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The Radiographic and Surgicopathologic Findings of Destroyed Lung at the Lung Center of the Philippines:

A Five-year Retrospective Study

ABSTRACT

Objective

This study investigated the composite picture of "destroyed lung" by cataloging the surgicopathologic findings of patients whose preoperative radiographs were consistent with that radiologic diagnosis.

Methodology

Chest radiographs of patients who underwent pneumonectomy or thoracotomy for lung resection at the Lung Center of the Philippines from 1991-1995 were retrospectively reviewed. "Destroyed Lung" was defined radiographically as a radiodensity or opacification involving at least three-fourths of a hemithorax together with other direct or indirect signs of atelectasis, bronchiectatic changes, fibrosis, and calcifications. Clinical data and surgicopathologic findings were retrieved and assessed for concurrence with the radiologic diagnosis using the kappa statistic.

Results

Preoperative chest radiographs of thirty-nine patients out of a total of 146 who underwent thoracotomy for lung resection met the criteria of destroyed lung. Radiographic opacification and crowding of vessels (direct signs of atelectasis), multiple cavities, cystic lucencies, and pleural thickening constituted the main features of "destroyed lung." Surgicopathologic findings corroborated the finding of atelectasis, described as contraction of segments with associated pleural adhesions and thickening. Microscopic findings, predominantly described as bronchiectasis, cavities, pulmonary infiltrates, and fibrosis, validated this radiographic definition.

Conclusion

A radiologic diagnosis of destroyed lung characterized as a radiodensity involving at least three-fourths of a hemithorax (atelectasis) variously associated with indirect signs of atelectasis, extensive pleural thickening, and bronchiectasis has been validated by surgicopathologic findings consistent with these conditions.

"Destroyed lung" is a term uniquely used at the Lung Center of the Philippines to refer to a permanently nonfunctioning lung characterized by mottled opacification of the entire hemithorax with extensive fibrosis, calcification, pleural thickening, bronchiectasis, and volume loss. It is clearly differentiated from fibrothorax—a thick radiodense peel encasing the lung ascribed to a thickened pleura. In fibrothorax, the underlying parenchyma may or may not be diseased. Despite these definitions, "destroyed lung" as a radiologic diagnosis remains to be divisive due to a host of multifaceted abnormalities that may bring about complex opacification of the lung. The study investigated the composite picture of "destroyed lung" by cataloging the surgicopathologic findings of patients whose preoperative radiographs were consistent with that diagnosis.

METHODOLOGY

Preoperative plain chest radiographs of patients who underwent pneumonectomy and thoracotomy lung resection between 1991-1995 were reviewed. Subjects included were those diagnosed with a "destroyed lung" as established by the following criteria:

1. Opacification or radiodensity of at least three-fourths of the hemithorax.
2. Any two of the following findings:
   - direct signs of atelectasis – crowding of vascular or bronchial markings; displaced interlobar septa
   - indirect signs of atelectasis – tracheal shift, mediastinal shift, hilar traction, diaphragmatic elevation/tenting, compensatory hyperaeration, narrowed intercostal spaces
   - thick-walled cavities, bullae, cystic lucencies
   - infiltrates, fibrosis, and calcifications

Subjects were excluded if the following were present:

- radiologic findings with well-defined mass lesion or neoplastic changes
- evidence of a previous surgical operation on the involved site
- congenital rib or chest wall abnormalities

The evolution of radiologic features through time and sites of involvement were studied. Clinical data such as presenting symptoms, physical diagnosis, and preoperative diagnosis were retrieved from the medical records of patients with destroyed lung. All surgicopathologic findings were tabulated and compared to the radiologic features defined as destroyed lung. The agreement between the radiologic features and surgicopathologic findings were computed using kappa statistic.

RESULTS

One hundred forty-six patients underwent pneumonectomy or thoracotomy for lung resection at the Lung Center of the Philippines from 1991-1995. Thirty-nine patients were radiologically diagnosed to have destroyed lungs. There were 20 males and 19 females whose ages ranged from 18-61 years. Table 1 shows the age and sex distribution of the study population. Hemoptysis was the most common presenting symptom, reported in 89.7% of patients. In 28 of these patients, hemoptysis was significant and considered massive. Other common complaints were cough, dyspnea, and chest pain.

Table 1. Age and sex distribution of study population

Age (years)	Male	Female	Total
	No. (%)	No. (%)	No. (%)
10-19	0 (0)	1 (5.3)	1 (2.6)
20-29	5 (25.0)	5 (26.3)	10 (25.6)
30-39	7 (35.0)	4 (21.0)	11 (28.2)
40-49	5 (25.0)	3 (15.8)	8 (20.5)
50-59	3 (15.0)	5 (26.3)	8 (20.5)
≥ 60	0 (0)	1 (5.3)	1 (2.6)
TOTAL	20 (100)	19 (100)	39 (100)

Table 2 lists the presenting symptoms and physical findings of destroyed lung. Pulmonary tuberculosis

Table 2. Clinical presentation of destroyed lung

		No. (%)
Symptoms	Hemoptysis	35 (89.7)
	Cough	27 (69.2)
	Phlegm	17 (43.6)
	Dyspnea	13 (33.3)
	Fever	6 (15.4)
	Weight loss	4 (10.3)
	Chest pain	3 (7.7)
	Anorexia	1 (2.6)
	Easy fatigability	1 (2.6)
Physical findings	Decreased breath sounds	26 (66.6)
	Crackles	15 (38.5)
	Chest lag	5 (12.8)
	Rhonchi	4 (10.3)
	Decreased tactile fremitus	4 (10.3)
	Wheezing	2 (5.1)
	Absent breath sounds	1 (2.6)
	Cervical adenopathy	1 (2.6)
Associated diagnosis	Pulmonary TB	35 (90.0)
	Bronchiectasis	16 (41.0)
	Asthma	8 (20.5)
	Hypertension	5 (12.8)
	Aspergillosis	5 (12.8)
	Empyema thoracis	4 (10.3)
	Pneumonia	4 (10.3)
	COPD	3 (7.7)
	Pleural effusion	3 (7.7)
	Diabetes mellitus	3 (7.7)

was the predominant comorbidity (35/39) followed by bronchiectasis, asthma, and aspergillosis. The "destroyed lung" seemed to be more common on the left side—seen in 25 of the 39 patients studied. More than half of the patients underwent lung resection within 3 months after their first radiologic diagnosis of "destroyed lung." One patient though had been diagnosed with the condition for two and a half years before the surgical intervention.

Table 3 details the radiographic findings seen in patients with a radiologic diagnosis of "destroyed lung." Opacification of at least 50%-75% of one lung and crowding of vessels were the most common signs of direct atelectasis. Indirect signs of atelectasis were manifested as ipsilateral mediastinal shift and compensatory hyperaeration. Multiple cavities, cystic lucencies, and pleural thickening were frequent auxiliary findings.

Table 3. Radiographic findings of destroyed lung

	Right	Left
	No. (%)	No. (%)
Atelectasis	**14 (100)**	**25 (100)**
Density/opacification	14 (100)	25 (100)
25%	1 (7.1)	1 (4.0)
50%	1 (7.1)	1 (4.0)
75%	6 (42.8)	8 (32.0)
100%	6 (42.8)	15 (60.0)
Tracheal shift	14 (100)	23 (92.0)
Ipsilateral, slight	5 (38.4)	8 (34.7)
Ipsilateral, marked	8 (61.5)	15 (62.5)
Contralateral	1 (7.1)	0 (0)
Mediastinal shift	14 (100)	24 (96.0)
Slight	5 (38.4)	9 (36.0)
Marked	9 (64.2)	15 (62.5)
Hilar traction	13 (92.8)	22 (88.0)
Diaphragmatic elevation	10 (71.4)	19 (76.0)
Intercostal space narrowing	9 (64.2)	20 (80.0)
Compensatory hyperaeration	13 (92.8)	23 (92.0)
Cavities (thick-walled)	**6 (42.9)**	**13 (42.0)**
Single	1 (16.6)	5 (38.5)
Multiple	5 (83.3)	8 (61.5)
Small	2 (33.3)	9 (69.2)
Large	3 (50.0)	4 (30.8)
Air-fluid level	1 (16.6)	3 (23.1)
Bulla (thin-walled cystic)	**1 (7.1)**	**4 (16.0)**
Single	1 (100)	3 (75.0)
Multiple	0	1 (25.0)
Small	1 (100)	2 (50.0)
Large	0	2 (50.0)
Air-fluid level	1 (100)	1 (25.0)
Bronchiectasis (cystic lucencies)	**11 (78.5)**	**19 (76.0)**
Infiltrates	**5 (35.7)**	**9 (36.0)**
Reticular	3 (60.0)	5 (55.5)
Alveolar	2 (40.0)	4 (44.5)
Fibrosis	**5 (35.7)**	**11 (44.0)**
Pleural thickening	**13 (92.8)**	**23 (92.0)**
Calcifications	**1 (7.1)**	**3 (12.0)**
Pneumothorax	**2 (14.2)**	**2 (8.0)**

Table 4 presents a comprehensive inventory of surgicopathologic data of what is termed as "destroyed lung." Grossly, there was contraction and/or atelectasis of the involved segments with associated pleural adhesions and thickening. Carnified or necrotic tissues and cavities were concurrent events. Atelectasis resulted in thoracic asymmetry and narrowing of intercostal spaces. Fluid and necrotic debris were found in some patients. Microscopically, three dominant occurrences were found: bronchiectasis, pulmonary infiltration admixed with fibrosis, and pleural thickening. The cavities contained hyphal elements, necrotic debris and proteinaceous material. Calcifications, caseating nodules, adenopathies, and vascular arteriopathy were evident in a few sections.

Table 4. Surgicopathological findings in destroyed lung

Surgicopathologic findings	Right	Left
	No. (%)	No. (%)
GROSS/SURGICAL		
Atelectasis/contraction	13 (92.8)	23 (92.0)
Pleural adhesions/thickening	13 (92.8)	23 (92.0)
Carnified/necrotic tissues	5 (35.7)	10 (40.0)
Cavities	6 (35.7)	9 (38.0)
Narrowed intercostals space	7 (40.0)	10 (40.0)
Pleural fluid/debris	3 (21.4)	2 (8.0)
MICROSCOPIC (Specimen)		
Atelectasis	8 (57.1)	13 (52.0)
Cavities	7 (50.0)	12 (48.0)
Thick-walled	5 (71.4)	8 (66.6)
Thin-walled	2 (28.5)	4 (33.3)
Necrotic debris/hyphal elements	6 (85.7)	8 (66.6)
Bronchiectasis	12 (85.7)	21 (84.0)
Pulmonary infiltrates	12 (85.7)	20 (80.0)
Lymphos/neutros/eos	9 (75.0)	15 (75.0)
Proteins/collagen	3 (25.0)	10 (50.0)
Congestion/hemorrhage	7 (50.0)	12 (48.0)
Fibrosis	10 (71.4)	18 (72.0)
Pleural thickening	6 (42.8)	16 (64.0)
Calcifications	3 (21.4)	4 (16.0)
Adenopathies	3 (21.4)	7 (28.0)
Caseating nodules	5 (35.7)	6 (24.0)
Vascular arteriopathy	7 (50.0)	11 (44.0)

Using the kappa statistic, the degree of agreement between radiologic features and surgicopathologic data were computed. Surgicopathologic findings corroborated the most common radiologic features found in "destroyed lung," namely, atelectasis, pleural thickening, and bronchiectasis. Fibrosis and infiltrates had only fair agreement.

DISCUSSION

Based on this review, a reliable set of criteria for a radiologic diagnosis of destroyed lung can be formulated as follows:

1. Major radiologic criteria:
   a. Presence of hemithoracic radiodensity or opacity involving at least three-fourths of a hemithorax.

b. Associated indirect signs of moderate to severe atelectasis in the form of:
   - tracheal or mediastinal shift
   - hilar traction
   - diaphragmatic elevation
   - narrowed intercostal spaces
   - compensatory hyperaeration of the contralateral lung

c. Presence of extensive pleural thickening
d. Presence of bronchiectasis

2. Minor radiographic criteria:
   a. Presence of thick-walled cavities
   b. Presence of infiltrates (reticular, alveolar)
   c. Presence of fibrosis
   d. Presence of calcifications

This study attempted to elucidate the elements of what is (radiographically) termed as "destroyed lung." Overall, there was fair to moderate agreement with the expected (based on radiologic equivalents) and actual surgicopathologic findings. Being a retrospective appraisal, it missed on the physiologic facet, which undoubtedly is a major factor in the diagnosis of destroyed lung. Blanchon et al. started an investigation on the pulmonary function of destroyed lung through careful analysis of pulmonary vascularity in angiographic studies. Ventilation-perfusion scanning is a useful tool to add to the comprehensive characterization of "destroyed lung."

GLOSSARY OF TERMS

Atelectasis

(pathologic-physiologic) Less than normal inflation of all or a portion of the lung with corresponding diminution in lung volume.

(radiologic) Radiologic evidence of diminished volume affecting all or part of a lung which may or may not include loss of normal lucency in the affected part of the lung. (This finding is not to be confused with diminished volume produced by resection of pulmonary tissue.)

Bullae

(pathologic-anatomic) a. A sharply demarcated region of emphysema 1 cm or more in diameter, b. An abnormal space within the lung 1 cm or more in diameter that may contain only gas or may contain, in addition, blood vessels and ruptured alveolar walls. A form of pulmonary air cyst.

(radiologic) Any sharply demarcated lucency a centimeter or more in diameter within the lung, the wall of which is less than 1 mm thick.

Bronchiectasis

Irreversible bronchial tree dilation characterized roentgenographically as:

1. Increase in size and loss of definition of lung markings in specific segmental areas of lungs;
2. Crowded markings indicating the almost invariably associated volume loss of the affected segments of the lungs. In more advanced cases, it may consist of cystic spaces up to several centimeters in diameter, sometimes containing air fluid levels; or atelectasis may occur, which may be complete and associated with total airlessness of lobe.

Calcifications

A calcific density within the lung that maybe organized but which does not display the trabecular organization of true bone. It is characterized by stippled, irregular, non-homogenous, extremely dense areas, usually suggesting healed lesions.

Cavity

(pathologic-anatomic) A gas-filled space within a zone of pulmonary consolidation or within a mass or nodule, produced by the expulsion of a necrotic portion of the lesion via the bronchial tree.

(radiologic) A lucency within a zone of pulmonary consolidation, a mass or a nodule; hence, a lucent area that may or may not contain a fluid level and which is surrounded by a wall usually of varied thickness.

Cavitation

An area of rarefaction or diminished density, often rounded, amidst caseous foci with loss of lung markings.

Cyst

(path anat) A circumscribed space 1 cm or more in diameter, containing gas or liquid, whose wall is generally thin, well-defined, and composed of a variety of cellular elements.

(radiologic) A circumscribed lucency or opacity within the lung or mediastinum 1 cm or more in diameter, which is presumed to represent a cyst in the pathological sense.

Density or Opacity

The shadow of an absorber that attenuates the X-ray beam more effectively than the surrounding absorbers. Hence, in a radiograph, it applies to any circumscribed area that appears more nearly white than its surrounding. It is usually applied to the shadows of nonspecific pulmonary collection of fluid or tissue whose attenuation exceeds that of the surrounding aerated lung.

Destroyed Lung or Fibroid Lung

A nonfunctioning lung characterized by mottled opacification of the entire hemithorax with extensive fibrosis, calcification, pleural thickening, bronchiectasis, and volume loss. The underlying fibrotic parenchyma cannot be restored to normal.

Fibrothorax

A thick peel of radiodensity surrounding the lung due to thickened pleura; an underlying parenchymal disease may or may not be present.

Fibrotic

Any opacity or pattern of opacities presumed to represent fibrous tissues.

Fibroid or fibrous strands

Dense, coarse bands of densities of varying sizes and generally interlacing that do not follow the usual distribution of bronchovascular markings.

Homogenous

Uniform opacity and texture all throughout.

Infiltrate

A poorly defined opacity in the lung that neither destroys nor displaces the gross morphology of the lung and is presumed to represent an infiltrate in the pathophysiologic sense.

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Curative Versus Palliative Radiotherapy in Stage III-B Non-Small Cell Lung Cancer (NSCLC):

The Lung Center of the Philippines Experience

ABSTRACT

Objective

The study compared the responses of two groups of patients with stage III-B non-small cell lung cancer, one which received a radiation dose of 60Gy (curative intent) and the other a radiation dose of 40Gy (palliative intent).

Methodology

This is a prospective randomized study of patients with a final diagnosis of stage III-B NSCLC based on TNM classification (Fourth Edition, 1987), which was done from January 7, 1992 to January 1, 1996. Patients were assigned to receive either the 60Gy or 40Gy radiation dose protocol at the Radiotherapy Section of the Lung Center of the Philippines. Excluded were patients diagnosed with stage III-B NSCLC who had malignant pleural effusion. Pretreatment evaluation consisted of a medical history, physical examination, extent of the disease based on the chest radiograph and performance status. Radiation treatment was administered using cobalt 60 teletherapy machine without using linear accelerator. A total of 60Gy radiation dose in 200cGy/fraction five times a week was required for the curative intent group, while 40Gy radiation dose in 200cGy/fraction, five times a week was given to the palliative intent group. Monthly clinical reassessment of the patient and disease monitoring were done. Differences between the responses of the two groups were analyzed using the Chi-square test.

Results

From a total of 163 patients initially included in the study, only 67 completed their radiation treatment. Thirty-three patients completed the 60Gy dose and 34 completed the 40Gy dose. The independent variables of age, sex, and histologic type of the two treatment arms were comparable. Post-radiotherapy, no significant difference was seen between the two treatment arms in terms of patient's performance status and disease progression.

Conclusion

The results revealed that the response of patients to 40Gy radiation dose (radiotherapy with palliative intent) is comparable to the 60Gy dose (radiotherapy with curative intent).

Non-small cell lung cancer (NSCLC) accounts for approximately one-third of all bronchogenic carcinoma. It represents a mixed group of tumors with overlapping histologies, clinical course, and responses to treatment. The main treatment modality for unresectable or inoperable non-small cell lung cancer (stage III-B and Stage IV) is external beam radiation therapy, administered alone or in combination with other modalities, e.g., chemotherapy.

When the treatment intent is palliative, a 40Gy dose given in 200cGy fractions can be used. When a curative intent (60Gy) is considered, patients can be treated with a more experimental approach as several options are available to increase selective radiation doses to the tumor areas. Nonetheless, many practitioners are still in a dilemma with regard to the right doses for radiotherapy as applied to stage III-B NSCLC especially in those with favorable prognostic factors. As patients with favorable prognostic features live longer compared to patients with poor prognostic features, the radiotherapy must then aim at prolonging the duration of its locoregional effect.[2] Several approaches try to increase the radiation dose selectively to the tumor, while avoiding unnecessary dose and toxicity to the surrounding tissues. This is based on the concept that the highest tumor dose is positively related to the probability of local control and local control means longer life for the patient, if not survival.

A retrospective study done by Slater, et al., at the M.D. Anderson Center showed that there was no significant difference in survival based on T stage or tumor histology but that the pathologic status of the hilar and mediastinal lymph nodes was the most significant factor affecting the frequency of malignant relapse.[3]

The management of N3 disease remains controversial in that some would place these patients under palliative care, while others put them on the curative intent of radiotherapy. Radiologists, however, consider tumor involvement of the contralateral and supraclavicular or scalene lymph nodes (N3 disease) as a regional disease so that there is a need to reclassify these subgroups of patients with regard to potential therapeutic curability.

Therefore, the study wanted to assess patients with stage III-B NSCLC, and specifically compare their responses to two radiation doses, curative (60Gy) or palliative (40Gy) intent. It also compared the effects of curative and palliative radiotherapy to the different prognostic factors (i.e., performance status, extent of disease, age, survival, etc.).

METHODOLOGY

Patients with a final diagnosis of stage III-B NSCLC based on TNM classification (AJCC) version were randomly assigned to curative or palliative treatment protocols at the Radiotherapy Section of the Lung Center of the Philippines. The period covered was from January 1, 1992 to January 1, 1996.

Patients diagnosed with stage III-B NSCLC with malignant pleural effusion were excluded in the study.

Before radiation treatment was administered, a pretreatment evaluation of each patient was done, consisting of a complete medical history, physical examination, assessment of performance status, weight, and extent of the disease based on chest radiographs. Radiation treatment was administered using cobalt 60 teletherapy machine. No linear accelerator was used.

A total of 60Gy radiation dose in 200cGy/ fraction 5 times a week for 6 weeks was given to the first group (curative intent), while 40Gy radiation dose in 200cGy/ fraction 5 times a week for 4 weeks was given to the second group (palliative intent).

