vial of bronchodilator concentrate would solve that problem and obviate the multi-dose bottle of concentrate currently used for such mixing. An overwhelm-

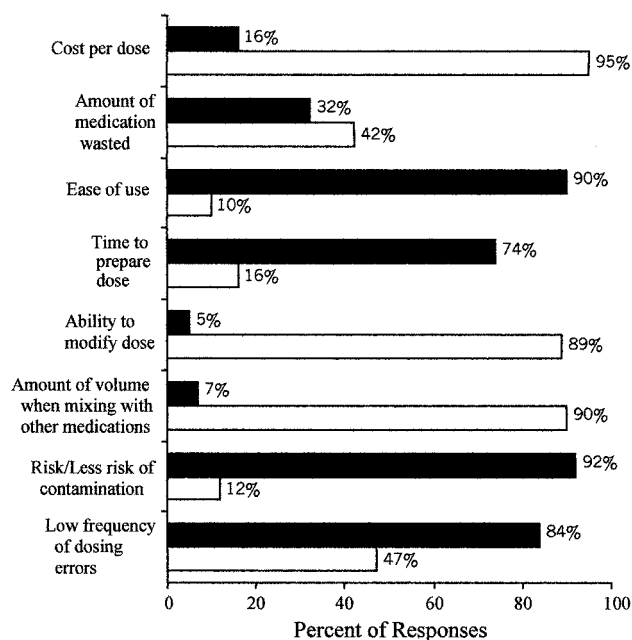


Fig. 7. Responses regarding advantages (black bars) and disadvantages (white bars) of unit-dose vials. The bars represent percentages of respondents who selected a given choice. There were 409 total responses. More than 1 choice could be selected.

ing majority of our survey respondents would prefer such a low-volume, unit-dose vial of concentrate, and three fourths said that a low-volume, unit-dose vial would replace multi-dose bottles.

Ramsey et al suggested in their 2001 report that 2 respiratory therapy practices probably contributed to the extrinsic contamination of multi-dose bottles: (1) the bottle was used among several patients, and (2) nebulizer assemblies were not always rinsed or dried between use.² Ramsey et al, Reboli et al, and Hamill et al concluded that the contamination occurred when the dispensing dropper contacted residual fluid in an incompletely dried nebulizer cup that harbored the bacteria. The multi-dose bottle was colonized when the dropper was returned to the bottle.²⁻⁴ It is also possible that the dropper contacted another environmental surface.³ In 1984 Craven et al demonstrated that inline nebulizers in ventilator circuits had high levels of contamination, and bacterial aerosols were produced by 10 out of 14 nebulizers studied.¹¹ Pegues et al reported that during their outbreak of *B cepacia* respiratory tract infection nebulizer reservoirs were not always rinsed after each use nor discarded after 24 hours.⁹

Although most respondents to the present survey thought that touching the nebulizer with a multi-dose dropper, with multiple patients, was the greatest risk of contamination (see Table 4) they also indicated that multi-dose solution was usually inserted into the nebulizer at the patient's bedside (see Table 3), and that multi-dose bottles were used with multiple patients (see Fig. 4). This is combined

NEBULIZED BRONCHODILATOR FORMULATIONS: UNIT-DOSE OR MULTI-DOSE?

Table 4. Sources Other Than Hand-Washing That Have the Greatest Influence on Risk of Contamination With Nebulizer Solutions*

	Number of Hospital-Beds				Total
	0-100	101-200	201-400	> 400	
Number of respondents	124	113	136	36	409
Source of Contamination					
The medication vial or dropper (%)	39	42	51	39	44
Re-use of incompletely dried nebulizer (%)	34	38	36	25	35
Touching nebulizer with multi-dose dropper (%)	59	66	68	58	64
Exposure of multi-dose bottle to multiple patients (%)	53	49	57	58	54

*Percentages are based on the number of respondents in each category. More than one choice could be selected for the survey item. There were no significant differences between the number-of-hospital-beds categories ($p > 0.05$).