Monthly follow-ups and reassessment of the clinical status of the patient were performed by the radiation oncologists involved in the study. Patients were assessed by their performance status based on the WHO Performance Criteria. (See Table 1)

Only one radiology consultant was assigned to read the entire set of initial chest radiographs and compared that with the follow-up study based on the following criteria: (1) improved—when there was diminution in the size and configuration of the primary lesion manifested as clearing or partial clearing of radiographic findings (i.e., obstructive pneumonitis, pleural effusion, etc.); (2) unchanged—when there was no change in the size and

Table 1. WHO performance status

0	Able to carry out all normal activity without restrictions.
1	Restricted in physically strenuous activity but ambulatory and able to carry out light work.
2	Ambulatory and capable of all self-care but unable to carry out any work; up and about more than 50% of waking hours.
3	Capable of only limited self-care; confined to bed or chair more than 50% of waking hours.
4	Completely disabled; cannot carry on any self-care, totally confined to bed or chair.

configuration of the primary lesion and other radiographic findings; (3) worsened—when there was an increase in the size or there had been changes in the configuration of the primary lesion or when other radiographic findings developed.

Survival duration was evaluated for all patients from the date of diagnosis and final staging until the death of or the date the patient was last known to be alive.

Differences between the responses of the two groups were analyzed using the Chi-square test.

RESULTS

One hundred sixty-three patients were recruited, 88 randomized to the curative intent group and 75 to the palliative intent group. Out of the 163 patients, only 33 patients were able to complete the 60Gy dose and 34 patients completed the 40Gy dose. Most of them refused further courses of treatment or were unable to complete the course due to unavoidable circumstances (i.e., financial constraints, relative inaccessibility). Some expired before the completion of the planned radiotherapy. Table 2 lists the characteristics of patients entered into the two treatment arms. Most of the patients were males who were on their fifth or sixth decade of life. Squamous cell bronchogenic CA was the most common histologic type.

Table 2. Demographic and clinical characteristics of study population

	Curative RT N = 33	Palliative RT N = 34	p value
	No. (%)	No. (%)	
Age, yrs.			
20-29	0 (0)	1 (2.9)	
30-39	3 (9.1)	0 (0)	
40-49	3 (9.1)	5 (14.7)	0.15
50-59	20 (60.6)	14 (41.2)	
60-69	6 (18.2)	13 (38.2)	
70-79	1 (3.0)	1 (2.9)	
Sex			
Male	31 (93.9)	28 (82.4)	0.28
Female	2 (6.1)	6 (17.6)	
Histology			
Squamous cell	20 (60.6)	14 (41.2)	
Adenocarcinoma	4 (12.1)	5 (14.7)	0.36
Large Cell	0 (0)	1 (2.9)	
Nonspecific NSCLC	9 (27.3)	14 (41.2)	
Baseline Performance Status			
1	7 (21.2)	0 (0)	
2	16 (48.5)	15 (44.1)	0.012**
3	10 (30.3)	17 (50.0)	
4	0 (0)	2 (5.9)	
**significant			

The independent variables of age, sex, and histologic type between the two treatment groups did not significantly differ from each other. Thus, the patient profiles of those who were given 60Gy dose and those who had 40Gy were comparable.

Comparison of the responses to the two treatment arms using performance status and disease progression showed no significant difference (see Tables 3 and 4).

In the curative intent group, one patient died in less than a month after completion of the treatment. Two patients died within six months. Records showed that two were still alive two to three years after therapy and

Table 3. Comparison of post-treatment performance status and chest X-ray status with curative RT versus palliative RT

Outcome	Curative RT	Palliative RT	p value
	No. (%)	No. (%)	
Performance status			
Improved	3 (9.1)	4 (11.8)	0.67*
Unchanged	21 (63.6)	18 (52.9)	
Worse	9 (27.3)	12 (35.3)	
Chest X-ray status			
Improved	3 (9.1)	4 (11 .8)	0.67*
Unchanged	21 (63.6)	18 (52.9)	
Worse	9 (27.3)	12 (35.3)	
*not significant			

Table 4. Comparison of clinical outcome according to baseline performance status

Baseline	Outcome	Curative RT	Palliative RT	p value
		No. (%)	No. (%)	
Performance Status 0-2	Performance status			
	Improved	0	0	0.78*
	Unchanged	14	9	
	Worse	9	6	
	Chest X-ray status			
	Improved	13	9	0.91*
	Unchanged	6	3	
	Worse	4	3	
Performance Status 3-4	Performance status			
	Improved	2	4	0.77*
	Unchanged	6	9	
	Worse	2	6	
	Chest X-ray status			
	Improved	6	7	0.18*
	Unchanged	0	5	
	Worse	4	7	
*not significant				

one died after eight months. Records also showed that one patient was still alive as of July 8, 1996 and his last treatment was in November 1995.

DISCUSSION

Radiation therapy has long been considered the standard treatment modality for inoperable/ unresectable NSCLC especially stage III-B. This is based on the concept that local control of the disease can be successfully translated into improvements in survival, at least in those patients without metastatic disease.[4]

The RTOG trial showed that the most important determinant of local control by radiotherapy in lung cancer is high total dose. The study confirmed the relationship of higher local control rates with higher total doses. Moreover, a dose-response relationship for survival at twenty-four to thirty months was seen, but its importance has been questioned since five-year survival rates did not differ among the total dose groups.[5]

Recent approaches to improving treatment have centered on whether to use curative intent or palliative dose to mitigate distressing symptoms. The repopulation of rapidly dividing tumor cells during prolonged treatment has been a concern that makes shortened treatment times theoretically more attractive.[6]

When patients with NSCLC stage III-B are treated with external beam radiotherapy for potential cure, a curative intent or a high total dose of 60Gy is usually employed, lasting for 6-7 weeks. Conversely, patients for palliative therapy have limited life expectancy, and treatment should be delivered in as short a time as possible. Radiotherapy with palliative intent with a total dose of 40Gy should be given for a period of 4-5 weeks.

Retrospective reports have established the efficacy of radiotherapy in NSCLC in relieving symptoms such as hemoptysis, cough, dyspnea and chest pain, which were effectively controlled.[7] Chances for patients to survive for five years is 6%. Although local control is achieved more frequently with higher doses of radiotherapy (60Gy versus 40Gy), survival is not improved by higher doses since most patients with locally advanced lung cancer ultimately develop distant metastases.

It should be noted that in this study, there was no statistically significant difference between the two treatment doses (curative vs. palliative). Inspite of this, treatment must be individualized for special circumstances. For example, patients with nonmetastatic disease, without scalene node involvement or malignant pleural effusion and with good performance status may benefit from high-dose radiotherapy.

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Radiologic Determinants of Resectability in Bronchogenic Carcinoma

ABSTRACT

Objective

The study aimed to identify which radiologic criteria (tumor size, location, presence of mediastinal lymph nodes) are useful in determining resectability of lung cancer. The correlation between histologic cell type and degree of differentiation versus resectability was also analyzed.

Methodology

The chest X-ray and CT scan of 74 patients with bronchogenic carcinoma, who were admitted at the Lung Center of the Philippines from January 1992 to May 1996, were reviewed.

Results

The degree of differentiation of the tumor and the presence of mediastinal lymph nodes seen on chest X-ray and chest computed tomography scan correlated with resectability ($p<0.05$). The other determinants like tumor size, location, and histologic cell type did not correlate with resectability.

Conclusion

Tumor size and location seen on chest X-ray are not good predictors of resectability of bronchogenic carcinoma. These findings indicate that other staging procedures should be done to determine accurately the resectability of the tumor. The presence of mediastinal fullness or widening as seen on chest X-ray is a good predictor of tumor unresectability in this series. Surgical staging procedures, like the use of mediastinoscopy, may be done directly even without the aid of a computed tomography scan.

Bronchogenic carcinoma is a leading cause of cancer death in men and the second leading cause of cancer death in women, after cancer of the breast. The incidence of lung cancer in both men and women has progressively increased in recent years. The overall five-year survival rate for patients with lung cancer may be as low as 7%-14%.[1] The best survival rates are found in the subgroups of lung cancer patients with surgically resectable tumors. Clinicians, therefore, are vitally interested in recognizing lung cancer early and determining surgical resectability accurately.

The preoperative recognition of unresectability should be detectable by sophisticated imaging technique. The reasons for unresectability of primary lung cancer include extra-thoracic and intra-thoracic metastasis, malignant pleural effusion, invasion of critical mediastinal structures, and contralateral mediastinal lymph node involvement.

The selective use of computed tomography (CT) scan for the preoperative staging of lung cancer has been advocated due to increasing cost of metastatic work-up prior to resective surgery.[2] No previous studies have been done to correlate radiologic criteria in terms of tumor size and location versus resectability and non-resectability of lung cancer.

Since the increasing size of the tumor correlates with progression of nodal status (N factor) and therefore, resectability, the study wanted to determine whether there is a cut-off tumor size beyond which the bronchogenic carcinoma is unresectable. For these patients, further work-up by CT scan may no longer be necessary because of the low yield of resectable lesions. Clinicians also wanted to know if there is an association between resectability and the differentiation, as well as the location (central or peripheral), of the tumor.

The objectives of this study were to identify radiologic determinants (tumor size, location, presence of mediastinal lymph nodes) useful in predicting resectability of lung cancer and correlate histologic cell type and degree of differentiation in predicting resectability.

METHODOLOGY

All patients admitted at the Lung Center of the Philippines from January 1992 to May 1996 who underwent surgery due to bronchogenic carcinoma were included in the study. The chest radiographs (CXR) and CT scans of these patients were assessed for (a) tumor size (in cm), (b) location (central or peripheral), and (b) presence of mediastinal lymph nodes. The assessment of the CXR plates was done by a single radiologist. Size, location, and the presence of mediastinal lymph nodes as noted in the CXR and CT scan were correlated with resectability of the tumor (defined as less than T4 or less than N2). Histologic cell type and degree of differentiation of the tumor were also analyzed.

RESULTS

A total of 142 patients underwent either a surgical staging procedure (mediastinoscopy, mediastinomy) or thoracotomy for bronchogenic carcinoma. Sixty-eight patients were excluded because their CXR were not available for study. Of the seventy-four patients included in this study, thirty-seven had a chest CT scan.

The mean age was 59.94±8.03 years for resectable cases and 54.86±11.39 years for unresectable cases. This difference was significant (p=0.03). Histopathologic studies showed adenocarcinoma in 47.3%, squamous cell carcinoma in 37.8%, large cell carcinoma in 8.1%. bronchoalveolar carcinoma in 4.1%, and adenosquamous carcinoma in 2.7% of the patients. While histologic cell type did not appear to have any relationship with resectability (p=0.34, Table 1), tumor differentiation showed a significant association with resectability. Well-differentiated tumors were all resectable but moderately differentiated tumors were resectable only in 71.4% and poorly differentiated tumors were resectable only in 57.1% (p=0.005, Table 1). Centrally and peripherally located tumors based on CXR had a resectability rate of 69.0% and 73.3%, respectively, with no correlation to ultimate resectability (p=0.886, Table 1).

Table 1. Resectability according to cell type and differentiation

Cell characteristics	No.	Resectable	Unresectable	p value
		No. (%)	No. (%)	
Cell type				
Adeno CA	35	22 (63.9)	13 (37.1)	
Adenosquamous CA	2	2 (100)	0 (0)	
Bronchioalveolar CA	3	3 (100)	0 (0)	0.34
Large cell CA	6	6 (100)	0 (0)	
Squamous cell CA	28	20 (71.4)	8 (28.6)	
Differentiation				
Well-differentiated	18	18 (100)	0 (0)	
Moderately differentiated	21	15 (71.4)	6 (28.6)	0.004*
Poorly differentiated	35	20 (57.1)	15 (42.9)	

*significant

Resectable tumors averaged 6.93±1.98 cm in size by CXR and unresectable tumors averaged 6.93±1.84 cm. This difference was not significant (p=0.98). The average size of resectable tumors by chest CT scan was 6.07±2.11 cm, and the average size of unresectable lesions was 6.35±1.20 cm. This difference was also not significant (p=0.70) (Table 2). The presence of mediastinal metastasis as evidenced by fullness on CXR showed an unresectability rate of 100% and was statistically significant (p=0.0002, Table 2). The evidence of mediastinal node metastasis on chest CT scan was associated with an unresectability rate of 63.6%. This difference was statistically significant (p=0.002, Table 2).

Table 2. Resectability according to radiologic findings

Radiologic findings	No.	Resectable	Unresectable	p value
		No. (%)	No. (%)	
Tumor Location				
Central	29	20 (69.0)	9 (31.0)	0.89
Peripheral	45	33 (73.3)	12 (26.7)	
Mediastinal widening				
Present	6	0 (0)	6 (100)	0.0002*
Absent	68	53 (77.9)	15 (22.1)	
Enlarged lymph nodes				
Present	11	4 (36.4)	7 (63.6)	0.002*
Absent	26	23 (88.5)	3 (11.5)	
*significant				

DISCUSSION

Despite identifying the risk factors and preventive measures directed against the development of bronchogenic carcinoma, its incidence and mortality rate have progressively increased in recent years. Aside from early diagnosis, patients are best served by accurate pre-operative staging in order to select for surgery only those patients who would benefit significantly from operative intervention.

Preoperative staging of bronchogenic carcinoma is generally established by a combination of clinical data, CXR, bronchoscopic examination, biopsy of involved structures, and thoracotomy. Staging of lung cancer is based on an estimate of the anatomic extent of the tumor using the TMN classification. In this system, stage I and stage II bronchogenic carcinomas are surgically resectable. Also, some stage III patients are candidates for resection if the extent of the disease is such that tumor can be removed en bloc.

In this study of patients admitted at the Lung Center of the Philippines who underwent surgery for bronchogenic carcinoma, factors for its resectability were compared and analyzed. The patient's age appeared to be a significant factor. Older patients with a mean age of 59.94±8.03 years, appeared to be good surgical candidates since most presented with slow-growing and well-differentiated lung cancer. In the younger age group with a mean age of 54.85±11.39 years, the lung cancer that developed showed a more aggressive and poorly differentiated type, and was usually unresectable when first diagnosed.

Primary lung cancer is initially detected on a routine CXR examination. The following T-staging criteria can be extracted from the plain film, including the size of the primary lesion, location, any lobar or segmental atelectasis, presence of pleural effusion, and mediastinal and hilar abnormalities. With the advent of CT, most clinicians support its routine use as a guide for surgical strategy. However, due to the higher cost of the procedure, a selective use of CT scan in the preoperative staging of lung cancer is being done. An example is a TI lesion (less than 3 cm in size) located peripherally. Some surgeons would proceed to surgery without using CT scan, since studies have shown that the lesion has only a small percentage for lymph node metastasis.[3] But no studies have been done to determine the resectability in lesions more than 4 cm based on its size, location, presence of mediastinal abnormalities, histologic type, and degree of tumor differentiation.

Studies by Libskitz,[4] Daly[5] and Mckenna,[6] showed that patients with larger and centrally located lesions have increased prevalence of mediastinal metastasis compared to those with smaller, more peripheral lesions. However, this study showed no significant relationship between the size and location of tumor with resectability and non-resectability.

Histologic cell type influences the incidence of lymphatic metastasis and undifferentiated small-cell carcinoma has the highest frequency of lymph node metastasis, followed by large-cell carcinoma, adenocarcinoma, and squamous cell carcinoma in order of decreasing frequency.[7] The degree of tumor differentiation of lung cancer in this study was significant, wherein the poorly differentiated type had more chances of unresectability (42.9%) compared to the moderately differentiated (28.6%) and well-differentiated types (0%). Except for large-cell carcinoma that had 0% unresectability, adenocarcinoma showed a higher unresectability rate (37.1%) compared to squamous cell carcinoma (28.6%).

The results of this study showed that it is not the size and location of the tumor that determine resectability but it is more the degree of differentiation of the tumor.

In this study, there was a very significant correlation between mediastinal fullness (or widening as seen on CXR) and resectability. Patients with a widened mediastinum showed 100% unresectability. However, patients with enlarged mediastinal lymph nodes seen on CT scan (>1 cm), had only 63.6% resectability.

RECOMMENDATIONS

Tumor size and location seen on plain CXR are not good predictors of resectability of bronchogenic carcinoma. It is recommended that other preoperative staging procedures be done to determine accurately the resectability of the tumor. The presence of mediastinal fullness or widening, as seen on CXR, may be a good predictor of tumor unresectability. Surgical staging (i.e., mediatinoscopy) may be done directly even without performing a CT scan. Tumor differentiation also correlates well with resectability. These findings may serve as a guide for clinicians in their preoperative staging and aggressiveness in treating bronchogenic carcinoma.

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The Use of Oxygen Concentrators as Oxygen Delivery System for the Home Oxygen Program of the Lung Center of the Philippines:

A Health Technology Assessment

ABSTRACT

Objective

The Home Oxygen Program (HOP) of the Lung Center of the Philippines (LCP) provides long-term oxygen therapy to indigent patients with chronic respiratory failure due to COPD, tuberculosis, and other lung diseases. Oxygen is delivered by large gas cylinders, which are heavy and cumbersome. Oxygen concentrators are being considered as alternative oxygen sources due to their convenience and widespread use in other countries. This study determined the feasibility of using oxygen concentrators in the local setting, in terms of both technical requirements and cost.

Methodology

A review of available medical literature and cost analysis were done to assess this health technology.

Results

Results showed that oxygen concentrators usually deliver reliable oxygen concentrations at low flow rates. However, regular maintenance is required to keep the equipment in good working condition and to maximize the benefits of long-term oxygen therapy. Noise is a problem in one-fourth to one-third of users and should also be considered. Oxygen concentrators are cheaper to operate than gas cylinders in the United Kingdom and the USA but not in the local setting. The cost analysis showed that gas cylinders are still preferable at usual flow rates of 3 liters per minute or less. Concentrators become the cheaper option only when flow rates of more than 3 liters per minute are required, when equipment is purchased instead of rented, and when prices of oxygen increase to 15% or more of present levels.

Conclusion

Although the technical requirements for the use of oxygen concentrators can be met by patients in the local setting, the current cost of the equipment does not favor the shift of oxygen delivery system from compressed gas cylinders to concentrators. However, actual clinical trials should be done to confirm the findings in the study.

Long-term therapy (LTOT) is fundamental in the treatment of chronic respiratory failure due to various respiratory diseases, particularly COPD and tuberculosis. It involves the delivery of low-flow oxygen, usually at 1 to 2 liters per minute by nasal cannula, at least fifteen hours a day to achieve arterial oxygen saturation of 90% to 92% or arterial oxygen tensions of 60-65 mmHg. It is given mostly in the home environment, hence it is synonymous with the terms "home oxygen therapy" or "domiciliary oxygen therapy."[1-4]

LTOT aims to correct hypoxemia due to chronic respiratory failure and reverse some of its physiologic effects. Two landmark studies, the British Medical Research Council (MRC) trial and Nocturnal Oxygen Therapy Trial (NOTT) showed that LTOT improves survival in COPD patients.[5-6] It has also been shown to improve quality of life (QOL) by increasing exercise capacity, reducing the work of breathing, and correcting the neuropsychological effects of hypoxemia.[7-9]

LTOT may be delivered through compressed gas cylinders, oxygen concentrators, or liquid oxygen and both stationary and ambulatory systems are available.[1,4,10] Petty[4] listed the advantages and disadvantages of each delivery system (see Table 1).

Table 1. Advantages and disadvantages of available home oxygen systems*

Considerations	Oxygen Concentrator	Compressed Gas	Liquid Oxygen
Availability	Widespread availability	Widespread availability	Not available in small or rural communities
Cost	Lower cost	Lower cost in general (may equal liquid in continuous use)	More expensive than concentrators used alone
Convenience of equipment	Convenient at home; attractive equipment; may need backup tank system; noisy	Heavy and unsightly tank; frequent deliveries needed	Light weight
Portability	Not Portable; does not assist in ambulation	Multiple tanks necessary for ambulation	Most practical ambulatory sytem; Long-range portable canister
Value in pulmonary rehabilitation	Does not assist in pulmonary rehabilitation	Not as effective in pulmonary rehabilitation	Valuable for pulmonary rehabilitation
Reliability of oxygen flow		100% oxygen at all flows	100% oxygen at all flows
*adapted from Petty (1)			

LTOT has been widely adopted in North America, most countries in Europe, and Australia. In Asia, it is most widespread in Japan, with only limited usage in Korea and Taiwan (see Table 2). The highest prevalence of home oxygen use is in the United States at 241 per hundred thousand population.[11]

LTOT is an expensive endeavor. Based on data from Medicare coverage, the total cost of home oxygen therapy is 1.4 billion dollars yearly in the United States.[11] In France, LTOT costs an average of US $3,640 yearly per patient with COPD.[12]

The Home Oxygen Program of the Lung Center of the Philippines

In the Philippines, LTOT is made possible largely by individual initiatives of patients or their physicians. There is no local data on the prevalence of home oxygen use.