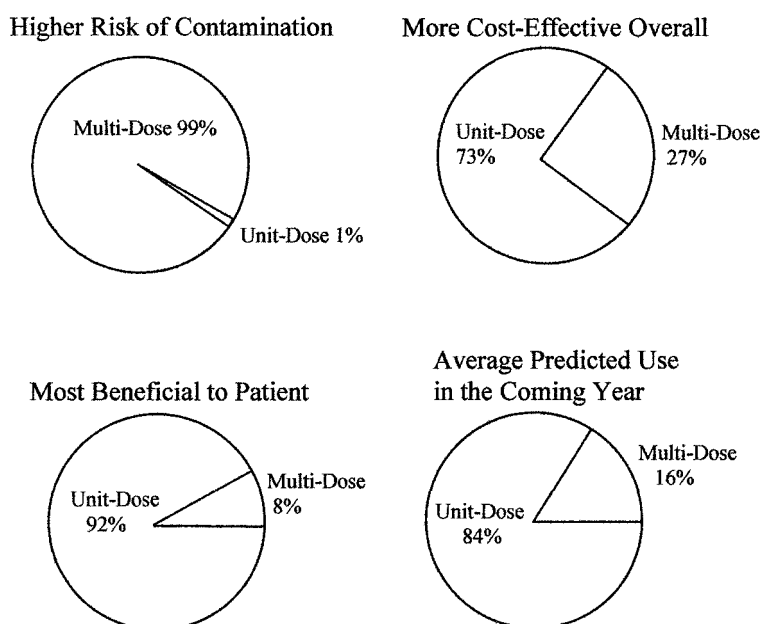


Fig. 8. Survey responses indicating opinions on multi-dose and unit-dose bronchodilator formulations. There were 409 total responses. Ninety-nine percent thought that multi-dose bottles are associated with a higher risk of contamination. Seventy-three percent thought unit-dose vials are more cost-effective overall. Ninety-two percent thought that unit dose vials are most beneficial to patients. The respondents predicted that in the coming year 84% of nebulized bronchodilator doses would be from unit-dose vials.

with the fact that 28% of respondents said they did not have policies and procedures dealing with proper use of nebulized bronchodilator solutions, and only one fourth of all respondents had monitoring guidelines for compliance with infection control policies (see Fig. 2). In Table 2 only 4 of the open-ended-response items are actually monitoring practices; the others are use/procedure guidelines. Only 56% of respondents indicated knowing about the reports of contamination from multi-dose bottles of bronchodilator solution (Fig. 9), which suggests a high potential for further contamination occurrences from the 20% of nebulized bronchodilator treatments administered with multi-dose bottles.

Hamill et al noted that there are 2 manufacturing methods used to inhibit bacteria growth in multi-dose albuterol sulfate: (1) addition of sulfuric acid to maintain a pH of 3.0-5.0, and (2) addition of the preservative benzalkonium chloride,⁴ which has optimal bacteriostatic effect at neutral or alkaline pH.¹² In addition, strains of *B cepacia* have been shown to survive in concentrated benzalkonium chloride solutions.¹³⁻¹⁴ Considering that benzalkonium chloride has been shown to cause bronchoconstriction, one group termed it a "risk without benefit."¹⁵⁻¹⁶ Antibacterial preservative is not needed in a unit-dose vial of bronchodilator solution, since the vial is not re-entered after opening.

NEBULIZED BRONCHODILATOR FORMULATIONS: UNIT-DOSE OR MULTI-DOSE?

Table 5. Survey Respondents' Sources of Information About Contamination Issues With Nebulized Bronchodilator Solutions*

	Number of Hospital-Beds				Total
	0–100	101–200	201–400	> 400	
Number of respondents	124	113	136	36	409
Information Source					
Government reports, FDA notices (%)	51	65	82†	67	67
Journal articles (%)	80	84	90	94	86
Professional newsletters and updates (%)	85	79	85	83	83
In-house communications (%)	51	45	61	64	54
Infection control nurse/committee (%)	2	4	4	0	3
Internet/Web list (%)	2	2	1	3	2
JCAHO (%)	2	2	1	3	2
All others (%)	3	2	2	3	2

*Percentages are based on number of respondents in each column and items could be selected more than once.

Total = percentage of selection by all hospital respondents.

FDA = Food and Drug Administration.

†Significantly higher than other number-of-beds categories ($p < 0.05$).

JCAHO = Joint Commission on Accreditation of Healthcare Organizations.

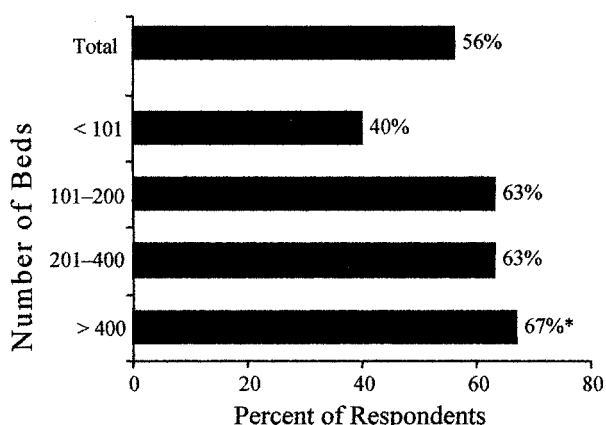


Fig. 9. Percentage of respondents who indicated awareness of reports on contamination with multi-dose bronchodilator solutions ($n = 409$). The total value is the percentage of all respondents who indicated awareness. * The average is significantly higher in the > 401 bed category than in the ≤ 100 bed category ($p < 0.05$).

Limitations of the Present Study

Limitations inherent in survey studies include possible response errors, both accidental and deliberate. As an example, in item 1 of the survey 76 hospitals (19%) said they did not use multi-dose bottles at all, but in item 9, 75 (18%) said they did not use multi-dose bottles (see Fig. 3). The survey section that dealt with practices relied on director responses, and those responses (eg, the percentage of multi-dose nebulizer treatments) may have been estimates not based on direct data. Future research might pro-

spectively quantify the percentage of multi-dose nebulizer treatments, number of patients treated with a single multi-dose bottle, amount of medication wasted with multi-dose bottles, and the reasons for using multi-dose bottles. There is also a risk that a survey will not be representative. Since invitations to participate precluded random sampling, we used quota sampling to ensure representation across regions and hospital sizes.

Conclusions and Recommendations

In summary, our survey results indicate that about 1 out of 5 nebulized bronchodilator treatments is given from a multi-dose bottle and three fourths of the multi-dose bottles are used with multiple patients. Without absolute adherence to good aseptic technique when administering medication, multi-dose bronchodilator formulations are a potential source of nosocomial infection that can cause morbidity, mortality, and increased hospital costs. Unit-dose vials of bronchodilator would remove the risk of infection from cross-contamination via multi-dose bottles. A sterile, low-volume, unit-dose vial of bronchodilator concentrate would be an alternative to a multi-dose bottle when there is a need to modify doses or mix two drugs for a nebulizer treatment. Given the reported bedside use of multi-dose bottles and the relative lack of knowledge of contamination occurrences, there is a need to educate personnel on the causes of cross-contamination with multi-dose bottles and to reinforce proper aseptic technique with nebulizer therapy, as outlined by the Centers for Disease Control and Prevention.¹⁷