In 1994, the Lung Center of the Philippines (LCP) established its Home Oxygen Assistance Program with the purpose of 1) aiding oxygen-dependent charity patients by lending them oxygen tanks and meters, 2) avoiding overstaying of charity patients whose only hospital requirement is oxygenation, and 3) maximizing the use of charity beds. A cost analysis done in 1994 to assess its feasibility showed that treatment of a patient under a home oxygen program only costs Php2,148 per month after an initial outlay of Php3,980 for oxygen tanks and therapy set. This already included the cost of oxygen used and transportation and manpower expenses for home visits. Inpatient treatment, on the other hand, cost the hospital Php18,960 per month per charity patient.

Under the Home Oxygen Program, qualified patients are provided with five oxygen-loaded tanks and an oxygen therapy set free of charge upon discharge from LCP. Refilling of oxygen tanks will be arranged between the patient's relatives and the oxygen supplier, Consolidation Industrial Gases, Inc. (CIGI). Oxygen refills are delivered at home and received (with corresponding signature) by the patient or relatives. CIGI bills LCP for the refills through debit notes. Payments of oxygen refills are determined by the social service of LCP and paid by the hospital cashier. The entire costs are shouldered by LCP if

Table 2. International prevalence of home oxygen therapy*

Country	Users/100, 000
Canada	
National	60
Ontario	150
Australia	43
Finland	21
France	26
Japan	19
Korea	1.7
Spain	
Catalonia	59
Other regions	25–85
Sweden	15
Taiwan	1.5
United Kingdom	20
United States	241
*From O'Donohue (11).	

the Medical Social Service has determined that the patient and his relatives are unable to pay for the refills.

Six years after its establishment, the HOP of LCP remains the only organized system for the delivery of LTOT in the Philippines. Preliminary data on the survival and quality of life of its patients are available from two studies.[13-14] In 1997, Aniceto and coworkers, with complete records, reported survival data from 61 patients recruited from August 1994 to December 1996. Survival rate was 46% after one year. Two patients (3.3%) survived for three years. Sera and Aniceto found a low overall quality of life in 15 patients on initial assessment, which remained the same after six months of home oxygen therapy. As of January 2000, of the 23 patients recruited since January 1996, 20 (87%) were still alive after one year; 12 survived beyond two years; 7 had been with the program at least three years and 4 have survived for 42 months or more.

In these days of increasing expenditures and budget cuts, available resources should be utilized with greater efficiency. The HOP continues to find ways to achieve better clinical outcomes and more efficient delivery of services at less cost. Some of the oxygen delivery system considerations include the following:

1. The five oxygen tanks take up a lot of space in the patient's living area so that patients may not be accepted to the program if there is not enough space in the patient's home or if safety from accidental fires cannot be assured.
2. Mobility of the patient is limited by the bulk of the oxygen tanks and the length of oxygen tubing. Patients are not free to roam from room to room.
3. Frequent deliveries are necessary for certain patients with higher oxygen requirements and deliveries can be difficult in certain areas not readily accessible to vehicles.
4. The problem of keeping track of the quantity of oxygen supplied and billing of the patient.
5. The problem of recovering tanks and meters from the homes of deceased patients because either relatives refuse to surrender them or there is no one to carry them back to the hospital.

A possible solution to these problems is a shift to oxygen concentrators (OC). In many countries, the OC is the most common delivery system for LTOT and also the cheapest. It is less bulky and lighter than a single oxygen tank. However, maintenance, noise, and electrical consumption should be considered. This study is a health technology assessment of oxygen concentrators as a delivery system for the Home Oxygen Program of the LCP. Findings will not only be applicable to the LCP but to any future LTOT program in the Philippines as well.

The study determined the feasibility of using oxygen concentrators as method of oxygen delivery to patients in the Home Oxygen Program of the Lung Center of the Philippines.

The study also determined if technical requirements for the use of oxygen concentrators could be met by patients and the local environment, the cost of delivering oxygen by oxygen concentrators and compared it with the cost of using compressed gas cylinders, and the conditions under which the use of oxygen concentrators would be preferable to gas cylinders.

The study was carried out through a review of medical literature and cost analysis.

METHODOLOGY

Review of Literature

An electronic search through MEDLINE was conducted to retrieve all available published literature on oxygen concentrators using the terms "home oxygen therapy" and "oxygen concentrators." All articles regardless of study design were retrieved if the abstract provided

information on the technical aspects and clinical use of oxygen concentrators. Clinical trials comparing oxygen concentrators with either gas cylinders or liquid oxygen systems in terms of clinical outcomes such as survival, quality of life, or cost were given particular attention.

Cost Analysis

The cost analysis was a simulation study comparing the cost of three methods of delivering home oxygen: 1) gas cylinders alone, 2) rented oxygen concentrators with backup gas cylinders, and 3) purchased oxygen concentrators with backup gas cylinders.

The analysis took the perspective of the supporting hospital (LCP) because it bore all of the costs of oxygen treatment under the Home Oxygen Program. For analysis purposes, the following assumptions were made:

1. Since there had been no studies to the contrary, other sources of direct costs were considered equal for the three options. These costs include cost of recruitment, medical evaluation, and financial evaluation of patients; cost of follow-up, including personnel and transportation expenses; maintenance treatment including drugs and vaccines; and hospitalization costs.
2. Measures of efficacy and effectiveness of oxygen therapy on survival and health-related quality of life (HRQOL) were considered equal for the three options.
3. Electrical costs from the use of the oxygen concentrators would be entirely shouldered by the patient, and would not be included in the costs incurred by the program. This was also done since it would have been very difficult to estimate costs for power consumption over time due to the frequent adjustments made by the power supplier.
4. Maintenance costs would be negligible or about the same for the three options and hence would not be included in the total costs.

The identified fixed and variable costs of the three methods of oxygen delivery are seen in Table 3.

The analysis was done assuming that the patient was prescribed oxygen for 24 hours at 2 liters per minute. It was anticipated that the oxygen concentrator would be shut down for a few hours every month for "rest" or due to power outages and it was calculated that the backup gas cylinder system would still consume one full oxygen tank per month. The useful life of all equipments including the oxygen concentrators, oxygen meters, and tanks was considered to be five years.

Table 3. Fixed and variable costs of the three methods of oxygen delivery

Type of Cost	Gas cylinders alone	Rented oxygen concentrator with gas cylinder backup	Purchased oxygen concentrator with gas cylinder backup
Fixed	– Purchase of oxygen meter – Deposit for 5 oxygen tanks	– Purchase of oxygen meter – Deposit for one oxygen tank – Initial deposit for rented unit	– Purchase of oxygen meter – Deposit for one oxygen tank – Purchase of oxygen concentrator
Variable	– Oxygen consumed – Delivery cost	– Oxygen consumed – Delivery cost – Monthly rentals	– Oxygen consumed – Delivery cost

For costs related to the use of oxygen cylinders, the prices quoted by the present provider, Consolidated Industrial Gases, Inc. (CIGI), was used. For costs related to the use of the oxygen concentrator, the price quotations of the sole available distributor, St. Patrick's Medical Systems was used. All costs were expressed in year 2000 prices, using a discount rate of 10%.

Sensitivity analysis was done using variations in the cost per tank of oxygen consumed (based on price quotations from the other oxygen suppliers), in the patient's average oxygen flow rate (from 1 to 5 liters per minute) and in the discount rate of 5% to 12%.

RESULTS

REVIEW OF LITERATURE

History

The idea of a molecular sieve oxygen concentrator was first described by Cooper in 1968. Within the following year, Coates and his colleagues had a prototype tested in the hospital setting and by 1973, Stark and Bishop had shown that a concentrator could be used successfully at home as the preferred oxygen delivery system for home use in numerous countries. Newer models are more compact and easily transported, they fit better into the home environment, create acceptable noise levels, require very little maintenance, and are capable of reliably delivering high flow of oxygen for long periods of time.[15]

Description of Technology

According to Johns and coworkers[16] most currently available concentrators make use of the properties of

a synthetic aluminum silicate belonging to a class of crystalline compounds known as zeolites. The molecular sieve has numerous minute pores linked by channels and characterized by its huge surface area. The molecular size of a gas and its polarity determine whether it is retained by the sieve material and there is a mechanism by which the nitrogen and water vapor components of room air are separated from the oxygen. A continuous supply of oxygen is achieved by using two sieve beds in a synchronized adsorption-desorption process. As one sieve adsorbs nitrogen under pressure, the other (saturated) sieve is depressurized and purged to remove oxygen. The oxygen-enriched air emerging from the sieve enters an accumulation tank where it is available to the patient at a selectable flow rate. The purged nitrogen is released back to the room air.

Prevalence of Use

Oxygen concentrators have replaced gas cylinders as the main source of oxygen home therapy in many countries especially in Europe because of their convenience and low cost. Table 4 shows the percentage usage of oxygen concentrators and other delivery systems in various countries in Europe as of December 1992. The oxygen concentrator is the preferred oxygen delivery for home use in Belgium, England, France, Ireland, Poland, Sweden, and Switzerland.[17] In the USA, all three delivery systems are readily available in virtually all areas. Cost often determines which system is used. And this varies with the patient's flow requirements, use pattern, and activity level. In remote areas, as in sparsely populated Alaska, concentrators are generally used with cylinder backups.[18] US Medicare regulations and reimbursement policies for home oxygen therapy specify that all oxygen delivery systems are "therapeutically equal and cost neutral"[19] so that the least expensive equipment is provided by oxygen suppliers and it is usually the oxygen concentrator.

Table 4. Oxygen delivery systems in use in Europe as of December 1992*

Country	Gas cylinder	Liquid oxygen	Oxygen concentrator
Belgium	–	33%	67%
Denmark	80%	–	20%
England	Yes	No	Yes
France (ANTADIR)	2%	13%	85%
France (private)	20%	40%	40%
Germany	Yes	Yes	Yes
Ireland	Yes	None	Essentially
Italy	5%	80%	15%
Netherlands	80%	5%	15%
Norway	45%	10%	45%
Poland	1%	–	99%
Spain	84%	1%	15%
Sweden	14%	1%	85%
Switzerland	Very Few	–	100%
*Adapted from Faroux et al. (17)			

Experience with Oxygen Concentrators

A. Reliability of Oxygen Delivery

1. Technical assessment

In an evaluation of six oxygen concentrators by Johns et al.,[16] the oxygen concentrations produced by five models were between 94% and 95% with a variation of 0.05% when running at 2 liters per minute or less, while the other model had a lower F_1O_2 of 90.5% and a higher variability (87.3 to 93.6%). However, at higher flow rates of 3 and 4 liters, only one model delivered oxygen concentrations according to the manufacturer's specifications (see Table 5).

In a study to assess the technical performance of four molecular sieve concentrators while running continuously for four weeks at a flow rate of 2 liters per minute, Gould and coworkers[20] showed that all four OCs delivered F_1O_2 greater than 92%. However, when running at 3 liters, F_1O_2 ranged from 85% to 94% while at 4 liters per minute the values ranged from 69.1% to 84.7% (see Table 6).

2. Clinical studies

Several studies have shown that delivery of the oxygen concentrations specified by manufacturers were not always met. An assessment of 2,414 concentrators provided by ANTADIR (National Home Treatment for Respiratory Insufficiency Association) in France, showed that only about 25% of the concentrators delivered F_1O_2 less than that predicted by the manufacturer. In addition, there was a progressive decrease in F_1O_2 delivered in relation to flow rate and working duration: the higher the flow rate and the longer the working duration, the lower the obtained F_1O_2.[21]

Escarrabill and colleagues[22] also found that only 42% of 31 concentrators used by patients for home oxygen therapy in Spain supplied a percentage of oxygen higher than 87% at a flow rate of 2 liters per minute. The concentrators did not supply adequate percentage of oxygen in 12 out of 29 patients taking them correctly so the effectiveness of the treatment can only be expected in 29% of the studied cases.

Table 5. Oxygen concentration with varying flow rates produced by six models of oxygen concentrators*

Flow Rate	DeVo 2	Dom 10	Ecoco2	Hudson 2000	Permos	Roomate
1 lpm	95%	90-92%	95%	96%	At least 90%	96%
2 lpm	95%	90-92%	95%	96%	At least 90%	96%
3 lpm	95%	90-92%	95%	96%	At least 90%	95%
4 lpm	88%	90-92%	90%	90%	80%	92%
*From Johns et al (16)						

Table 6. Oxygen concentration produced by four models of oxygen concentrators*

Flow Rate	Econo2	Mini DeVo2	Roomate III	MiniO2
2 lpm	93.2%	94.1%	93.3%	94.2%
3 lpm	89.6%	93.9%	92.0%	85.0%
4 lpm	78.0%	84.7%	83.3%	69.1%
* From Gould et al (20).				

In Israel, Shiner et al.[23] also showed that "most" of the oxygen concentrators used by 63 patients on domiciliary LTOT did not yield the recommended oxygen concentration and the flow rate meters on them tended to be "underread."

In Switzerland, 12 concentrators with a working time of 28 to 18,099 hours running at the usual flow rate of 2 liters per minute (Type A) were usually delivering less than 92% expected oxygen, with a mean of 82.9% based on 102 measurements made at least once a month for a twelve-month period. Four of these OCs were delivering less than 40% oxygen after a working time of only 4,000 hours.[24]

B. Controls and Safety Features

Concentrators usually have two simple controls, a power switch and a flow control valve or dial to regulate flow. Safety features in some but not all oxygen concentrators include bacterial and outlet filters, power failure alarm, time elapse meter, thermal cut off, circuit breaker, oxygen analyzer, and connection to a backup oxygen facility. However, not all concentrators have all of these features. Most concentrators will have audible alarms, a time elapse meter, and inlet dust filter.[16]

C. Noise Levels

Since oxygen concentrators will be running continuously for long periods of time, noise will be a concern. Most concentrators run at noise levels between 50 to 55 decibels. Some models produce high-pitched noise that vary in intensity with the adsorption-desorption pressure cycle.[16] In a survey of patients using OCs in Israel, 24% thought that their unit was unduly noisy.[23] In Spain, among 54 patients with COPD requiring LTOT, almost one-third refused to use oxygen concentrators due to excessive noise.[25]

D. Maintenance and Repairs

In his evaluation of six oxygen concentrators, Johns and coworkers[16] found that the equipment was relatively easy to maintain. The only routine maintenance requirement was changing (or washing) the inlet filter and ensuring adequate water levels in the humidifier.

In the evaluation of 2,414 OCs under ANTADIR, 61% that had a molecular sieve changed sieve after a mean duration of 10,000 hours and the compressor after a mean duration of 11,000 hours, but in both cases the variability was wide (SD about 5,000 hours). After four years of working (over 20,000 hours), 95% of machines had at least one of their parts changed.[21]

In Spain, in 54 patients using the DeVilbiss concentrator (devo/44), 18 devices needed to be changed due to machine failure.[25]

Strom and Boe,[2] in a two-year follow-up of patients on LTOT, found that the rate of technical defects and breakdowns in the oxygen equipment was considerably higher in the case of concentrators than it was for compressed gas cylinders ($p<0.001$). As a mean, 11.6% of the concentrators were reported to have some defects during a six-month period while 2.8% of the gas cylinders were reported to have some defect during the same period.

In terms of patient compliance to the required maintenance procedures for the use of OC, Shiner and

colleagues found that only 5% of patients waited for the recommended ten minutes of OC warm-up before connection, only 30% had the filters cleaned weekly, and only 25% had the OC serviced for three to four times a year.[23]

E. Patient Compliance

Walshaw et al.[26] found that only 55% of patients receiving LTOT using a domiciliary oxygen concentrator in the Liverpool district in the United Kingdom were both using the oxygen therapy correctly and had stopped smoking. In Israel, only 33% of 63 patients received oxygen treatment for the recommended 12 to 24 hours per day.[23] In France, only 45% received oxygen treatment for the recommended duration while in Spain, 31% (19 out of 62) complied adequately with their oxygen prescription.

F. Clinical Outcomes

The NOTT[6] and BMRC[5] trials have shown that LTOT improves survival in COPD patients with resting hypoxemia. In both trials, oxygen concentrators, liquid oxygen, and compressed gas were all used but no information could be derived on the most effective system in prolonging survival. However, Strom and Boe[2] did not find any significant difference in the survival rate of patients treated with concentrators or compressed gas.

The other important clinical outcome in LTOT is quality of life (QOL). Again, the two landmark trials on LTOT did not indicate which delivery system resulted in improved QOL. Dilworth[9] studied 30 patients with mainly COPD who had been started on oxygen via an oxygen concentrator. Of these, more than 80% reported considerable improvements in well-being and breathlessness, and more than half, in exercise tolerance and sleep pattern. However, no controls were used. Strom and Boe[27] compared the oxygen concentrator and compressed gas in terms of quality of life using the Sickness Impact Profile (SIP). They did not find any significant difference in the mean SIP scores in the two groups. However, in a study done by Andersson and coworkers,[28] comparing the use of liquid oxygen and oxygen concentrators in patients with chronic hypoxemia, in terms of health-related QOL using the SIP, they found significant differences in favor of the group receiving liquid oxygen in categories and dimensions of physical function, body care, ambulation, social interaction, and total SIP score.

G. Costs

An economic appraisal of the different methods of long-term treatment with oxygen in the United Kingdom in 1981 by Drummond and Bishop has shown that the oxygen concentrator was the cheapest and the most convenient, and that the use of small gas cylinders was the most expensive and least convenient of the methods studied.[29] In 1998, in a costing study of 26 patients in two health districts in the UK. Jackson and Shneerson,[30] found that both in theory and in practice, oxygen concentrators are cheaper than cylinders when oxygen is used for more than 1.4 hours per day. In a cost-minimization study in Northern Ireland in 1996, Heaney and coworkers[31] also found it cost effective to provide oxygen by oxygen concentrator when the patient uses three or more cylinders per month, independent of the duration of prescription. If the period of oxygen usage exceeds 12 months, it is more cost effective to provide oxygen by concentrator when the patient uses two cylinders per month.

Comparison with liquid oxygen shows that the use of oxygen concentrators is less costly. Andersson and colleagues[28] found that the average total cost per patient for concentrator use for a six-month period was US$ 1,310 and US$ 4,950 for liquid oxygen use, although the quality of life of patients on liquid oxygen was better.

In France, oxygen is home-delivered by both not-for-profit associations and profit-making health organizations. The not-for-profit association prefer the oxygen concentrators because of lower daily tariffs. Tariff per day was US$ 18.67 for liquid oxygen at the time the study was done.[12]

COST ANALYSIS

Based on current prices, an oxygen meter costs ₱8,000 each and the deposit for an empty oxygen tank is ₱4,400 per tank. A full tank contains 5,660 liters of oxygen and costs ₱135, inclusive of delivery fees.

The oxygen concentrator (Mobilaire, USA) costs ₱120, 000 for the 3-liter model (flow rates up to 3LPM) and ₱140,000 for the 5-liter model (up to 5 LPM). The 5-liter model was preferred for purchase because of the wider range of flow rates available. For rental of oxygen concentrator, there is an initial deposit of ₱10,000 and monthly rates of ₱3,800 for the flow rates of 3 liters or less and ₱4, 800 for flow rates of 4 to 5 liters per minute. The fixed and variable costs for each of the three options are shown in Table 7.

Table 7. Estimate costs for the three oxygen delivery systems

Costs	Gas cylinders alone	Rented oxygen concentrator with backup tank	Purchased oxygen with backup tank
Fixed (installation) costs	Oxygen meter = **₱8,000** Deposit for 5 empty tanks = **₱4,400** x 5 = **₱22,000**	Oxygen meter = **₱8,000** Deposit for one empty tank = **₱4,400** Deposit for OC unit = **₱10,000**	Oxygen meter = **₱8,000** Deposit for one empty tank = **₱4,400** Purchase of OC unit = **₱140,000**
Total	**₱30,000**	**₱22,400**	**₱162,400**
Variable (running) costs	Annual oxygen consumption at 2 LPM = 186 tanks x **₱135**/tank = **₱25,110**	Annual oxygen consumption = 12 tanks x **₱135**/tank = **₱1,620** Rentals = 12 months x **₱3,800** = **₱45,600**	Annual oxygen consumption = 12 tanks x **₱135**/tank = **₱1,620**
Total	**₱25,110**	**₱47,220**	**₱1,620**

Using a discount rate of 10% for all fixed (installation) costs, the annual costs for the three options are shown in Table 8. When fixed costs are incurred only during the first year of the program and variable costs for the whole five years, annual costs of the program for one patient is ₱33,023 for the gas cylinders, ₱55,129 for the rented oxygen concentrators and ₱41,820 for the purchased oxygen concentrator. Thus, under usual conditions, the use of gas cylinder is the least costly method of oxygen delivery.