REFERENCES

1. Public Health Advisory: Contamination of multi-dose bottles of albuterol sulfate solution for inhalation (0.5%). Available at <http://www.fda.gov/cder/drug/advisory/albuterol.htm> (accessed 8/7/03).
2. Ramsey AH, Skonieczny P, Coolidge DT, Kurzynski TA, Proctor ME, Davis JP. *Burkholderia cepacia* lower respiratory tract infection associated with exposure to a respiratory therapist. *Infect Control Hosp Epidemiol* 2001;22:423-426.
3. Reboli AC, Koshinski R, Arias K, Marks-Austin K, Stieritz D, Stull TL. An outbreak of *Burkholderia cepacia* lower respiratory tract infection associated with contaminated albuterol nebulization solution. *Infect Control Hosp Epidemiol* 1996;17(11):741-743.
4. Hamill RJ, Houston ED, Georgioui PR, Wright CE, Koza MA, Cadle RM, et al. An outbreak of *Burkholderia* (formerly *Pseudomonas*) *cepacia* respiratory tract colonization and infection associated with nebulized albuterol therapy. *Ann Intern Med* 1995;122(10):762-766.
5. Technique with multidose vials leads to pseudomonad infections. *Hosp Infect Control* 1990;17:73-74.
6. Scharer L. *Burkholderia cepacia* and nebulized albuterol. (Letter). *Ann Intern Med* 1996;124(2):274.
7. Mertz JJ, Scharer L, McClement JH. A hospital outbreak of *Klebsiella* pneumonia from inhalation therapy with contaminated aerosol solutions. *Am Rev Respir Dis* 1967;95(3):454-460.
8. Mangram A, Jarvis WR. Nosocomial *Burkholderia cepacia* outbreaks and pseudo-outbreaks. *Infect Control Hosp Epidemiol* 1996;17(11):718-720.
9. Pegues CF, Pegues DA, Ford DS, Hibberd PL, Carson LA, Raine CM, et al. *Burkholderia cepacia* respiratory tract acquisition: epidemiology and molecular characterization of a large nosocomial outbreak. *Epidemiol Infect* 1996;116(3):309-317.
10. Rothschild JM, Federico FA, Gandhi TK, Kaushal R, Williams DH, Bates DW. Analysis of medication-related malpractice claims: causes, preventability, and costs. *Arch Intern Med* 2002;162(21):2414-2420.
11. Craven DE, Lichtenberg DA, Goularte TA, Make BJ, McCabe WR. Contaminated medication nebulizers in mechanical ventilator circuits: source of bacterial aerosols. *Am J Med* 1984;77(5):834-838.
12. Karabit MS, Juneskans OT, Lundgren P. Studies on the evaluation of preservative efficacy. III. The determination of antimicrobial characteristics of benzalkonium chloride. *I J Pharmaceutics* 1988;46:141-147.
13. Frank MJ, Schaffner W. Contaminated aqueous benzalkonium chloride: an unnecessary hospital infection hazard. *JAMA* 1976;236(21):2418-2419.
14. Geftic SG, Heymann H, Adair FW. Fourteen-year survival of *Pseudomonas cepacia* in a salts solution preserved with benzalkonium chloride. *Appl Environ Microbiol* 1979;37(3):505-510.
15. Beasley R, Fishwick D, Miles JF, Hendeles L. Preservatives in nebulizer solutions: risks without benefit. *Pharmacotherapy* 1998;18(1):130-139.
16. Asmus MJ, Sherman J, Hendeles L. Bronchoconstrictor additives in bronchodilator solutions. *J Allergy Clin Immunol* 1999;104(2 Pt 2):S53-S60.
17. Simmons BP, Wong ES. Guidelines for prevention of nosocomial pneumonia. *Infect Control* 1982;3(4):327-333.

Appendix

SURVEY: Unit-Dose Versus Multi-Dose Bronchodilator Formulations
(Administered as a Web-based instrument)

INTRODUCTORY GREETING: The Respiratory Therapy Program at Georgia State University is conducting a survey to look at perceptions, habits, and practices regarding use of multi-dose and unit-dose bronchodilator solutions for nebulizer therapy. There are only 29 items in the survey, which should take approximately 30 minutes or less to complete. The survey is funded by the American Respiratory Care Foundation. No individual hospitals or personnel will be identified in reports from this survey; only group data will be reported. Information from this survey can be helpful in providing data on the current practice and understanding of multi-dose and unit-dose bronchodilator formulations for nebulizer therapy. This information can also help with development of guidelines on use of these formulations.

If you qualify and complete the survey, you will be given an executive summary of the survey results once all of the data is compiled and analyzed.

A. Which of the following titles best describes your position at your current institution?

- Director of Pulmonary Medicine – Business Director/Administrator
- Manager or Coordinator of Respiratory Care Services
- Director of Respiratory Therapy – Business Director/Administrator
- Director of Respiratory Therapy – Medical Director/Practicing Physician
- None of the above

B. How many beds would you estimate are in your primary institution? _____

ITEMS ON HABITS AND PRACTICES

1. In a typical week what percentage of each nebulized bronchodilator formulation (multi-dose bottle of concentrate or pre-mixed unit-dose vial) do you use currently in your hospital? Total must equal 100%.

- a. Pre-mixed unit-dose vial _____%
- b. Multi-dose bottle of concentrate _____%
- Total = 100%

2. Who chooses or decides whether to use either multi-dose concentrate bottles or pre-mixed unit-dose vials for nebulized bronchodilators? (select all that apply)

- a. Pharmacy director
- b. Respiratory care department director/manager
- c. Medical director of respiratory care services
- d. Other: _____

3. Which department/unit budget pays for the cost of nebulizer solution drugs? (select all that apply)

- a. RT department
- b. Pharmacy
- c. Other: _____

4. In the following items, indicate all of the places in the hospital where each bronchodilator formulation is used. Select all that apply.

- | <u>Unit-dose</u> | <u>Multi-dose</u> |
|--|--|
| <input type="checkbox"/> Adult/pediatric critical care units | <input type="checkbox"/> Adult/pediatric critical care units |
| <input type="checkbox"/> Neonatal critical care units | <input type="checkbox"/> Neonatal critical care units |
| <input type="checkbox"/> Emergency department (ED) | <input type="checkbox"/> Emergency department (ED) |
| <input type="checkbox"/> Outpatient clinics | <input type="checkbox"/> Outpatient clinics |
| <input type="checkbox"/> General floor care | <input type="checkbox"/> General floor care |

(continued)

Appendix
(continued)

5. What percentage of nebulized bronchodilator treatments in your hospital are given by each of the following? Total must equal 100%.

- a. RTs _____%
- b. RNs _____%
- c. Others: _____%
- Total = 100%

6. Is there a section in your Respiratory Therapy Department infection control Policies and Procedures Manual that deals specifically with the proper use of nebulized bronchodilator solutions?

- a. Yes
- b. No

7. If yes, does your department have any internal monitoring guidelines for compliance that relate to infection control *specifically* when using nebulized bronchodilator solutions?

- a. Yes
- b. No

8. If yes, what are the guidelines? (Please describe briefly) _____

IF YOU USE ANY MULTI-DOSE BOTTLE BRONCHODILATOR FORMULATIONS:

9. How long is a multi-dose bottle kept once it is opened and used before it is recommended to be discarded by your department's Policy and Procedures Manual? (select one)

- a. 24 hours
- b. Until empty
- c. For 14 days
- d. Until end of shift
- e. Other (specify): _____
- f. Do not use multi-dose bottle bronchodilator formulations

10. Is the multi-dose bottle initialed and dated by the person who opens it?

- a. Yes
- b. No

11. How are multi-dose bronchodilator bottles utilized and assigned to patients in your institution? (select one)

- a. One multi-dose bottle for each single patient
- b. One multi-dose bottle for multiple patients

12. If a multi-dose bronchodilator bottle is used with multiple patients, on average how many patients are treated with the same bottle?

_____ patients

13. How do you prepare doses from a multi-dose bottle of bronchodilator solution? (select all that apply)

- a. At the patient's bedside
- b. At the nursing station
- c. In the Respiratory Therapy Department
- d. Other (please explain): _____

14. How do you add diluent to the nebulizer dose? (select all that apply)

- a. Using unit-dose saline
- b. Using multi-dose vial of saline with no syringe
- c. Pressurized multi-dose canister of saline
- d. Other (specify): _____

(continued)

Appendix
(continued)

15. When multi-dose bottles of bronchodilator solution are used in a hospital, what percentage are discarded on average with some volume of medication still remaining? _____ %

16. You stated that _____ % of multi-dose bronchodilator bottles are not used until completely empty; what is the most common cause of unused medication? (select one)

- a. Spills
- b. Discarded solution in multi-dose bottles
- c. Expired drug thrown out
- d. Contamination of a multi-dose bottle
- e. Inadvertent loss or misplacement
- f. Other (please explain): _____

ITEMS ON OPINIONS

17. In your opinion, what are the **advantages** to use of **multi-dose** bottle bronchodilator solutions? Rank the first four in order of importance, beginning with #1, which is the most important advantage to you, and then #2, etc.