Table 8. Annual cost of the three delivery systems using a discount rate of 10%

	Gas cylinder	Rented oxygen concentrator	Purchased oxygen concentrator
Annualized cost of equipment	Php 7,913	Php 5,909	Php 40,200
Annual variable costs	Php 25,110	Php 47,220	Php 1,620
Total	**Php 33,023**	**Php 53,129**	**Php 41,820**

The sensitivity analysis using variations in the flow rate and cost of oxygen from gas cylinders shows that even with an increase in the price of oxygen up to ₱180/tank, the use of gas cylinders remains the cheaper option if the oxygen requirement remains at 2 liters per minute. However, when the oxygen requirement becomes 3 liters per minute or more, it is already cheaper to purchase oxygen concentrators. At flow rates of between 2 and 3 liters, the cost of each gas cylinder becomes crucial and the sole determinant of which option to use will be its price, that is, the choice should be the least expensive. Rental of concentrator units is the most expensive option and always more expensive than the purchased unit. It is only cheaper than gas cylinders in the long run when the use requires very high flow rates.

There is also a variation in costs with different discount rates. Again, even at a low discount rate of 5% or a high of 12%, the conclusions remain the same. The cost of the purchased concentrators is most affected by the changes in discount rates but the variability is narrow and hardly makes a difference.

DISCUSSION

Based on the results of the review of literature and cost analysis, the oxygen concentrator is an acceptable mode of oxygen delivery in the home setting, especially if the oxygen requirement of the patient is 2 liters per minute or less. However, the following technical and clinical factors should be considered by the physician or policy maker in deciding whether or not the oxygen concentrator is the most appropriate delivery system for a particular patient or groups of patients:

1. *Safety*. The setting for the concentrator should be well-ventilated, clean, dry, and away from open fires or gas heaters. However, the same considerations probably hold true for the oxygen delivery systems.
2. *Maintenance*. Machine checkup should be done on a regular basis, according to the manufacturer's specifications or probably every quarter of the year to ensure that the equipment is always in good working condition and delivering the desired oxygen concentration. Equipment maintenance is something that Filipinos are not usually good at. We prefer to fix things only when they get broken. Maintenance costs should be keyed in the overall costs of oxygen delivery since if the unit breaks down frequently,

Appendix A

Annual cost of the three options with changes in flow rate and cost per tank of oxygen and a discount rate of 10% for all equipment

O_2 flow rate	Tanks per year	Cost per oxygen tank	Total cost of gas cylinder	Total cost of rented OC	Total cost of purchased OC
1L	93	135	20,468	53,129	41,820
		150	21,863	53,309	42,000
		165	23,258	53,489	42,180
		180	24,653	53,669	42,360
2L	186	135	33,023	53,129	41,820
		150	35,813	53,309	42,000
		165	38,603	53,489	42,180
		180	41,393	53,669	42,360
3L	279	135	45,578	53,129	41,820
		150	49,763	53,309	42,000
		165	53,948	53,489	42,180
		180	58,113	53,669	42,360
4L	372	135	58,113	63,509	41,820
		150	63,713	63,689	42,000
		165	69,293	63,869	42,180
		180	74,873	64,049	42,360
5L	465	135	70,688	63,509	41,820
		150	77,663	63,689	42,000
		165	84,638	63,689	42,180
		180	91,613	64,049	42,360

Appendix B

Annual cost of the three options with changes in flow rate and cost per tank of oxygen and a discount rate of 5% for all equipment

O_2 flow rate	Tanks per year	Cost per oxygen tank	Total cost of gas cylinder	Total cost of rented OC	Total cost of purchased OC
1L	93	135	20,876	53,433	39,125
		150	22,271	53,613	39,305
		165	23,666	53,793	39,485
		180	25,061	53,973	39,665
2L	186	135	33,431	53,433	39,125
		150	36,221	53,613	39,305
		165	39,011	53,793	39,485
		180	41,801	53,973	39,665
3L	279	135	45,986	53,433	39,125
		150	50,171	53,613	39,305
		165	54,356	53,793	39,485
		180	58,541	53,973	39,665
4L	372	135	58,541	65,433	39,125
		150	64,121	65,613	39,305
		165	69,701	65,793	39,485
		180	75,281	65,973	39,665
5L	465	135	71,096	65,433	39,125
		150	78,071	65,613	39,305
		165	85,046	65,793	39,485
		180	92,021	65,973	39,665

oxygen delivery to the patient is jeopardized, and costs will further increase since there will be greater dependence on the backup cylinders.

Appendix C

Annual cost of the three options with changes in flow rate and cost per tank of oxygen and a discount rate of 12% for all equipment

O_2 flow rate	Tanks per year	Cost per oxygen tank	Total cost of gas cylinder	Total cost of rented OC	Total cost of purchased OC
1L	93	135	20,876	53,433	46,668
		150	22,271	53,613	46,848
		165	23,666	53,793	47,028
		180	25,061	53,973	47,208
2L	186	135	33,431	53,433	46,668
		150	36,221	53,613	46,848
		165	39,011	53,793	47,028
		180	41,801	53,973	47,208
3L	279	135	45,986	53,433	46,668
		150	50,171	53,613	46,848
		165	54,356	53,793	47,028
		180	58,541	53,973	47,208
4L	372	135	58,541	65,433	46,668
		150	64,121	65,613	46,848
		165	69,701	65,793	47,028
		180	75,281	65,973	47,208
5L	465	135	71,096	65,433	46,668
		150	78,071	65,613	46,848
		165	85,046	65,793	47,028
		180	92,021	65,973	47,208

Appendix D

Five-year cost of oxygen therapy in a hypothetical patient with progressive increase in oxygen flow requirements and death after five years

	Gas cylinder		Rented OC		Purchased OC	
	Annual cost	Cumulative cost	Annual cost	Cumulative cost	Annual cost	Cumulative cost
Year 1(1L)	20,468	20,468	53,129	53,129	41,820	41,820
Year 2(2L)	33,023	53,491	53,129	106,258	41,820	83,640
Year 3(3L)	45,578	99,069	53,129	159,387	41,820	125,460
Year 4(4L)	58,113	157,182	63,509	222,896	41,820	167,280
Year 5(5L)	70,688	227,870	63,509	286,405	41,820	209,100

3. *Electrical supply*. The power supply should be reliable in the area, with few power outages or fluctuations expected. Occasional power failures can be tolerated since there is usually an oxygen cylinder available as a backup system. More frequent power outages increases cost since there will be greater dependence on the backup oxygen system. At present, the power supply has been reliable and frequent power failures are not really expected in the future.
4. *Noise*. Some individuals are more sensitive to sounds than others. The studies cited show that one-fourth

to one-third of patients may consider the noise intolerable. Due consideration should be given these people when choosing the concentrator for oxygen delivery. However, oxygen concentrators usually run at 50-55 decibels, which is the same as a running electric fan or air conditioner, appliances that are ubiquitous in the Filipino home.

5. *Patient Compliance*. To maximize the benefit of LTOT in terms of survival or quality of life, patients should be advised that oxygen should be taken at least 15 hours a day, and not on PRN or as needed basis, and that the flow rate should always be at the prescribed setting. Regular checking of oxygen saturation will ensure that the proper levels of oxygen concentration is given. Patient education can be done by the Home Oxygen Program nurse, respiratory therapist or physician before LTOT is started, and is frequently reiterated during monthly visits.
6. *Costs*. Based on the cost analysis where 2 liters per minute was considered the usual oxygen flow rate, the use of compressed gas cylinders is still cheaper than oxygen concentrators. This is not the same as the conclusions from studies done in the United Kingdom where oxygen concentrators are less expensive when the patient's oxygen requirement is 1.4 liters per day or more. The difference may be due to cheaper oxygen concentrators and/ or more expensive oxygen delivery costs in the UK as compared to the Philippines. Under local conditions, the oxygen concentrator is more cost effective than gas cylinders only if it is purchased and not rented, if the flow rate requirement is 3 liters per minute or more, or if the cost of oxygen increases by at least 15% from the current levels. This is under the assumption that clinical outcomes such as survival and quality of life are identical for both delivery systems. Previous studies from abroad have shown that these assumptions are correct although more studies of this nature are probably required. In the local setting, there is probably no reason to assume that same conditions do not hold true. However, due to the fact that the cost analysis was done under simulated conditions, it is desirable that actual clinical trials be done to test the conclusions of the present study.

From the results of the present study, it is concluded that the technical requirements for the use of oxygen concentrators could be met by patients under local conditions. However, under usual clinical conditions and at current prices of oxygen equipment and supplies, the use of gas cylinders is still the least expensive method of delivering oxygen to the patients in the Home Oxygen Program. For the oxygen concentrator to be more cost effective than the present system, it should be purchased by the institution and not just rented on a monthly basis and it should be used in patients with daily oxygen requirements of 3 liters per minute or more. It can also become the cheaper option if the price of oxygen increases by at least 15% above current levels.

RECOMMENDATIONS

At present, a complete shift from gas cylinders to oxygen concentrators under the Home Oxygen Program is not practical and probably not cost effective. However, a few may be utilized for patients with higher flow rate requirements and who are able to meet the standards for safety and maintenance required by the equipment. A clinical trial will be necessary to confirm the conclusions of the present study.

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ORIGINAL ARTICLE

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Adverse Drug Reactions to Anti-TB Medications:

Knowledge of Physicians and Nurses in the Local Health Centers

ABSTRACT

Objective

A survey of physicians and nurses in 53 health centers in Quezon City was conducted to determine their knowledge on the directly observed treatment strategy (DOTS) program currently being implemented by the Department of Health under the National Tuberculosis Program.

Methodology

An open-ended questionnaire contained questions on knowledge of adverse drug reactions (ADR) to antituberculosis drugs. This study analyzed the responses of the physicians and nurses to these questions to determine their knowledge level of ADR monitoring in TB treatment.

Results

Forty-five physicians and 43 nurses completed the questionnaire and comprised the study population. Results show that knowledge of physicians and nurses in the local health center regarding adverse drug reactions to isoniazid, rifampicin, pyrazinamide, and streptomycin is quite inadequate.

Conclusion

Further training on adverse drug reactions to anti-TB drugs should be provided for physicians and nurses in the health centers. This will ensure improved compliance to and safety of treatment under the National TB Program.

The incidence of adverse reactions to antituberculosis agents vary according to regimen and patient characteristics. Among hospital patients, adverse reactions were seen in 24% to 28% while abnormal laboratory findings were observed in 42% to 47%. The incidence of adverse reactions in patients treated with three drugs was 44% and four drugs, 82%. Adverse reactions commonly appear within one month after starting treatment, and disappear within one month from its onset. However, there may be side effects such as neurological symptoms, arthralgia, and general fatigue that may appear after one month and last for a long duration.[1-2]

In the outpatient setting, nausea and vomiting are the most common complaints occurring in about 40% of patients. Hepatic toxicity may be seen in less than 20%. However, side effects are seldom serious, and only about 5% or less require termination of one or more drugs.[3-6]

Monitoring of adverse reactions is an important aspect in the follow-up of patients on anti-TB treatment. Setting up of follow-up programs in antituberculosis treatments helps to improve the compliance and safety of treatment. Under the National TB Program of the Department of Health, local health units are responsible for diagnosis, instituting treatment, and monitoring of adverse drug reactions. Physicians, nurses, and other health unit personnel should be fully aware of these conditions, so that patients may be adequately informed at the onset of treatment and prompt treatment may be instituted, including stopping of medications, when these occur. There are only a few studies on the knowledge of physicians in adverse drug reactions to anti-TB medications whether in the hospital or outpatient setting. This study hopes to provide some information in this regard.

The study determined the level of knowledge of physicians and nurses in the local health centers on the adverse drug reactions to anti-TB medications used in the National Tuberculosis Program.

METHODOLOGY

This is an analysis of an earlier survey done among 53 health centers in Quezon City on the knowledge of health workers on the various aspects of the directly observed treatment short-course or DOTS program being implemented by the City Health Department under the National Tuberculosis Program of Health. A random sampling of the 275 employees in the 53 health centers was done. The subjects were asked to answer an open-ended questionnaire based on the guidelines for implementation contained in Administrative Order No. 24 S,1996 from the DOH summarizing the basic information that should have been disseminated to the health workers. The heads of the health centers, which were the physicians, were gathered in the Quezon City Hall and given the questionnaires sealed in an envelop. They were instructed to distribute the questionnaires to health center staff included in the random sampling (including the physicians themselves). The data was collected from September to October 1999. Response rate was 82%.

The questionnaire (see Appendix A) consisted of 12 open-ended questions on various aspects of the DOTS program and an item to elicit suggestions for the program. Included were questions on what the DOTS program is, as well as on recruitment, treatment, supervision, and monitoring of patients. Knowledge of adverse reaction to anti-TB drugs was also determined.

The study was limited to the portion of the questionnaire dealing with adverse drug reactions (Question #1) and to the responses of health center physicians and nurses. The responses to the questions were classified as correct or incorrect according to the information provided on Section 2.7 (Management of adverse reaction to drugs) of the Instruction Material on the DOTS program. Listings of individual responses were done for both physicians and nurses. Knowledge of at least 75% of respondents on a particular adverse reaction was considered adequate. Since this was a purely descriptive study, no statistical test was applied.

RESULTS

Table 1 shows the responses of the 45 physicians and 43 nurses who completed the questionnaires to questions on adverse reactions to isoniazid, rifampicin, pyrazinamide, and streptomycin. However, the percentage of correct response was lower (69%) for pyrazinamide.

Table 2 shows the major and minor adverse effects of each drug mentioned by the physicians and nurses. Physicians were fairly aware of the major hepatotoxic effects of isoniazid and rifampicin. Seizure was a commonly cited adverse reaction of isoniazid, although this was not mentioned in the manual. The symptom is associated with isoniazid overdose but rarely on the usual dose given to Filipinos. Neuritis or peripheral neuropathy was also mentioned by a majority of the doctors. Hepatotoxicity

Table 1. Percentage of physicians and nurses with correct responses to questions on adverse drug effects

Question	Physicians N = 45	Nurses N = 43
	No. (%)	No. (%)
Adverse effects of isoniazid?	38 (84.4)	31 (72.1)
Adverse effects of rifampicin?	42 (93.3)	31 (72.1)
Adverse effects of pyrazinamide?	31 (68.9)	20 (46.5)
Adverse effects of streptomycin?	43 (95.6)	35 (81.4)

Table 2. Adverse effects of isoniazid and rifampicin mentioned by physicians and nurses

Drug	Adverse effect	Physicians N = 45	Nurses N = 43
		No. (%)	No. (%)
Isoniazid	Jaundice/hepatitis/ hepatotoxicity	30 (66.6)	20 (46.5)
	Neuritis/peripheral neuropathy	28 (62.2)	14 (32.6)
	Rash/hypersensitivity	22 (48.9)	14 (32.6)
	CNS effects/seizures/ psychosis	11 (24.4)	15 (34.9)
Rifampicin	Jaundice/hepatitis/ hepatotoxicity	35 (77.7)	28 (65.1)
	Itchiness/rash	20 (44.4)	17 (39.5)
	Thrombocytopenic purpura	14 (31.1)	8 (18.6)
	Vomiting	13 (28.9)	7 (16.3)
	Abdominal pain	10 (22.2)	5 (11.6)
	Flu-like symptoms	10 (22)	6 (14)

as an adverse effect of pyrazinamide was not mentioned in the manual but was cited by 25 of the 45 physicians. Arthralgia or acute gout was correctly cited as minor and major adverse effects of pyrazinamide, respectively. As regards streptomycin, ototoxicity, either to the auditory or vestibular nerve and nephrotoxicity was commonly cited by the physicians. However, the most common adverse reaction, which is pain in the injection site, was mentioned by only one physician.

The pattern of responses was similar among the nurses but the percentage of correct answers was even lower. The question for pyrazinamide's side effects got the least correct answers. Again, an adverse effect of streptomycin, which is expected to be known by the nurses because they are the ones giving the intramuscular injection (local pain), was only mentioned by a few.

A common occurrence, although not really a side effect, is the discoloration of the urine associated with rifampicin. Only one physician and six nurses gave this answer.

DISCUSSION

Knowledge of the possible adverse effects of anti-TB drugs among the health center staff, particularly the physicians and nurses, is important. Patients who are being started on anti-TB treatment, whether daily or intermittent, should be adequately advised on the possible adverse reactions of these drugs. Adverse reactions are some of the reasons cited by noncompliers for noncompletion of the treatment. Some patients stop medications completely, and worse, never consult a physician when they develop bothersome side effects and only do so when the disease has become advanced. Adequately informing patients of the possible adverse effects provide reassurance when these do occur and make the patient more likely to consult their physician to obtain a remedy. In a local study by Simbulan on factors influencing noncompliance to antituberculosis treatment, occurrence of side effects were cited by patients and health providers as causing premature termination of treatment. Pyrazinamide was reported as the drug commonly associated with adverse reactions.[7]

The result of the survey shows that the level of knowledge of physicians and nurses assigned to local health centers in Quezon City on adverse drug reactions to antituberculosis drugs is somewhat inadequate.

Although the physicians fared better than the nurses in the number of correct responses, nearly one in three was unable to give all of the expected adverse effects for each drug. This could indicate that some emphasis should be given on the subject whenever there is a training of physicians in health centers. Some physicians may be deficient in this area because the number of adverse drug reactions is not among the data being collected for report to the DOH.

Further training for a better ADR monitoring system is also required for the nurses who deal with patients more than the doctors. Since nurses are often tapped to provide patient education to TB patients, they should have the proper knowledge of these adverse effects, which is a part of the standard instructions given to patients whenever commencing treatment.

It should be ideal that ADR monitoring be part of the regular activities of health centers treating patients with TB. Having physicians and nurses with the proper knowledge of ADR is a good first step.

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Smoking and Postoperative Pulmonary Complications in Elective Surgery:

A Meta-analysis

ABSTRACT

Objectives

The study determined the risk of postoperative pulmonary complications in smokers undergoing elective surgery as compared to nonsmokers.

Methodology

Literature review using Medline search and ancestry method was done.

Cohort studies comparing the incidence of any type of postoperative complications among smokers and nonsmokers undergoing predominantly elective surgery were included for analysis.

Using prepared data collection forms, incidence of postoperative complications(POPC) as main outcome in smokers and nonsmokers were obtained. Among smokers, incidence of POPC in current smokers, ex-smokers, light smokers (less than 20 cigarettes/day) and heavy smokers (20 cigarettes/day or more) were also obtained. Data from included studies were combined and analyzed for heterogeneity and statistical significance using Rev Man 4.0.

Results

Although the study involved a heterogenous group, postoperative complications were higher in the smoking group. However, using the random effects model, the difference remained significant. The risk was also greater in patients who were smokers at the time of surgery as against those who smoked in the past but have stopped prior to surgery.

Discussion

The findings indicate that preoperative smoking is associated with a small but significant increased risk of POPC and that current smokers should be encouraged to stop smoking before any elective surgical procedure.

Tobacco use is the leading cause of preventable death from ischemic heart disease, cardiovascular disease, lung cancer, and chronic lung disease and it follows that smoking cessation is the single most important step a smoker can take to avoid these conditions and live a longer and healthier life.[1]

However, the adverse effects of smoking are not limited to the development of cardiovascular and respiratory diseases from long-term exposure. Its effects may be more immediate, such as the increased incidence of acute upper and lower respiratory infections in children and adults. Smoking is generally perceived as a risk factor to perioperative morbidity and mortality. However, despite the numerous studies on this subject, there are still some questions on the magnitude of the risk posed by tobacco exposure before a surgical procedure and how smoking cessation can alter such a risk. Bluman[2] observed that many studies have found that current smokers are two to six times more likely than nonsmokers to develop postoperative pulmonary complications but added that many of these studies may not have been adequately controlled for potential confounding variables such as age, type of surgery, and presence or absence of pre-existing pulmonary disease. In addition, definition of postoperative pulmonary complication vary with each study, so that the incidence of atelectasis may range from 20 to 69%, and for postoperative pneumonia from 9 to 40%.[3]

Smetana[4] concluded that the relative risk of pulmonary complications among smokers as compared to nonsmokers ranges from 1.4 to 4.4. However, his review was not systematic and did not assess studies according to their validity. To date there has been no meta-analysis on the magnitude of the risk for smokers in developing postoperative respiratory morbidity. This study aimed to determine the risk of postoperative pulmonary complications in smokers undergoing elective surgery as compared to nonsmokers.

METHODOLOGY

Electronic search (mainly MEDLINE) of articles dealing with postoperative complications in smokers undergoing surgery was done using the search terms "smokers or smoking," "postoperative complications," "pulmonary or respiratory." Titles and abstract of articles from the initial search were examined to determine whether or not the articles met the eligibility criteria. Articles that did not meet the eligibility criteria based on the available information were excluded outright. Otherwise the complete text was retrieved to determine further if the article would be included. References of the retrieved articles were also examined to determine if abstracts of these additional articles could be evaluated and/or complete text could be retrieved.

An article was included if it was a cohort study, either prospective or retrospective, whose population consisted of patients who underwent predominantly elective surgery and if it compared the incidence of postoperative pulmonary complications among smokers and nonsmokers. Evaluation of articles was done by a single reviewer. The identity of the authors, the institution involved, journal publication, and the results of the study were not concealed during the assessment of the article.