- a. Cost of the drug per dose
- b. Amount of medication wasted
- c. Ease of use
- d. Personnel time required to prepare dose
- e. Ability to modify standard doses
- f. Amount of volume (in mL) when mixing with other medications
- g. Less risk of contamination to medicine, equipment, or patient
- h. Low frequency of possible dosing errors

18. In your opinion, what are the **disadvantages** to use of **multi-dose** bottle bronchodilator solutions? Rank the first four in order of importance, beginning with #1, which is the most important advantage to you, and then #2, etc.

- a. Cost of the drug per dose
- b. Amount of medication wasted
- c. Ease of use
- d. Personnel time required to prepare dose
- e. Ability to modify standard doses
- f. Amount of volume (in mL) when mixing with other medications
- g. Risk of contamination to medicine, equipment, or patient
- h. Frequency of possible dosing errors

19. In your opinion, what are the **advantages** to use of **unit-dose** vial bronchodilator solutions? Rank the first four in order of importance, beginning with #1, which is the most important advantage to you, and then #2, etc.

- a. Cost of the drug per dose
- b. Amount of medication wasted
- c. Ease of use
- d. Personnel time required to prepare dose
- e. Ability to modify standard doses
- f. Amount of volume (in mL) when mixing with other medications
- g. Less risk of contamination to medicine, equipment, or patient
- h. Low frequency of possible dosing errors

20. In your opinion, what are the **disadvantages** to use of **unit-dose** vial bronchodilator solutions? Rank the first four in order of importance, beginning with #1, which is the most important advantage to you, and then #2, etc.

- a. Cost of the drug per dose
- b. Amount of medication wasted
- c. Ease of use
- d. Personnel time required to prepare dose
- e. Ability to modify standard doses
- f. Amount of volume (in mL) when mixing with other medications
- g. Risk of contamination to medicine, equipment, or patient
- h. Frequency of possible dosing errors

(continued)

Appendix
(continued)

21. In your opinion, which of the following sources other than hand-washing has the greatest influence on the potential risk of contamination associated with nebulizer solutions? (select all that apply)

- a. The medication vial or dropper
- b. Re-use of an incompletely dried nebulizer from treatment to treatment
- c. Touching the nebulizer with a multi-dose dropper
- d. Exposure of a multi-dose bottle to multiple patients

22. In your opinion, which of the following formulations is associated with a higher risk of contamination? (select one)

- a. Pre-mixed unit-dose vial
- b. Multi-dose bottle of concentrate

23. In your opinion, which of the following formulations is more cost effective overall, after all factors are taken into account, such as length of treatment, therapist time, cost of medicine, cost of saline, dosing errors, and possible contamination issues? (select one)

- a. Pre-mixed unit-dose vial
- b. Multi-dose bottle of concentrate

24. In your professional opinion, with all of the knowledge that you have, which formulation would you prefer to use in your hospital that would be most beneficial to your patients? (select one)

- a. Pre-mixed unit-dose vial
- b. Multi-dose bottle of concentrate

25. In the next year what percentage of nebulized bronchodilator doses by formulation, do you foresee using in your hospital? (total must equal 100%)

- a. Unit-dose _____%
 - b. Multi-dose _____%
- Total = 100%

26. In your opinion, would a low-volume (0.5 mL) sterile unit-dose vial of concentrated bronchodilator formulation be useful in your institution?

- a. Yes
- b. No

27. Would this alternative formulation of concentrated bronchodilator replace multi-dose bottles?

- a. Yes
- b. No

ITEMS ON AWARENESS

28. Are you aware of any reports in the literature in the last year or two on contamination of multi-dose bronchodilator solutions?

- a. Yes
- b. No

29. What sources of information are available or do you use to find out about problems with contamination issues in nebulizing solutions? (select all that apply)

- a. Government reports and FDA notices
- b. Journal articles
- c. Professional newsletters and updates
- d. In-house communications
- e. Other (specify): _____