Assessment of Study Quality

The quality of the study was evaluated using the User's Guide to Medical Literature for an article about prognosis.[5] Studies with an acceptable procedure for the recruitment of the inception cohort, some adjustment for factors other than smoking status, a uniform or consistent method of evaluation of the occurrence of postoperative pulmonary complications in smokers and nonsmokers, and dropout rates of less than 20% were included in the analysis. Blinding of the investigator doing the assessment of postoperative complications of the smoking status of the subjects was considered desirable but this was not considered crucial because several risk factors were usually considered and knowledge of the smoking status would not necessarily bias the observation. Validity evaluation was done by two separate reviewers (pulmonologist and anesthesiologist) using a prepared checklist. In the event of disagreement between the two reviewers on the validity assessment, the two reviewers met and tried to reach a consensus.

Data Collection

Data were collected using a prepared Data Collection Form (DCF). The following data were gathered:

1. Study name
2. Study design: Prospective or retrospective
3. Number of patients in the cohort
4. Number of dropouts
5. Inclusion criteria
6. Exclusion criteria
7. Presence of blinding
8. Definition of postoperative pulmonary complications (POPC)

9. Other outcome measures
10. Procedure and frequency of measurement of outcomes
11. Incidence of all POPC in:
    a. all smokers, both current and past history
    b. current smokers only
    c. ex-smokers or quitters only
    d. heavy and light smokers
    e. all lifetime nonsmokers
12. Incidence of certain types of postoperative complications such as pneumonia, atelectasis or respiratory failure

Analysis

Analysis was done by comparing the incidence of all forms of postoperative pulmonary complications among smokers, its subgroups, and nonsmokers. Incidence among smokers and nonsmokers of particular types of pulmonary complications such as pneumonia, atelectasis or respiratory failure were also compared when data were available. Data from included studies were combined and the relative risk for smoking was obtained and analyzed using both fixed effects and random effects models using the Mantel-Haenszel and DerSimonian and Laird tests, respectively. Analysis was done using a statistical package (Rev Man 4.0). A p value of less than 0.10 for tests of heterogeneity and $p<0.05$ for z test were considered significant.

Subgroup analysis was planned a priori to determine the effect of 1) the type of surgery, whether cardiothoracic or noncardiothoracic, and 2) year the study was done, whether before and after the 1990s.

RESULTS

From the initial electronic search and subsequent ancestry method, 100 articles were considered for retrieval and evaluation for eligibility. Of these 100 articles, 69 were actually retrieved, the rest were not available. Of the 69 articles retrieved, 11 were excluded based on the study design (six reviews, three case-control studies, one editorial, and one clinical trial), 32 cohort studies were excluded because smoking was not studied as a factor for POPC, ten were excluded because there were no comparisons between smokers and nonsmokers and one because other outcomes were combined with nonpulmonary postoperative complications. Fifteen articles were considered to meet all eligibility criteria. Table 1 shows the 15 articles and their study characteristics.

Of the 15 eligible articles, only 12 were finally included based on the validity or quality assessment. One[13] was excluded because outcome was only delayed extubation and markedly different from other studies, one[15] was excluded for low completion rate of 30% and another[17] was excluded because no definition of the outcome criteria was given.

Table 2 shows the list of both included and excluded studies. Of these 12 articles, ten were prospective cohort studies and one retrospective cohort. The other study[12] was a cohort analysis of an RCT on anesthetic agents and was included because of the large number of patients and good follow-up. Two studies included patients for cardiac or thoracic surgery, five on abdominal surgery and five on combination of the two. Definition of conditions included as postoperative pulmonary complications for the studies was varied. Pneumonia was considered in 12 studies, atelectasis in nine, respiratory failure in four, pleural diseases in three, and bronchospasm in two studies. In terms of quality assessment, all had formed a suitable cohort at a similar point in time, and follow-up rates were excellent. However, blinding of the investigator determining outcome was only done in three studies, and multivariate analysis as a statistical method of adjustment for other variables was only done in five studies. Thus, overall quality of the studies was only fair.

Considering all types of postoperative pulmonary complications, all smokers had a relative risk (RR) of 1.83 as compared to lifetime nonsmokers ($p<0.00001$). There was considerable heterogeneity in the nine studies included using the fixed effect method ($p<0.10$). However, even with the use of the random effect method, the findings remained the same and at a significant level ($p<0.00001$). Smokers also had a higher risk for postoperative pneumonia (RR=1.42, p=0.02) and postoperative atelectasis (RR=2.23, $p<0.00001$) when compared to nonsmokers.

Because the results may be due to variations in medical care provided to patients through the years, the results from studies done in the 1970s (RR=1.77) and those in the 1980s and 1990s were also compared, (RR=1.96) but again they showed the same increased risk for smokers.

Current smokers had a higher relative risk than nonsmokers (RR=3.14, [95% CI: 1.84, 5.56], p=0.3) and ex-smokers (RR=1.49 [1.06, 2.10], p=0.00002) but the number of cigarettes smoked by patients prior to surgery did not affect the incidence of POPC, with smokers taking more than 20 sticks/day having comparable incidence of any of the complications mentioned (RR=1.86) to

Table 1. Articles meeting the eligibility criteria

Reference	Study design	Patients	Risk factors	Outcomes
Latimer, 1971 (6)	Prospective cohort	46 elective upper abdominal surgery	Pulmonary function, smoking and 3 other factors	Atelectasis, pneumonia
Laszlo,1973 (7)	Prospective cohort	80 elective surgery	Chest physiotherapy, smoking and 3 other factors	Bronchitis, pneumonia, atelectasis
Ti, 1973 (8)	Prospective cohort	663 emergency and elective non-cardiothoracic surgery	Smoking and 6 other factors	tracheobronchitis pneumonia, atelectasis pleurisy
Presley, 1974 (9)	Retrospective Cohort	200 elective surgery for chronic cholecystitis and duodenal ulcer	Smoking and 10 other factors	Postoperative infections
Chalon, 1975 (10)	Prospective cohort	123 elective surgery under GA	Tracheobronchial cytology, smoking, FEV1, PEFR	Pneumonia, atelectasis
Warner, 1989 (11)	Prospective cohort	200 elective coronary artery bypass surgery	Smoking and 24 other factors	Tracheobronchitis pneumonia, atelectasis bronchospasm, effusion, pneumothorax
Forrest, 1990 (12)	Cohort analysis of RCT	17,201 elective surgery requiring GA	100 potential risk factors including smoking	Severe perioperative outcomes including respiratory outcomes
Ingersoll, 1991 (13)	Prospective cohort	47 electric cardiac surgery	Smoking and 16 other factors	Delayed extubation
Hall, 1991 (14)	Prospective cohort	1000 elective abdominal surgery	Current smoking and 12 other factors	Pneumonia, atelectasis
Dales, 1993 (15)	Prospective cohort	117 thoracotomies	Quality of life smoking and 5 other factors	Pneumonia, atelectasis, pleural effusion, Pneumothorax, embolism, MV>72 hrs
Ephgrave, 1993 (16)	Prospective cohort	140 elective surgery	Gastric colonization, smoking and 8 other factors	Postoperative pneumonia
Kearney, 1994 (17)	Prospective cohort	331 pulmonary resections	Predicted postoperative FEV1, current smoking and 8 other factors	Pneumonia, atelectasis, MV>2 days, respiratory failure, cardiac and renal complications
Ziekmann, 1996 (18)	Prospective cohort	10 emergency and 203 elective cardiac surgery	Microbiologic monitoring, smoking and 14 other factors	Postoperative pneumonia
Brooks-Brunn, 1997 (3)	Prospective cohort	400 elective abdominal surgery	Smoking and 22 other factors	Pneumonia, atelectasis
Bluman, 1998 (2)	Prospective cohort	410 noncardiac surgery	Smoking and 9 other factors	Pulmonary infection, atelectasis bronchospasm, respiratory failure

smokers taking less than 20 cigarettes/day (RR=1.70) when compared to nonsmokers.

DISCUSSION

The studies included were considerably heterogeneous. The heterogeneity most probably arises from varying patient populations and characteristics, varying surgical procedures, variable criteria for defining postoperative complications, and even varying periods of follow-up. But despite these differences, the present analysis was able to confirm the general belief that smoking is associated with an increased risk of developing postoperative complications, particularly postoperative pneumonia and atelectasis. However, the actual risk, which is less than two-fold, did not manifest in the lower end of values cited by a previous review.[4]

Other findings tend to support the small but significant role of smoking on perioperative respiratory morbidity. There seems to be a decrease in the magnitude of the risk when smoking is stopped prior to surgery. The present study showed that the risk of ex-smokers was significantly lower than that of smokers who continued to smoke before surgery, but still higher than lifetime nonsmokers. The relative risk for POPC in current smokers was 1.49 [95% CI:1.06,2.10] when compared to past smokers (p=0.0002) and 3.14 [95% CI: 1.84, 5.56] when compared to lifetime nonsmokers (p=0.3).

An interesting finding is the absence of a difference in the incidence of POPC among heavy smokers, or smokers taking more than one pack/day and light smokers, or

Table 2. Quality assessment of included and excluded articles

Reference	Inception cohort formed?	Follow-up period	Follow-up rate	Outcome criteria definition	Blinding?	Multivariate analysis of factors
INCLUDED STUDIES						
Latimer,1971	Yes	3 days	100%	CXR + PE	No	No
Laszlo,1973	Yes	2 days	100%	CXR + sputum	Yes	No
Ti,1974	Yes	to discharge	80%	CXR+Cough+fever	No	No
Presley,1974	Yes	3 days	97%	Cough + Temp >38°C + PE	No	No
Chalon,1975	Yes	3 days	90%	Cough + fever + PE	No	No
Warner,1989	Yes	7 days	100%	Requiring added care	Yes	Yes
Forrest,1990	Yes	7 days	100%	Severe respiratory outcomes	No	Yes
Hall,1991	Yes	to discharge	100%	Positive sputum or Temp >38°C or CXR	No	Yes
Ephgrave,1993	Yes	to discharge	100%	CXR +3/4 criteria for pneumonia	Yes	No
Zickmann,1996	Yes	5 days	100%	3/5 criteria for pneumonia	No	No
Brooks-Brunn,1997	Yes	6 days	100%	2 criteria present for two days	No	Yes
Bluman,1998	Yes	to discharge	100%	Major and minor	No	Yes
EXCLUDED ARTICLES						
Ingersoll,1991	Yes	48 hrs after extubation	100%	Extubation not per protocol	No	No
Dales,1993	Yes	to discharge	30%	Fever + leucocytosis + hypoxemia	No	No
Kearney,1994	Yes	to discharge	100%	Criteria not defined, and included non-respiratory complications	No	Yes

those taking less than one pack/day. This may be due to the small number of studies and patients included. On the other hand, it may indicate that POPC may be related to the date of the last cigarette taken before surgery rather than the amount of tobacco being consumed when regularly smoking. This could indicate that regardless of the number of cigarettes smoked prior to surgery, a period of smoking cessation will have the same effect for every smoker. This should encourage smokers to stop smoking before undergoing surgery.

Findings were the same when considering the differences in the year of the studies included, whether done in the 1970s or after. This took into account the role of improvement over the years, in surgical and anesthetic techniques, and postoperative care, which might alter the incidence of postoperative morbidity. But regardless of the level of surgical or anesthetic expertise available, the results indicate that smoking still poses a considerable risk for patients undergoing elective surgery.

Smoking is associated with a small but significant risk of developing postoperative pulmonary complications in elective surgery. The risk is higher for current smokers than ex-smokers so that all smokers, regardless of the number of cigarettes smoked per day, should be encouraged to stop smoking prior to any elective surgical procedure.

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The Effects of the Philippine Clinical Practice Guidelines on Clinical Outcome in the Treatment of Moderate-Risk Community-Acquired Pneumonia (CAP)

ABSTRACT

Objective

This study assessed the utilization of the "Philippine Clinical Practice Guidelines" among practicing pulmonologists at the Lung Center of the Philippines in the treatment of moderate-risk community-acquired pneumonia and its effects on clinical outcomes.

Methodology

A retrospective cohort study was conducted involving all patients admitted at the Pay Ward of the Lung Center of the Philippines from July 1999 to June 2001 with a discharge diagnosis of community-acquired pneumonia.

The following data were collected: demographic characteristics, coexisting illnesses, laboratory, radiographic findings and physical examination, and a regimen of antibiotics given as an initial empiric treatment. Outcomes including resulting morbidity, development of respiratory failure, revision of antibiotics, and length of hospital stay were investigated.

Independent variables such as compliance to the guidelines, macrolide use, age, sex, comorbidities, and temperature were analyzed to determine factors related to outcome.

Results

One hundred six charts were reviewed and of these, data of 75 patients were available for analysis. Sixty-one percent of the subjects were male and 39% were female with chronic obstructive pulmonary disease as the most common comorbidity.

Fifty-seven of 75 subjects (76%) were treated with a regimen consistent with the guidelines. From the 57 patients who were treated according to the guidelines, 72% (41) were given an additional macrolide. Adherence to guidelines and use of macrolides shortened the duration of fever with a p value of 0.025 and 0.035, respectively. Any revision of initial empiric antibiotic was associated with increased length of stay at p value of 0.0103.

Conclusion

Compliance to the guidelines, particularly on the use of macrolides is associated with earlier lysis of fever and may decrease the length of hospital stay.

Community-acquired pneumonia remains a disease with important diagnostic and therapeutic implications because it is common and potentially fatal. Incidence rates reported in studies from the United States and Finland are between 10 and 14 per 1000 persons per year. Attack rates are highest at the extremes of age, with >30 per 1000 of those aged 75 years and above being affected yearly. Mortality rates in foreign literatures vary between 8-16 % depending on the study population. In the Philippines, pneumonia is the fourth leading cause of morbidity and the third leading cause of mortality based on the 1994 Philippine Health Statistics.

Patients, regardless of age, with any of the following physical findings: respiratory rate > 30 breath/min., pulse rate > 125 beats/min. with or without comorbidities; those with radiographic findings of bilateral or multilobar involvement, progression of lesion to 50% of initial finding within 24 hours, pleural effusion, abscess; those with suspected aspiration; and those with extrapulmonary evidence of sepsis, are associated with a complicated outcome and higher mortality rate of 21% and are thus categorized as Moderate-Risk CAP (III).

Clinical and radiographic features are not consistently reliable in the identification of a specific microorganism and despite extensive investigation, the etiologic agent remains unidentified in up to 50% of cases. To assist in narrowing down the spectrum of the empiric antibiotic therapy, guidelines for the initial antimicrobial therapy in CAP have been proposed by several groups.

The "Philippine Clinical Practice Guidelines" on community-acquired pneumonia has been based on evidence derived from a critical review of the literature. This has been drafted to provide the clinician with practical approaches in the resolution of important issues on the diagnosis, management, and prevention of CAP in adult patients. This guideline is specific only for the empiric therapy of immunocompetent adults based on the likely etiology of the pneumonia. In moderate-risk CAP, initial empiric treatment is intravenous (IV) beta-lactams with or without anaerobic coverage or a second-generation cephalosporin plus or minus a macrolide or Levofloxacin alone.

This study set out to assess the utilization of these guidelines among practicing pulmonologists at the Lung Center of the Philippines in the treatment of moderate-risk community-acquired pneumonia and its effects on clinical outcomes.

METHODOLOGY

This is a retrospective cohort study. All patients admitted at the Pay Ward of the Lung Center of the Philippines from July 1999 to June 2001 with a discharge diagnosis of community-acquired pneumonia were included in the study. Each patient's medical chart was then reviewed and incomplete charts were excluded from the study.

The following data were collected for each patient using a standard form: demographic characteristics including age and sex; coexisting illnesses including chronic obstructive lung disease, diabetes mellitus, congestive heart failure, renal failure, chronic liver disease, and neurologic disorders; length of hospital stay; a regimen of antibiotics given as an initial empiric treatment; laboratory and radiographic findings and physical examination; resulting morbidity including the development of respiratory failure and revision of antibiotics were analyzed. All data were entered into a computerized data editor.

Ordinal logistic regression analysis was used to analyze important factors affecting lysis of fever. Nominal logistic regression was used to analyze factors affecting any revision of antibiotics. Independent variables such as compliance, macrolide use, age, sex, comorbidities, and temperature were initially analyzed using multiple logistic regression analysis to determine factors related to outcome. Three-stage least square regression equation was used to analyze factors affecting hospital stay.

RESULTS

One hundred six charts were reviewed. Thirty-one patients were excluded from the study because they did not meet the classification criteria for moderate-risk community-acquired pneumonia upon admission, and some patients had incomplete charts. Data of 75 patients were therefore considered for analysis. Demographic data and comorbidities are summarized in Tables 1 to 3.

Of the 75 patients included in the analysis, 61% were male and 39% were female. Majority of the subjects were more than 60 years old and the most common comorbidity was chronic obstructive pulmonary disease.

Majority of patients came in with normal blood pressure and cardiac rate, 63% had respiratory rate of more than 22 breaths/min., and 43% had baseline temperature of more than 38°C. Length of hospital stay ranged from 3-22 days with a mean duration of 6.5 days

Table 1. Sex distribution of CAP III patients

Sex	N	%
Male	46	61
Female	29	39
Total	75	100

Table 2. Age distribution of CAP III subjects, LCP, 1999-2001

Age group (years)	N	%
Less than 20	1	1.33
20-30	3	4.00
30-40	3	4.00
40-50	3	4.00
50-60	7	9.33
60-70	27	36.00
Over 70	31	41.33
Total	75	100

Table 3. Comorbidities of CAP III patients

Comorbidities	N	%
COPD	32	42.67
CHF	2	2.67
DM	12	16.00
Renal Failure	1	1.33

(SD 3.5 days). There were no mortalities recorded but 4 patients developed hypoxemic respiratory failure during the course of hospital stay.

With respect to guidelines' adherence, 57 of 75 subjects (76%) were treated with a regimen consistent with the guidelines. Eight patients were treated with a second-generation cephalosporin alone and 29 had a macrolide added to this. Three were treated with Co-Amoxiclav alone and 6 had macrolide added to the regimen, 3 were with Sulbactam-Ampicillin and 8 were treated with Levofloxacin alone (Table 4).

Of the 18 cases of deviations from guidelines, 9 were treated with third-generation cephalosporin alone, four were given Ciprofloxacin alone, 4 with Tazobactam and aminoglycosides and one with macrolide monotherapy (Table 4).

From the 57 patients who were treated according to guidelines, 72% (41) were given a combination of macrolide and cephalosporin or β-lactam. Through chart review, an outcome assessment according to guideline

Table 4. Empiric antibiotic given to 75 CAP III patients upon admission

Antibiotic used	N	%
Empiric antibiotic per guideline	**57**	**76%**
2nd generation cephalosporin	8	
2nd generation cephalosporin + macrolide	29	
β-lactam	6	
β-lactam + macrolide	6	
Levofloxacin	8	
Empiric antibiotic not consistent with guideline	**18**	**24%**
3rd generation cephalosporin	9	
Ciprofloxacin	4	
Tazobactam + aminoglycoside	4	
Macrolide	1	

adherence, with or without macrolide, lysis of fever, and length of hospital stay was performed.

With ordinal logistic regression analysis of fever lysis at 10% level of significance, age and comorbid condition did not affect the onset of lysis. Male subjects had a longer time to fever lysis, and the higher the temperature the longer the fever duration (Table 5). Adherence to guidelines and giving of additional macrolides shortened the duration of fever with a p value of 0.025 and 0.035, respectively.

Table 5. Lysis of fever (Ordinal logistic regression)

Lysis	Regr. Coeff.	Std. Error	95% Conf. Interval	p value	Remarks
Compliance	–1.428	0.639	–2.680/–0.176	0.025	S
Macrolide	–1.374	0.651	–2.649/–0.098	0.035	S
Age	0.001	0.019	–0.035/0.0384	0.939	NS
Sex	1.368	0.610	0.172/2.563	0.025	S
Comorbid	0.020	0.676	–0.080/1.530	0.976	NS
Temp	0.725	0.411	–0.080/1.531	0.078	S

Multiple regression analysis showed that guideline compliance and use of macrolide had no effect on the length of hospital stay. The most important factor that increased length of hospital stay in this study was any revision in initial empiric antibiotic (see Table 6) and this can be affected by compliance and the use of macrolide. Therefore compliance and macrolide use may have a significant effect on the length of hospital stay.

Table 6. Factors affecting length of hospital stay analyzed by multiple regression

LOS	Regr. doeff	Std. error	95% Conf. interval	p value	Remarks
Any revision	3.625	2.224	-0.734/7.984	0.0103	S
Hypoxemia respiratory failure	7.680	7.482	-6.983	0.305	NS
Age	0.033	0.022	-0.010/0.0758	0.139	NS
Sex	0.847	0.710	-0.546/2.240	0.233	NS
Temp	0.474	13.626	-0.204/1.153	0.171	NS

DISCUSSION

Community-acquired pneumonia is one of the most common infectious diseases encountered by physicians. Mild or walking pneumonia is treated in the ambulatory setting, whereas sicker patients with CAP usually require hospitalization. Optimal antimicrobial therapy of CAP depends on an accurate assessment of the presumed or known pathogens and detailed knowledge of the spectrum, pharmacokinetics, resistance potential, safety profile, and cost of the antimicrobial agent selected to treat CAP. Optimal selection is based on a combination of these factors and for this reason it is better to refer to an antimicrobial agent as the preferred antimicrobial agent rather than the drug of choice.

The recommended empiric initial antibiotic therapy should subsequently be modified based on the isolated pathogen. If microbiologic data is available, the revised treatment should be pathogen-directed based on antimicrobial susceptibility test.

In moderate-risk CAP, potential pathogens are *S. Pneumonia, H. influenza*, *Legionella*, *C. pneumonia*, *M. pneumoniae*, gram-negative bacilli, and anaerobes. Empiric therapy based on guidelines is IV β-lactams, with or without anaerobic coverage, with or without macrolide or a second-generation cephalosporin or Levofloxacin.

This study, which assessed the utilization of the "Philippine Clinical Practice Guidelines" for empiric treatment of moderate-risk CAP at a tertiary-care center, provided some insight into how guidelines might be usefully modified. Likewise, it attempted to address the effects of using the guidelines on clinical outcomes and patient care.

The guidelines were widely used in our institution with an adherence rate of 76%. Despite limited dissemination of these guidelines, the compliance rate at the Lung Center of the Philippines was quite high, similar to the compliance rate at another institution, which was 78%, according to their descriptive retrospective study in 1998. It is interesting to note that the addition of a macrolide in this study conferred benefit to hospitalized patients. This fits very well with recent studies suggesting that atypical pathogens are common in patients with community-acquired pneumonia and that serologic evidence for atypical pathogen infection can be found in up to half of all outpatients and inpatients with community-acquired pneumonia. The recently published American Thoracic Society guidelines for the management of adults with community-acquired pneumonia stated that all populations with CAP should be treated for the possibility of atypical pathogen, and this should be with a macrolide.

This is the first study to validate the Philippine guidelines on moderate-risk CAP with or without the use of macrolide. Adherence to guidelines and the use of macrolides decreased the need for revising and shifting to another regimen. Compliance with CPG's empiric antibiotic means a shorter hospital stay. Indeed, adherence to guidelines improves the consistency of care, so that patients with similar conditions are treated according to a protocol regardless of where, or from whom they receive care.

Being a retrospective investigation, the conclusions of this study may be further validated by conducting a prospective randomized multicenter trial involving all categories of community-acquired pneumonia.

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Testing Susceptibility of Mycobacterium tuberculosis to Pyrazinamide:

Comparison of BACTEC to the Conventional Method

ABSTRACT

Objective

The objective of this study was to determine the agreement between BACTEC and the conventional methods in testing the susceptibility of *Mycobacterium tuberculosis* to pyrazinamide.

Methodology

A total of 59 isolates of *Mycobacterium tuberculosis* were analyzed by the two methods.

Results

Results obtained by these 2 methods were compared for agreement with regard to the susceptibility patterns of the isolates. There was 75% observed overall agreement between the results obtained by the two methods and the agreement of 20(34%) and 24(41%) for susceptible and resistant isolates, respectively. The kappa is 0.496301, which reveals a fair agreement beyond clearance. The observed disagreement between the result obtained through the two methods, in which 11 reported resistance and 4 reported sensitivity or vice versa, was twenty-five percent. The mean time for reportable results by the conventional method was 16.2 days compared to BACTEC, which was 7.7 days (p=<0.001).

Conclusions

This study reveals a fair agreement between both methods. BACTEC method is preferred over the conventional method because the former yields faster results and detects more susceptible than resistant isolates. This study requires further investigation to validate this result in a larger number of specimens.

Tuberculosis is one of the most common infectious diseases known to man and remains a great problem in most low-income countries. It kills more people than any other single infectious agent[1] and is the most frequent cause of death in individuals aged fifteen to forty-nine years.[2] It is estimated that by the year 2000, there will be 10 million new cases annually, and 12 million by the year 2005.[3] In the Philippines, tuberculosis remains as the fifth leading cause of mortality and the fifth leading cause of morbidity.[4]

Three periods in the history of the use of pyrazinamide (PZA) have been distinguished: 1) the initial studies (1952-1959) colored with reservation about its use because of the rapid emergence of drug resistance and the drug's potential for hepatotoxicity; 2) the use of second-line drug (1958-1970) in the treatment of chronic cases resistant to isoniazid and streptomycin; 3) the employment of clinical trials of short-course treatment for new cases (1971-1980).[5]

PZA is an effective antituberculosis drug when used in combination with isoniazid and rifampin, and the duration of treatment could be shortened to 6 months.[5,6,7,8] Depending on the assay system and conditions applied, minimum inhibitory concentrations (MICs) of PZA vary from 8 µg/ml to 60 µg/ml. However, even at very high MICs, PZA has no significant bactericidal effect and is primarily considered a "sterilizing drug."[9] One of the complicated issues surrounding the enigma of PZA is the so-called sterilizing activity in vivo, often interpreted as its bactericidal activity. Activity of PZA is highly specific for *Mycobacterium tuberculosis* (*M. tb*); PZA has scant or no effect on other mycobacteria, including *Mycobacterium bovis*, which demonstrate high-level intrinsic resistance to PZA. Naturally resistant strains of *M. bovis* lack the enzyme pyrazinamidase (Pzase), which hydrolyzes PZA to pyrizinoic acid, the presumed active form of PZA.[9,10,11,12] PZA in this context is similar to INH; it is transported as a neutral species into the cell, where it is converted into its active form. *M. tb* has both pyrazinamidase and nicotinamidase activities. The cellular targets for PZA, however, has not been identified, although the apparent similarity of PZA to nicotinamide suggests that enzymes involved in pyridine nucleotide biosynthesis are probable targets.[9]

Pyrazinamide is one of the first-line drugs in the standard treatment regimen[13] and now considered the third most important drug in the modern chemotherapy of tuberculosis.[5,8,14] It is expected that, as with other antimycobacterial drugs, the increasing use of PZA will lead to the emergence of drug-resistant strains. In order to detect such resistance, in vitro testing of the susceptibility of *M. tb* to PZA is widely advocated.[15] In this study we used two methods in testing for the susceptibility of *M. tb* to PZA. These are conventional proportion agar-based methods and BACTEC.

Conventional agar-based testing for PZA susceptibility often leads to uninterpretable results because of insufficient growth in acidified medium. However, the addition of an albumin-dextrose-catalase (ADC) supplement to the medium has been shown to decrease the number of such uninterpretable results.[15] The incorporation of an enrichment mixture, usually oleic acid-albumin-dextrose-catalase (OADC), into 7H10 agar is necessary for optimal growth of *M. tb* at acid pH.[1]

The BACTEC method for mycobacterial culture, identification, and susceptibility testing includes a radiometric test to assay for PZA susceptibility. It measures the $^{14}CO_2$ produced by metabolic breakdown of (1-^{14}C) palmitic acid.[16] Satisfactory interpretation depends on adequate growth in the acidified Middlebrook 7H12 (BACTEC 12B) medium at the time when a growth index (GI) of at least 200 is reached in the control vial within 4 to 20 days.[15,17]

The increasing prevalence of tuberculosis in the Philippines prompted the study on the use of PZA as part of the therapeutic regimen. This study proposed to evaluate two methods in susceptibility testing of *M. tb* isolates to Pyrazinamide. The study also wanted to determine the agreement between BACTEC and the conventional methods in testing the susceptibility of *Mycobacterium tuberculosis* to pyrazinamide and identify which of the two methods could yield a faster result.

METHODOLOGY

A total of 3,180 specimens were submitted for mycobacterial culture to the LCP Laboratory from March 1999 to August 2001. Of these, 819 grew *M. tuberculosis*. A set of 90 *M. tuberculosis* isolates finally comprised the study sample. The rest of the isolates were either contaminated or likely to grow contaminants on future processing. All 90 isolates were initially grown on BACTEC media and then subcultured to Lowenstein Jensen (for PZA conventional method) and to 12B (for PZA-BACTEC). Subculture was done in LJ media with a waiting period of at least 3-4 weeks to ascertain good growth. For the 12B media, daily reading was done until the growth index (GI) was

greater than 300. Readings with a growth index greater than 499 was diluted further with 12B media.

Procedure:

For the conventional method, culture media was prepared using 7.2g Middlebrook 7H10 agar base (BBL-Becton Dickinson) dissolved in 360 ml distilled water to which was added 2 ml of glycerol. The mixture was autoclaved for 15 minutes at 121°C. The media was split into two sterile flasks, 180 ml each. The flask was allowed to cool down at 54°C. After that, 20 ml oleic acid-albumin-dextrose-catalase (OADC) was added to both flasks. The pH of the resulting mixture was checked prior to the addition of 4 ml PZA solution in one flask. The other flask served as control. The media was poured into the 100 × 15 mm four quadrant disposable plastic dishes, one quadrant for drug-free (control) media and one for agar test PZA concentration. After quality control for sterility and ability to support growth, the plates were stored in a refrigerator for a period not longer than 4 weeks.

For drug-susceptibility test, several single colonies of *Mycobacterium tuberculosis* were scraped from Lowenstein-Jensen slant and placed into a sterile screw-capped tube with plastic beads containing three (3) ml. of Middlebrook 7H9 broth with albumin-dextrose-catalase (ADC). The turbidity of the isolate was adjusted using the optical density of Mc Farland standard no. 1. Two dilutions of this suspension, 10^{-2} and 10^{-4}, were used as an inoculum, 0.1 ml. per segment, to inoculate two plates. The plates were sealed in individual polyethylene $C0_2$ – permeable bags and incubated right side up (agar down) at 37°C in the presence of 5-7% CO_2 for a period of 21 days. Afterwards the plates were removed from the incubator and placed on the bench upside down (agar up) at room temperature for at least 4 hours (or overnight) to eliminate condensate. The plates were examined after a week then every 3 days until a period of 21 days to observe for growth. The colonies on each segment were counted and the number of colonies on drug-containing segments were compared with that on the drug-free control. For a test to be valid, the control should show good bacterial growth (at least 50-100 colonies).

Percentage of resistant organisms was calculated as the number of colonies on the drug over the number of colonies on the control multiplied by 100. If there was more than 1% growth in the presence of the drug in comparison with the control medium without the drug, the isolate was considered resistant.[12,18] On the basis of clinical and bacteriologic studies, the significant proportions of organisms resistant to an antituberculosis drug above which a clinical response is unlikely has been set at 1%.[19,20]

The BACTEC preparation used a mixed test culture in 12B medium where 0.1 ml of isolate and 0.1 ml of reconstituting fluid were added to the control vial while 0.1 ml of isolate and 0.1 ml of PZA solution to the test vial. Both were incubated at 37°C. Daily readings of the growth index (GI) in both bottles were done until the day of interpretation when the GI of the control vial reached a growth of at least 200. The percentage of resistant organisms was calculated as the number of growth index of the test drug over the number of GI of the control multiplied by 100. The recommended interpretive criteria for the ratio of the GI of the drug-containing vial to the GI of the control vial were followed, and the interpretations were as follows: less than 9%, susceptible; 9 to 11%, borderline; and greater than 11%, resistant. If a GI of 200 was not obtained within 20 days in the control vial, the result was considered uninterpretable.[21]

All isolates with discrepant or uninterpretable susceptibility results had a repeat BACTEC and conventional test. Both methods used PZA drug concentration of 100 µg/ml. Quality control strain used was MTB H_{37}Rv that is susceptible to all antituberculosis drugs.

Statistical Analysis:

In this study kappa was used to quantify the actual level of agreement between the two methods and paired t-test to compare the number of days in which reportable results were available with a p value of <0.05 to be considered significant. According to Byrt, the kappa may be interpreted as:

0.93 – 1.0 = Excellent agreement
0.81 – 0.92 = Very good agreement
0.61 – 0.80 = Good agreement
0.41 – 0.60 = Fair agreement
0.21 – 0.40 = Slight agreement
0.01 – 0.20 = Poor agreement
< 0.00 = No agreement

RESULTS

A total of 90 cultures were processed. Of these, 12 grew only a few colonies on LJ medium after 2 months of incubation, 6 were contaminated or non-viable and 13 were analyzed but not included because the usual subculture procedure was not followed. Thus 59 cultures of *M. tb* were analyzed in this study.

Drug susceptibility results obtained by the two methods show 24 (41%) cultures were susceptible and 35 (59%) were resistant by the conventional method and 31 (53%) susceptible and 28 (47%) resistant by the BACTEC method. Overall there was 75% observed agreement between the two methods with 24 cultures resistant and 20 susceptible in both. The kappa is 0.496301, which reveals a fair agreement. This is based on typical cut off defining agreement on kappa value reference. There was 25% observed disagreement between the two methods. Of the 15 cultures for which disagreements were noted, 11 were observed to be resistant by the conventional method and susceptible by the BACTEC method. Only 4 isolates were found to be resistant by the BACTEC method whereas the conventional method indicated them to be susceptible (see Table 1).

The mean time to achieve reportable results by the BACTEC method for the 59 isolates was 7.7 days with a 95% confidence interval range of 6.8 to 8.5 days. Seventy-six percent (76%) of the cultures were reportable within 9 days and 97% within 14 days. The mean time for reportable results by the conventional method for the 59 isolates was 16.22 days, with a 95% confidence interval of 15.5 to 16.9 days. Seventy-three percent (73%) of the culture specimens were reportable within 16 days and 86% within 19 days. The p value between these two methods is <0.001 (Table 2).

The number of cultures reportable by the BACTEC method with 0 ≤ 9 percent resistance was 31(53%) and the remaining 28(47%) of the cultures were reportable with >11-100 percent resistance and 9 cultures which were evaluated showed 81-100 percent resistance. Twenty-four (41%) of the cultures were reportable by the conventional method with 0 ≤ l percent resistance and the remaining 35 (59%) of the cultures were reportable with 1-100 percent resistance and 14 cultures which were evaluated showed 81-100% resistance (Table 3.).

Table 1. Analysis of susceptible (S) and resistant (R) cultures encountered by the two methods

Result of BACTEC method	Result of conventional method		Total
	R	S	
R	24	4	28
S	11	20	31
Total	35	24	59

DISCUSSION

Conventional methods for PZA drug susceptibility testing of mycobacteria are not well standardized compared with other primary drugs, but the main disadvantage of this method is the long waiting period before results can be obtained. In this study, the incubation period is almost the same for both methods, the PZA conventional is about 2-3 weeks and PZA BACTEC is about 1-3 weeks, which depends upon the result of the control. One important advantage of the agar proportion test with PZA is that it has a potential of being used not only as an indirect test with previously isolated cultures but also as a direct test with raw specimens.[13] In addition, the PZA conventional method is much cheaper compared to the PZA BACTEC.

The BACTEC method yields faster result than the conventional method and many investigators consider the BACTEC method as the only reliable technique for a test with PZA.[18,22,23] The total turn around time of this method is about 3-4 weeks.[24] The BACTEC method though reliable, has certain disadvantages: a) it can be used only as an indirect method, which requires initial isolation of a pure culture; and it cannot be used as a direct test with acid-fast bacillus-positive specimens; b) it is costly; c) there is a need for disposal of a substantial volume of ^{14}C-radiolabeled culture vials (which is not permitted in many countries); d) most of the tuberculosis laboratories in the world do not use, and cannot afford to use, the BACTEC system; and e) does not provide information on the actual proportion of the PZA-resistant bacteria in the patient's isolate.[13]

In this study the average time required by the BACTEC method for indirect drug susceptibility was 6 to 9 days and 76% of the results were reportable in 9 days compared to PZA conventional, which was 15 to 17 days and 73% of the results were reportable in 16 days. However, the time required by this depended upon the nature of the inoculum and its standardization. It took more than 4 days to obtain reportable results, if the inoculum was too light, or of low viability.[22] On the other hand, if the inoculum was too heavy the GI of the control was more than 30 within two to three days, but the results could not be interpreted clearly unless the bottles were further incubated to observe an actual decline of the GI in the drug-containing bottles. The indication of the inoculum's resistance to a drug could be observed much earlier than its susceptibility; since the inoculum in the drug bottle was heavy (100 times that of the control), the release of labeled CO_2 occurred more rapidly if there was no inhibition by the drug.[22] In the PZA conventional

Table 2. Number of days for reportable results by BACTEC and conventional method

BACTEC			Conventional		
Number of days	No. of cultures evaluated	Percent cumulative	Number of days	No. of cultures evaluated	Percent cumulative
1	1	1.69	13	17	28.81
2	5	10.17	16	26	72.88
3	2	13.56	19	8	86.44
4	2	16.95	21	8	100
5	2	20.34			
6	10	37.29			
7	5	45.76			
8	9	61.02			
9	9	76.27			
10	3	81.36			
11	3	86.44			
12	3	91.53			
14	3	96.61			
15	2	100.00			

Table 3. Percentage distribution of resistance reportable by BACTEC and conventional method

BACTEC			Conventional		
Percent resistance	No. of culture evaluated	Percent cumulative	Percent resistance	No. of culture evaluated	Percent cumulative
0 ≤ 9	31	52.54	0 ≤ 1	24	40.68
9-11	0	0	1-20	7	52.54
>11-20	7	64.41	21-40	4	59.32
21-40	3	69.49	41-60	3	64.41
41-60	5	77.97	61-80	7	76.27
61-80	4	84.75	81-100	14	100
81-100	9	100.00			

method, the inhibitory effects of the drug were masked after 3 weeks incubation in a CO_2 concentration of 7% in air. Presumably, the effect was related to the growth-enhancing effects of carbon dioxide (CO_2). The degree of the effect was influenced by the size of the inoculum, which had been reported to cause local neutralization of pH, resulting in the ineffectiveness of PZA.[6]

The observed disagreement in the result of the two methods was found to be 25%. It is important to emphasize that in instances of disagreement the conventional method reported 11 (18%) resistance and 4 (7%) susceptible isolates while the radiometric method reported the opposite. Disagreement of this type is often attributed to imperfect dispersion of the bacteria in the inoculum, which is critical for plate-counting methods but not for metabolic methods. One reason also for disagreement between the two methods is that conventional PZA is greatly affected by the sterility of surroundings during incubation period since it is an open system. Ubiquitous fungi and bacteria may be isolated after 2-3 weeks incubation in not so sterile areas that yield to erroneous results. PZA conventional and BACTEC are also affected by technical processes from preparation of reagent to the digestion and decontamination of specimen for culture. Lowenstein-Jensen agar should have a 100% pure *M. tb* isolate to yield a more accurate result but the presence of bacteria and fungi may mask the growth of *M. tb*, leading to false results. However, in BACTEC PZA, since it is a closed system, environment is not a main factor for contamination. Moreover, it is possible that the radiometric method is more sensitive because in a liquid medium there is more cell-to-drug contact, and shorter incubation time.

Testing the susceptibility of mycobacterium to PZA using BACTEC and comparing it to the conventional method yields fair agreement. The mean time to achieve reportable results by the BACTEC method was 7.7 days, which is much faster than the conventional method (16.22 days). The BACTEC method detects slightly more susceptible isolates than the conventional method.

The BACTEC method is preferred since its result is comparable with the conventional method and the former yields a faster result and detects more susceptible than resistant isolates. This study, however, requires further investigation to validate these results on a greater number of specimens. For future studies, we would like to recommend susceptibility testing of *M. tb* to PZA by these two methods in multiple-drug-resistant tuberculosis cases and in new cases of tuberculosis to compare which one is more practical to use, since the conventional method is cheaper than BACTEC.

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Protocol-Directed Weaning versus Physician-Directed Weaning

ABSTRACT

Objective

The study assessed the efficacy of using a protocol to wean the patient from mechanical ventilation compared to the traditional practice of physician-directed weaning. The two types of weaning were then compared in terms of length of hospital stay of the patient, and the duration and success of weaning.

Methodology

A prospective randomized study using a protocol in weaning patients from ventilatory support was conducted at the Lung Center of the Philippines Medical Intensive Care Unit from year 2000 to 2001. Patients 18 years old and above who were mechanically ventilated were included in the study. Trauma patients, transferred patients from other hospitals with prior mechanical ventilation, and those who were mechanically ventilated due to brain death to allow organ retrieval were excluded in the study. The APACHE scores, indications for medical ventilation, comorbid conditions, length of hospital stay, applied weaning strategy, and duration of weaning were determined. Patients were randomly assigned at the time of ICU admission to receive protocol-directed weaning or physician-directed weaning. The primary data analysis was an intention-to-treat analysis, comparing the duration and success of weaning between patients randomized to receive protocol-directed and physician-directed weaning.

Results

A total of 26 patients were randomly selected, 13 patients in the protocol-directed and 13 in the physician-directed group. Both groups had comparable demographic characteristics.

There was failure of weaning in six patients under physician-directed weaning and none in the protocol-directed weaning (p=0.014). The length of hospital and ICU stay, the duration of ventilation and weaning were longer in the physician-directed group, but only the duration of weaning was statistically significant (p=0.0004).

Conclusion

Protocol-directed weaning resulted in successful liberation from mechanical ventilation and shorter duration of weaning compared to physician-directed weaning.

Mechanical ventilation is the most common form of treatment given to patients in respiratory failure. Weaning or discontinuation of respiratory support requires identification of patients able to sustain unassisted breathing without clinical or physiologic deterioration. For a physician this remains as a challenge and most often is based on judgement and experience. With the increasing recognition of the risk and economic consequences of prolonged ventilation, identifying strategies that can reduce the duration of mechanical ventilation is a high priority, but no single strategy has been established as the best one. Many measures have been proposed to identify patients who are ready for liberation, ranging from simple measures such as measuring spontaneous breathing parameters to the use of computerized decision support models. Recent studies proposed the use of protocol-directed weaning from mechanical ventilation with the increasing involvement of intensive care unit (ICU) nurses and respiratory therapists.

The purpose of this study was to assess the efficacy of using protocols to wean the patient from mechanical ventilation compared to the traditional practice of physician-directed weaning. A secondary objective was to compare the two types of weaning in terms of length of hospital stay, and the duration and success of weaning.

METHODOLOGY

Patients

The study was conducted at the Lung Center of the Philippines Medical Intensive Care Unit from year 2000 to 2001. Patients 18 years old and above who were mechanically ventilated were included in the study. Trauma patients, transferred patients from other hospitals with prior mechanical ventilation, and those who were mechanically ventilated due to brain death to allow organ retrieval were excluded in the study. The age, sex, acute physiologic and chronic health evaluation (APACHE) scores,[1,2] indications for medical ventilation, comorbid conditions, length of hospital stay, applied weaning strategy, and duration of weaning were determined. An informed consent was obtained from patients or their relatives prior to inclusion in the study.

Study Design

Patients were randomly assigned at the time of ICU admission to receive protocol-directed or physician-directed weaning. The ICU head nurse was in charge of the randomization and the pulmonary fellow in charge was then informed which protocol to implement. The protocol included the guide for assessment of weaning readiness and the weaning process to be used. The ICU pulmonary fellows, respiratory therapists, and ICU nurses were trained in the use of the protocol.

Patients assigned to the protocol-directed group were assessed for weaning readiness and were weaned from mechanical ventilation according to the guidelines of the protocol. Any interventions by the attending physician and ICU fellows that resulted in either hastening or delaying of the weaning and its progression were recorded.

Weaning Protocol

Weaning was started when the indication for mechanical ventilation has resolved or significantly improved based on assessment evaluation forms, which were filled up by the ICU fellows. The assessment checklist (Panel A) included a

Panel A: Assessment Checklist

General assessment	YES	NO
Primary problem corrected Specify:		
Hemodynamic stability BP HR Hct Hgb WBC		
Absence of Vasopressor		
Electrolyte within normal limits Na K Ca Mg PO4		
Appropriate level of anxiety, agitation, and nervousness		
Adequate sleep/rest		
Chest X-ray Stable Improved		
Respiratory assessment	**YES**	**NO**
Eupneic respiratory rate and pattern (RR < 25 w/o dyspnea and absence of accessory muscle use)		
Absence of abdominal distension, ileus		
Absence of neuromuscular blocking agent		
Cough and swallow reflexes adequate		
Ventilation criteria: • $PaCO_2$ (< 50 torr, with normal pH) • Spontaneous tidal volume (STV) > 5 ml/kg • Vital Capacity (VC) > 10 – 15 ml/kg • Spontaneous RR (f) • Minute ventilation		
Oxygenation Criteria: • PaO_2 (> 60 torr) • PEEP < 5 cm H_2O • SaO_2 > 90% • P (A-a)O_2 < 350 mm HG • PaO_2/ FiO_2 > 200 mm Hg		
Pulmonary reserve and strength: • Maximum voluntary ventilation (2x minute ventilation) • Maximum insp. pressure (MIP) ≥ -20 cm H_2O		
Pulmonary measurements: • Static compliance > 30 ml/cm H_2O • RSB < 105 bpm		

Panel B: Protocol-Directed Weaning

1. The physicians' written order identifies the patient as eligible for weaning (Time and date of weaning process is recorded).
2. Timing of weaning is in the morning about 8:00 AM and ends at 8:00 pm.
3. A patient is eligible for weaning once these ABG parameters are achieved:
   - pH ≥ 7.3
   - pCO_2 < 50 torr
   - paO_2 > 60 torr
   - SaO_2 > 90%
   - FiO_2 < 50%
   - PEEP < 5 cmH_2O torr
4. PSV weaning proceeds following the guidelines below:
   - 4.1. Start PSV at a level of 5 – 15 cm H2O (up to 40 cm) and CPAP up to 5 cm to augment spontaneous Vt until a desired (high) Vt of (low) spontaneous RR is obtained.
   - 4.2. PSV is reduced by 2 cm H_2O decrements until it reaches < 7 cm H_2O. ABG is obtained.
   - 4.3. Pace of weaning is determined by the patients' tolerance of the reductions in pressure support ventilation (at least 2×/day, to as fast as every 30 minutes).
   - 4.4. During the course of weaning, patients falling under any of the weaning failure criteria should have his/her pressure support increased by 2 cm H_2O increments until these criteria are no longer present. Inform the attending physician (AP).
   - 4.5. If the weaning process is tolerated, it should be noted on the chart informing the AP of the successful trial.
   - 4.6. AP will decide when to do the extubation.

Panel C: Weaning Failure Criteria

1. PaO_2 < 60 torr
2. $PaCO_2$ > 50 torr (except in chronic cases or if baseline CO_2 is available)
3. SPO_2 or SaO_2 < 90%
4. HR > 20% increase or ≥ 140 bpm
5. BP change ≥ 20%
6. RR > 30 breaths/min
7. Diaphoresis, dyspnea, agitation, and decrease in level of consciousness

general assessment wherein hemodynamic stability, use of vasopressor, electrolytes, level of anxiety, agitation or nervousness, adequateness of sleep/rest, and radiologic findings were evaluated. For respiratory assessment, the respiratory rate and pattern, the presence of abdominal distension/ileus, neuromuscular blocking agent, and cough/swallow reflexes were noted. The spontaneous breathing parameters and arterial blood gases used for measurement of respiratory function were computed and recorded by the respiratory therapists before beginning the weaning process. Patients progressed through the weaning protocols (Panel C) to extubation unless they fell into any of the predetermined weaning failure criteria, in which case, the weaning protocol was interrupted and mechanical ventilation was reinstituted. Patients were considered successfully weaned when they could tolerate pressure support (PS) of < 7 cm H_2O on spontaneous mode for 2 hours. The presence of any of the following was considered signs of poor tolerance: PaO_2 < 60 torr, $PaCO_2$ > 50 torr (except in chronic cases or if baseline CO_2 was available), SpO_2 or SaO_2 < 90%, heart rate > 20% change from baseline or ≥ 140 bpm, blood pressure change ≥ 20% change from baseline, respiratory rate > 30 breaths/min and presence of diaphoresis, dyspnea, or agitation and decrease in level of consciousness.

Measurements

Blood gases were determined by extraction of arterial blood and the use of a blood gas machine (ABL 50). Wright respirometer was used for measuring tidal volume and an aneroid manometer was used for measuring maximum inspiratory pressure (MIP). The MIP was measured three times in succession and the most negative value was selected. The PaO_2/FiO_2 (P/F) ratio, alveolar-arterial oxygen difference [$P(A\text{-}a)O_2$], maximum voluntary ventilation (MVV), static compliance, and rapid shallow breathing index (RSBI) were computed based on available data.

Statistical Analysis

The primary data analysis was an intention-to-treat analysis, comparing the duration and success of weaning between patients randomized to receive protocol-directed and physician-directed weaning. Interim analysis of 10 patients for each group was done for ethical issues. An x- Error of 0.05 was used and Fisher's exact test Mann-Whitney U test for analysis.

RESULTS

A total of 26 patients were randomly selected, 13 patients in protocol-directed and 13 in the physician-directed group. Both groups had comparable demographic characteristics. The mean age for protocol-directed weaning (Pro-DW) was 63 years old and for physician-directed weaning (Phy-DW) was 61 years old. Both had APACHE score of 30 with male to female ratio of 8:5 in the Pro-DW group and 10:3 in the Phy-DW group, with male predominance at 61% and 75%, respectively. Table 1 summarizes the profile of the study population at baseline. In both groups, AECOPD was the most common cause of respiratory failure; CAP IV was also prominent at 38% in the PDW group.

Weaning procedure used under Phy-DW was SIMV/PSV, implemented in 7 patients, T-piece in 4 patients and PSV/CPAP in 1 patient. Arterial blood gases determinations were done prior to weaning process

Table 1. Characteristics of population at baseline according to study group

Characteristics of study population	Protocol (n = 13)		Physician (n = 13)	
Age (mean, SD)	63 (10)		61 (12)	
Sex M/F ratio	8/5		10/3	
APACHE (mean , SD)	30 (4.4)		30 (4.6)	
Cause of respiratory failure	**N**	**%**	**N**	**%**
COPD exacerbation	4	31	5	38
CAP IV	3	23	5	38
Bronchiectasis in infectious exacerbation	2	15	2	15
HAP	2	15	1	7
Bronchial asthma	2	15	0	0
Comorbid condition	**N**	**%**	**N**	**%**
COPD	8	61	9	69
HTN/ CAD	6	46	4	31
Cor pulmonale	3	15	2	15
Bronchiectasis	2	15	3	23
DM	2	15	1	7
BCA	1	7	1	7
Others (BA, Acute renal failure)	1	7	1	7

in both groups. Spontaneous breathing parameters were measured in all patients under Pro-DW and in 3 patients under Phy-DW.

The length of hospital and ICU stay, the duration of ventilation and weaning were longer in Phy-DW, but only the duration of weaning was statistically significant with p value of 0.0004. Weaning failure was higher under Phy-DW (p=0.014). Six patients under Phy-DW failed the weaning process (Table 2). Reasons for termination of the weaning process were dyspnea, desaturation, seizure, and hypokalemia in which case, the patients were reintubated within 24 hours of extubation. Tracheostomy was done in one patient under Phy-DW. He was eventually diagnosed with Stage IV bronchogenic carcinoma with pleural effusion and obstructive pneumonia. He stayed at the ICU for 39 days and was discharged on home ventilation. Failure of weaning was noted in 46% of patients under Phy-DW.

Table 2. Outcome measures of the study group

Outcome	Protocol (n = 13)		Physician (n = 13)		p value
	Mean	SD	Mean	SD	
ICU stay (days)	7	3	10	10	0.80
Hospital stay (days)	15	7.3	17	10.6	0.59
Duration of ventilation (days)	6	2.7	9	10	–
Duration of weaning (days)	4	3	12	0.4	0.0004
Main outcome	No.	%	No.	%	0.014
Failure of weaning	0	0	6	46	

DISCUSSION

Prompt identification of patients who have recovered from respiratory failure and liberating them to return to spontaneous breathing are important. Shortening the duration of mechanical ventilation is vital to a good quality of life. The results of the study support the conclusion of other investigators who have suggested that using protocol guidelines can safely and effectively hasten weaning and lower failure rate and the need for reintubation, thus lowering morbidity and complications.[3,4,5] Our study documented that assessing the physiologic, hemodynamic, and respiratory function of patients prior to weaning produce better outcomes than clinical judgement by physicians alone. Patients who received the protocol-directed weaning process compared with physician-directed weaning had success rate of 100% and 46%, respectively. Kollef noted the same observation (59.2% compared with 37.6%; p<0.001).[3] Failure rate was higher under physician-directed weaning due to lack of objective parameters that can be used in predicting the capability of patients to be weaned from support (p=0.014). Protocol-directed weaning resulted in shorter hospital and ICU stay and shorter duration of ventilation and weaning.

Weaning by pressure support was preferred in this study based on the reported advantages over the other methods of weaning. An important feature of pressure support is that it improves the efficacy of spontaneous breathing and reduces the external respiratory work and oxygen consumption by respiratory muscles during weaning. It also compensates for the additional work imposed by the endotracheal tube.[7,8] The parameters used in the assessment of respiratory function are already proven to be predictive of weaning success by assessing the oxygenation, pulmonary reserve, and ventilatory strength.[9,10] With the current economic pressures to reduce medical care costs, hospitals can use the methods outlined in this study to evaluate new strategies for providing intensive care.[6]

Since this is a preliminary study, further studies should be conducted using a bigger population to compare

the different modes of weaning. It is also recommended that different protocols be formed using the T-piece and SIMV/PSV weaning process. There should be a randomization by cluster wherein a physician is one cluster to prevent contamination bias.

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ORIGINAL ARTICLE

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Pulmonary Complications Following Lung Resection:

The Lung Center of the Philippines Experience

ABSTRACT

Objective

This study determined the incidence of pulmonary complications following lung resection and identified the risk factors that predispose to the development of postoperative complication.

Methodology

A retrospective, descriptive study was conducted by reviewing charts of patients who underwent elective lung resection from January 2000 to January 2002. Information recorded were preoperative assessment (pulmonary and clinical parameters), intraoperative and postoperative events, and pulmonary and nonpulmonary complications. Data were analyzed using Pearson x^2 Test or Fisher's Exact Test. Continuous variables were compared using the two-sample Wilcoxon Rank-Sum or Mann-Whitney U Test. A p value of <0.05 was considered significant.

Results

Fifty-three patients were included in the study. Seventeen patients developed pulmonary complications (32%). Hospital-acquired pneumonia was the most common pulmonary complication noted (11%). Mortality rate was 3.7%. Variables predictive of pulmonary complications were longer operation time (p=0.037), longer hospital stay (p=0.0237), and prolonged chest tube use (p=0.0137). There was no association between age, smoking history, sex, ASA score, blood loss, and pulmonary function test (including predicted postoperative values) and the development of postoperative complications.

Conclusion

The incidence of postoperative pulmonary complications was 32% and the mortality rate was 3.7%. The most common complication was hospital-acquired pneumonia. Factors predictive of postoperative complications were longer operation time, longer hospital stay, and prolonged chest tube use.

Lung resection offers the best prospect for long-term survival in patients with nonmetastatic bronchogenic carcinoma and a definitive treatment for chronic hemoptysis associated with bronchiectasis and aspergilloma. Patients undergoing thoracotomy associated with resection are thought to be at high risk for the development of postoperative complications due to coexistence of chronic airflow limitation, and removal of lung tissue may grossly impair postoperative lung function. In most but not all studies, the predictors for postoperative complications include the American Society of Anaesthesiologist (ASA) score, the length of surgical procedure, and the need for postoperative mechanical ventilation. Other studies indicate positive correlation with patients' age, smoking history, predicted postoperative force expiratory volume in 1 second (FEV_1- ppo), predicted postoperative carbon monoxide diffusing capacity (DLCO-ppo), and maximum oxygen consumption during exercise (VO_2max). Considering the results of recent studies, the Lung Center of the Philippines (LCP) came up with an algorithm for functional assessment of lung resection candidates but no validation has yet been made. Thus, this study was conducted to review the incidence of pulmonary complications following lung resection and identify the risk factors that may predispose patients to develop postoperative pulmonary complications. The results may be of use in future research for the validation of the LCP algorithm.

METHODOLOGY

Charts of patients who underwent elective lung resection from January 2000 to January 2002 were reviewed. Pulmonary resection included those requiring either chest wall resection or other extended resections including sleeve, tracheal, atrial, intrapericardial, aortic, and diaphragmatic resection. The following data were abstracted from all charts by means of a standardized form: age, sex, smoking history, preoperative diagnosis, and clinical evaluation, which included comorbid conditions, ASA status, and risk assessment evaluation. Included here were the results of the electrocardiograph (ECG), arterial blood gases (ABG), and pulmonary function test (PFT). Predicted postoperative FEV1 was computed using the formula: ppo FEV1 = Preoperative FEV1 x (no. of lung segment remaining after resection divided by the total no. of segments in both lungs.), or if lung perfusion study was available, by this formula: ppo FEV1 = preoperative FEV1 × % perfusion of total function of remaining lung.

The type of operation performed, anaesthesia and endotracheal tube used, length of operation, approximate blood loss, intraoperative complications, and postoperative complications were also included in the analysis. Complications, both pulmonary and nonpulmonary, were ascertained by detailed chart review according to the operational definitions itemized in panel 1.

Panel 1

Definitions of postoperative complications (those complications occurring within 30 days of thoracotomy)
Pulmonary complications: 1. Nosocomial pneumonia – infection of the lung parenchyma that was neither present nor incubating at the time of hospital admission and confirmed by appearance of new infiltrates on chest X-ray (1) 2. Lobar or whole lung atelectasis – evidenced on chest radiograph and requiring bronchoscopy 3. Acute respiratory failure – postoperative ventilator dependence for more than 24 hours or reintubation for controlled ventilation 4. Prolonged air leak – air leak requiring more than 7 days of postoperative chest tube drainage 5. Empyema – presence of more than 25,000 neutrophils/ml or by the demonstration of micro-organism by examination of smears or by culture of the pleural fluid 6. Bronchospasm – wheezing or prolonged expiratory phase
Nonpulmonary complications: 1. Cardiovascular complications: a. Acute symptomatic cardiac arrhythmia requiring treatment b. Acute myocardial infarction (ECG and elevation of cardiac enzymes) or unstable angina (2) c. Stroke 2. Genitourinary tract complications 3. Gastrointestinal tract complications 4. Bleeding through the chest tubes could be considered as a significant complication when a re-operation was required or when three or more packs of red blood cells were transfused.

Statistical Analysis

Categorical variables were compared using the Pearson x^2 Test or Fisher's Exact Test. Continuous variables were compared using the Two-sample Wilcoxon Rank-Sum or Mann-Whitney U Test. A p value lower than 0.05 was chosen as significant.

RESULTS

Study Population

Fifty-three patients, 33 males and 20 females, underwent pulmonary resections. The mean age was 48. Twenty-one patients were nonsmokers while 32 were previous smokers (1.25-110 pack-years). No pulmonary function test was performed in 9 patients who underwent resection. In the 44 patients who had PFT, DLCO was performed in 11 patients and perfusion studies in 7 patients. Eleven patients were cleared for surgery without PFT and ABG. Lobectomy was the most common operation

performed in 87% (Table 1). Twenty-four patients were diagnosed with malignant neoplasm. Cell types included adenocarcinoma (54%), squamous cell carcinoma (29%), and large cell carcinoma (8%). One patient was diagnosed with carcinoid and another one with teratoma. The remaining pathologic lung diseases were bronchiectasis, tuberculosis, and aspergilloma (Figure 1).

Table 1. Number and type of surgical procedure

Operation	No. of cases
Lobectomy	46 (87%)
Pneumonectomy	5 (9%)
Wedge resection	1 (2%)
Enbioc + LUL	1 (2%)
Total	53

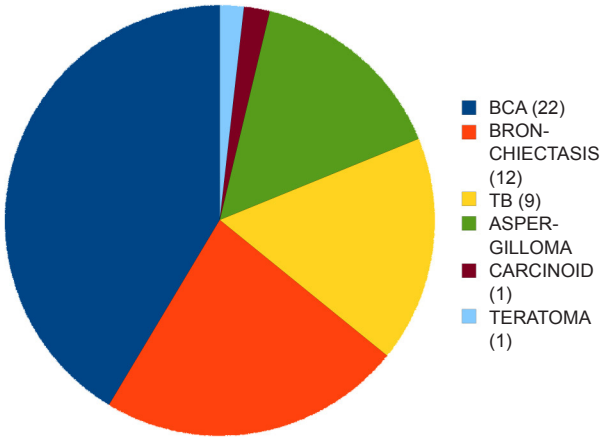

Figure 1. Diagnosis of patients who underwent resection

The most common ECG finding was nonspecific ST-T wave changes seen in 22 patients and 17 patients had normal ECG. The rest of the ECG findings were sinus tachycardia and bradycardia, poor R wave progression, and complete and incomplete right bundle branch block. There were three patients without ECG. Chronic obstructive pulmonary disease (COPD) was the most common comorbid condition noted in 27 cases followed by diabetes mellitus in 7 cases and hypertension/CAD in 5 cases. Other comorbid conditions were tuberculosis, rheumatic heart disease, and liver cirrhosis. Six patients had more than one comorbid condition (Table 2).

Forty-three patients were assessed as low risk for resection, 3 with acceptable risk, 6 with moderate risk, and 1 was high risk for resection. Twelve patients had an ASA score of 1, thirty-eight with ASA score of 2, and three with ASA score of 3. Single lumen endotracheal tube was used in 43 patients and 10 were intubated using double lumen.

Table 2. Coexisting medical illness in 26 patients

Comorbid condition	With pulmonary complications	Without pulmonary complications	Total
COPD	10	10	20
DM	4	3	7
HTN/CAD	2	3	5
PTB	0	1	1
RHD	0	1	1
Liver cirrhosis	1	0	1

Intraoperative complications recorded were hypertension, bleeding, hypotension, and arrhythmia (premature atrial fibrillation). One patient developed premature ventricular contraction and atrial fibrillation. One patient developed ventricular tachycardia followed by cardiac arrest but immediate resuscitation was done and no postoperative complication was noted. This patient was diagnosed with a Stage IIIA adenocarcinoma and underwent left pneumonectomy. His pulmonary assessment was low risk for pulmonary complication. He had COPD and hypertension and ECG result was nonspecific ST-T wave changes with left atrial deviation.

Recorded blood loss in forty-three patients ranged from 200 – 4500 ml. The shortest operation time was 120 minutes and the longest was 580 minutes. Postoperative analgesia used was Morphine sulphate, Nalbuphine, Demerol, and Ketoprofen delivered by epidural, patient-controlled analgesia (PCA) or IV route. The shortest hospital stay was 4 days and the longest was 30 days. Six patients were discharged with a chest tube.

Postoperative Complications

Seventeen (32%) patients developed pulmonary complications, the most common of which was hospital-acquired pneumonia (11.3%) and the earliest was recorded on Day Two after surgery. The most common organism isolated was *Pseudomonas aeruginosa* followed by Enterobacter and Alpha hemolytic streptococcus. No organism was isolated in one case. Other complications were air leak (9.4%), bronchospasm (9.4%), atelectasis (7.5%) that were noted on the second and third post-op day, acute respiratory failure, pneumothorax, and empyema with *P. aeruginosa* isolated in the pleural fluid (Table 3).

Nonpulmonary complications were noted in eighteen patients (Table 4) as follows: urinary tract infection (7.5%), upper gastrointestinal intestinal bleeding (3.8%), and atrial fibrillation (3.8%).

Table 3. Incidence of pulmonary complications postoperative (n=53)

Complications	No.	% (total px)
HAP	6	11.3
Air leak	5	9.4
Bronchospasm	5	9.4
Atelectasis	4	7.5
ARF	2	3.8
Empyema	1	1.9
Pneumothorax	1	1.9
Total	24	

Table 4. Incidence of nonpulmonary complications postoperative (n=18)

Complications	No.	% (total px)
Urinary tract infection	4	7.5
Upper GI bleeding	2	3.8
AF	2	3.8
Congestion	2	3.8
Hypertension	1	1.9
CVD Infarct	1	1.9
Acute MI	1	1.9
Acute renal failure	1	1.9
Dyspepsia	1	1.9
Ileus	1	1.9
Hyperglycemia	1	1.9
Amoebiasis	1	1.9

Mortality rate was 3.7% (two deaths). Pre- and perioperative historical data for patients with or without pulmonary complications are tabulated in Table 5. Variables predictive of pulmonary complications were a longer operation time (p=0.0370), longer hospital stay (p=0.0237), and prolonged chest tube use (p=0.079). Other variables like age, smoking history, comorbid condition, risk assessment, ASA score, blood loss, and pulmonary function test results were not predictive of occurrence of pulmonary complications.

Table 5. Characteristics of patients with and without pulmonary complications

Variable	Px with pulmonary complication (17)	Px without pulmonary complication (36)	p value
Age	48 (18)	48 (12)	0.99
Smoking history (pack years)	30	29.5	0.68
*Sex Male Female	 11 6	 22 14	1.00
*Class Pay Charity	 6 11	 22 14	0.08
*ASA 1 2 3	 0 8 2	 1 7 0	0.48
Comorbid condition: COPD HTN DM	 10 2 4	 10 3 3	 0.03 0.65 0.19
*Risk assessment Low Mod High Acceptable	 13 2 0 2	 30 4 1 1	0.67
*Post-op analgesia MgSO4 Nalbuphine Demerol Ketoprofen	 14 1 1 1	 22 10 2 2	 0.12 0.08 1.00 1.00
Blood loss (ml)	850	1000	0.63
Operation time (min)	345.56 (92.81)	280 (11)	0.04
Length of CTT stay (days)	9 (5)	5 (3)	0.01
Hospital stay (days)	16 (7)	12 (6)	0.02
FEV1 (ml)	1900	1990	0.37
FEV %	65 (18)	7 (21)	0.58
PpoFEV1	1429 (473)	1508 (528)	0.63
FVC (ml)	2495 (932)	2554 (789)	0.83
FVC%	72 (18)	73 (20)	0.81
PCO2	37 (3)	36 (5)	0.62
PO2	88 (8)	87 (13)	0.80

• Actual number of case, ( ) standard deviation, smoking history, blood loss and FEV1 are reported as median. The rest are mean values unless specified otherwise.

DISCUSSION

Pulmonary complications are the most common form of postoperative morbidity in patients who undergo lung resection, with an incidence of about 30%. This may be related not only to the removal of lung tissue but also caused by alterations in chest wall mechanics due to thoracotomy itself.[3] Thoracotomy alone was found to decrease chest wall compliance to 47% of preoperative levels and increased work of breathing to 143% of preoperative levels.[4] Table 6 shows the comparative incidence of pulmonary complication and mortality in several studies. The highest incidence was reported by Cerfolio et al. (49%) but there was no identifiable factor that predicted postoperative morbidity and mortality.[5] Pate's study included 12 high-risk patients with borderline pulmonary function (mean FEV1 was 1.38L, 48% of predicted and ppoEV1 based on pneumonectomy was 700ml) and the incidence of complications was 42%.[6] Based on their results, age higher than 65 years, right-

Table 6. Incidence pulmonary complications and mortality rate of selected studies

Author	Year/Study	Number of cases	Incidence of pulmonary complication (%)	Mortality (%)
Markos, James	1989 Prospective	55	29	5.7
Dales, Robert	1993 Prospective	117	37	–
Cerfolio, Robert	1996 Retrospective	85	49	2.4
Pate, Preston	1996 Prospective	12	42	–
Harpole, David	1996 Prospective	136	17	3
Wyser Cristoph	1999 Prospective	132	11	1.5
Stephan, Francois	2000 Retrospective	266	25	7.5
LCP	2002 Retrospective	53	32	3.7

sided procedures, and dysrhythmias were associated with an increased risk of a major complication.[6] Wyser and coworkers obtained the lowest incidence of complications and mortality with 11% and 1.5%, respectively. They used an algorithm which incorporated the cardiac history including ECG, and 3 other parameters such as FEV_1, DLCO, and maximal oxygen uptake (VO_2 max), as well as their respective predicted postoperative values calculated based on radionuclide perfusion scan.[7] The results of this study were comparable with other studies that obtained 32% incidence of pulmonary complication and 3.7% mortality rate.

This study showed a correlation between postoperative complications and the presence of COPD (p=0.03), a longer operation time (p=0.04), longer hospital stay (p=0.02), and prolonged chest tube use (p=0.014) as shown in Table 5. Risk of complications was greater in operations lasting ≥ 4 hours regardless of the site of operation. There was a higher complication rate for operations lasting ≥ 5 hours. Harpole et al. reported 17% incidence of major complications for patient admitted with median length of stay of 7-11 days. This study failed to establish associations with patient's age, smoking history, sex, ASA score, blood loss, and PFT (including predicted postoperative values). The difference in the results may be due to the type of pulmonary complications studied, clinical criteria used in the definition, patient selection, and type of surgery performed.

Table 7. Postoperative pulmonary complication in selected studies

Study	Post Op pulmonary complication	Percentage (%)
Stephan, F.	Prolonged air leak, BPF Bacterial pneumonia ARF	8.3 6.4 6.0
Cerfolio, R	Prolonged air leak ARF Pneumonia	21 7.0 3.5
Wyser, C.	Atelectasis	8.0
Harpole, D.	Pneumonia Reintubation	5.8 5.1
LCP	HAP Air leak Bronchospasm Atelectasis	11.3 9.4 9.4 7.5

Atelectasis, which is the most common postoperative complication in literature, ranked third in this list of pulmonary complications. The most common complication in this study was hospital-acquired pneumonia, which is about 11% (Table 7). This incidence is higher than in other studies, which ranged from 3.5 to 6.4%, and it may be due to differences in the study population, isolation procedure, and clinical criteria used in the diagnosis of pneumonia. The most common isolates were gram-negative organisms. Lastly, the most common nonpulmonary complication recorded was UTI, manifested as occurrence of fever after surgery and confirmed by the presence of pyuria and hematuria on urinalysis.

This retrospective investigation may help to identify variables associated with perioperative pulmonary complications.

The incidence of postoperative complication in this study was 32% with mortality rate of 3.7%. Factors predictive of postoperative complications were longer operation time, longer hospital stay, and prolonged chest tube use. The most common complication was hospital-acquired pneumonia (11.3%).

It is recommended that the existing algorithm of LCP be validated prospectively to include patient characteristics and risk assessment for intraoperative and postoperative events.

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Use of Bilevel Positive Airway Pressure (BiPAP) for Chronic Obstructive Pulmonary Disease in Acute Hypercapneic Respiratory Failure

ABSTRACT

Objective

This study determined the success rate in the use of Bilevel Positive Airway Pressure (BiPAP) for Chronic Obstructive Pulmonary Disease (COPD) in Acute Hypercapneic Respiratory Failure. Patient characteristics that could predict a successful outcome were identified.

Methodology

This was an observational prospective cohort study in a tertiary specialty hospital. Twelve patients met a predetermined definition of acute hypercapneic respiratory failure upon admission or during hospitalization and needed mechanical ventilation. Noninvasive positive pressure ventilation (NPPV) was administered using a BiPAP ventilation assist system. Inspiratory and expiratory pressures were titrated to patient comfort. Once stable settings were achieved for 8 hours, the patient was liberated from the BiPAP machine.

The main outcome measure was whether or not there was a need for intubation and mechanical ventilation when BiPAP protocol was used.

Nonparametric test was used to analyze variables as well as secondary outcomes. The binomial test was used to analyze results in comparison with historical controls. A p value less than 0.05 was considered as statistically significant.

Results

Although three patients (25%) needed intubation, there was no statistically significant difference noted between the successful BiPAP patients and the intubated patients. The average IPAP at 24 hours was 8±2 cm H_2O. Binomial test showed that the failure rate for this study was comparable with foreign literature (31%) with a p value of more than 0.46. No complications were noted and no mortality was recorded. The length of hospital stay was significantly shorter for BiPAP patients than intubated patients.

Conclusions

NPPV therapy with BiPAP in selected COPD patients with ARF was associated with significantly reduced need for intubation and conventional mechanical ventilation. The success rate of 75% is comparable with foreign literature.

Chronic Obstructive Pulmonary Disease (COPD) patients presenting with acute respiratory failure (ARF) frequently require some form of assisted ventilation. In the past, intubation and mechanical ventilation were the treatment of choice. However, these forms of management may result in various adverse outcomes including infectious (e.g., nosocomial pneumonia, sinusitis) and noninfectious (e.g., barotrauma, oral and laryngeal trauma, muscle weakness) complications. Noninvasive methods of ventilatory assistance have become a popular alternative to intubation and mechanical ventilation in selected COPD patients with acute respiratory failure. The potential advantages of this approach are obvious. Airway defense mechanisms as well as speech and swallowing functions are left intact, trauma to the larynx and trachea are avoided, and patient comfort may be improved. However, the noninvasive delivery of positive pressure ventilation also has potential limitations including the lack of direct access to the airway for removal of secretions, discomfort and facial trauma related to the mask, need for patient cooperation, and the potential for abrupt respiratory deterioration if the mask is dislodged or if patient breathing does not synchronize with the ventilator.

The recent prospective randomized studies strongly suggest the use of noninvasive mechanical ventilation in patients with severe exacerbation of COPD. These studies showed that the noninvasive ventilation group had significantly lower rates of complication, reduced need for endotracheal intubation, shorter hospital stay, and lower mortality than the group that received standard treatment.

No local study has been done to evaluate BiPAP use in acute respiratory failure for COPD patients. In view of this limitation, an observational prospective cohort study was conducted to determine the success rate in the use of BiPAP ventilation and the results were compared with foreign literature. Patient characteristics that could predict the successful use of BiPAP ventilation were identified and complications associated with the use of BiPAP, mortality, and length of hospital stay were determined. Results on the need for intubation and failure rate were compared with foreign literature that used the same BiPAP protocol.

METHODOLOGY

The study was an observational prospective cohort study that followed the BiPAP protocol used in Kramer's study in 1995, which served as the historical control and with which results were compared and analyzed. The study was performed from September 2001 until May 2002. Eligible subjects were alert, responsive and hemodynamically stable COPD patients in acute hypercapneic respiratory failure refractory to conventional treatment. Patients in acute hypercapneic respiratory failure were those exhibiting a respiratory rate of more than 24 breaths per minute and ABG values of pH < 7.35 and $paCO_2$ > 45 mm Hg. They were excluded if they had any of the following: an immediate indication for intubation, hypotension defined as systolic BP lower than 90 mmHg, presence of ventricular tachycardia and other fatal arrhythmia, upper airway obstruction or facial trauma; inability to clear secretions from airways; those with severe nasal congestion, inability to cooperate with fitting and wearing mask, and presence of pneumothorax or chest trauma. Informed consent was obtained from each patient or next of kin prior to enrolment.

Once enrolled, the patient was first fitted with a tight-fitting nasal mask. Noninvasive pressure ventilation was administered using a BiPAP ventilatory assist system (knightStar 335 Respiratory support system), a pressure-limited device that cycles between adjustable inspiratory and expiratory pressures using patient flow-triggered modes.

The initial inspiratory positive airway pressure (IPAP) was set at 8 cm H_2O and the expiratory pressure (EPAP) was set initially at the lowest possible setting approximately 3 cmH_2O. Supplemental oxygen was blended in via a mask port to maintain an oxygen saturation greater than or equal to 90%. The patient was then encouraged to coordinate his/her breathing with the ventilator.

Subsequent adjustments of IPAP were made if arterial blood gases still showed persistent respiratory acidosis (pH less than 7.35) or if there were clinical signs of continued respiratory distress. If the patient could not tolerate the nasal mask or if there was excessive air leak, an oronasal face mask was used instead.

The patients used the BiPAP for as long as tolerated, aiming for at least 8 hours a day. In addition, the patients received all standard therapy as ordered by their attending physicians. The mask was removed intermittently during meals.

Once clinical stability was achieved, patients successfully treated with BiPAP were freed from the machine no sooner than 8 hours. Clinical stability was defined as a reduction in respiratory rate (less than 24 breaths/min), a heart rate of 110 beats/min, a compensated pH of more than 7.35, and adequate oxygen saturation

of more than 90% with an oxygen flow rate of no more than 3L/min. When BiPAP was discontinued, oxygen was provided via a nasal cannula or face mask. If the patient remained stable, BiPAP was not reinstituted. If there was fatigue as evidenced by increased dyspnea and tachypnea, or ABG deterioration, BiPAP was restarted at the prior setting and then was weaned gradually. Patients who were able to tolerate 24 hours of oxygen/nasal cannulae were considered successfully weaned from BiPAP.

The primary outcome measured was whether or not there was a need for intubation and mechanical ventilation when BiPAP protocol was used. Intubation was necessary if progressive clinical deterioration occurred after entry into the study as manifested by worsening mental status, dyspnea or tachypnea, development of hypotension, a rise in paCO2 of more than 5-10 mmHg or a fall in pH by 0.05 to 0.10 unit. The secondary outcome measured included heart and respiratory rates, arterial blood gases, length of stay, complications, and mortality.

A nonparametric test was used to analyze variables as well as secondary outcomes. The binomial test was used to analyze results in comparison with the historical control. A p value less than 0.05 was considered as statistically significant.

RESULTS

A total of 12 patients were enrolled in the study. All patients were male with a mean age of 71±5 years. Three (3) patients (25%) needed intubation during the course of noninvasive ventilation.

Baseline characteristics are shown in Table 1. The systolic and diastolic blood pressure as well as the cardiac rate and respiratory rate baseline mean were much lower in successfully treated BiPAP patients compared to patients who were eventually intubated. The pH baseline mean was longer in nonrespondents with higher pCO_2 although this may not be statistically significant. Initial coaching was necessary to encourage patients to relax and synchronize their breathing with the ventilator. However, after several hours most of them synchronized well and appeared comfortable. Most patients, however, did not tolerate the initial 8 cm H_2O IPAP as compared to the historical control. Most of the patients tolerated only lower levels initially with an IPAP average of 6±1cm H_2O. Subsequently, upward adjustments were made as tolerated, in attempts to lower $paCO_2$. The average IPAP at 24 hours was 8±2 cmH_2O. The EPAP was adjusted to the lowest setting, which remained at 3±0.4 cm H_2O for the duration of the study. The average duration of BiPAP use was 27±5 hours. At 4 hours BiPAP, patients who were eventually intubated still showed much lower pH, and still with an unacceptable elevation of pCO_2.

Table 1. Patients' characteristics at baseline

Characteristics	Successful BiPAP patients Mean [Standard deviation] n = 9	Intubated patients Mean [Standard deviation] n = 3
Systolic blood pressure	131.1 [17.6]	143.3 [15.2]
Diastolic blood pressure	83.3 [10.0]	93.3 [5.77]
Cardiac rate	98.2 [10.5]	110.3 [0.57]
Respiratory rate	27.7 [4.9]	31.3 [1.15]
pH	7.28 [0.03]	7.25 [0.05]
pCO_2	66.2 [10.5]	68.4 [2.26]
pO_2	75.08 [25.5]	72.1 [8.82]

Binomial test also showed that failure rate was comparable with foreign literature (31%) with a p value equal to 0.46.

Like those in most studies on the use of bilevel pressure ventilation for acute respiratory failure, successfully treated BiPAP patients in this study experienced a significantly greater decline in heart and respiratory rates within the first hour. However, the difference in vital signs between those successfully treated BiPAP patients and those intubated afterwards was not statistically significant.

Likewise, patients who received BiPAP had significant improvements in $paCO_2$, pH, pCO_2 within 1 hour from initiation of treatment. These rapid improvements occurring with BiPAP use were most likely related to the higher inspiratory than expiratory pressures, which enabled BiPAP to actively assist inspiration, augment tidal volume, and decrease the work of breathing.

Complications such as nasal ulceration, pneumothorax, hypotension, and myocardial infarction were not seen among the twelve patients on BiPAP. No mortality during the entire study period was recorded. The length of hospital stay was significantly shorter for successful BiPAP patients as compared to intubated patients, with a mean of 5.7 days and 19.37 days, respectively.

DISCUSSION

NPPV is a safe and effective means of ventilatory support for many patients with ARF, and is generally well tolerated, with reduced complications. BiPAP ventilation is a noninvasive positive pressure ventilation with the

Table 2. Patients' characteristics at 4 hours BiPAP

Characteristics	Successful BiPAP patients (Mean, Standard deviation) n = 9	Intubated patients (Mean, Standard deviation) n = 3
Systolic blood pressure	12.6 [7.07]	133.3 [5.7]
Diastolic blood pressure	80.0 [5.0]	90.0 [10.0]
Cardiac rate	91.8 [7.4]	109.3 [8.14]
Respiratory rate	22.5 [2.78]	28.0 [2.64]
pH	7.36 [0.05]	7.28 [0.05]
pCO_2	54.7 [9.81]	66.56 [3.48]
pO_2	80.7 [20.6]	68.1 [2.67]

application of positive airway pressure that varies in magnitude during inspiration and expiration, similar in concept to the pressure support ventilation, but differs in terminology, wherein the expiratoty pressure with BiPAP is equivalent to the PEEP, and the inspiratory pressure is equivalent to the sum of PEEP and the pressure support level.

BiPAP ventilation can be given effectively by nasal or by face mask hooked to a mechanical ventilator. In this prospective observational study, 4 patients who were initially on nasal mask were shifted to face mask due to persistent air leak. The application of BiPAP ventilation delivered by face mask or nasal mask to patients with acute exacerbation of COPD has been shown to reduce the inspiratory workload of breathing and the magnitude of inspiratory efforts, leading to improvement in gas exchange.

Several published studies support the use of BiPAP ventilation as a treatment for acute exacerbation of COPD. These controlled trials have shown an improvement in gas exchange, a decrease in hospital stay, and a lower in-hospital mortality rate. Ambrosio et al. retrospectively reviewed their experience with BiPAP ventilation in patients with COPD, and after an analysis of multiple variables, the baseline pH remained the best predictor of success (sensitivity = 97%, specificity = 71%).

Although it is difficult to predict which patients will be successfully treated with BiPAP ventilation, patients with preserved neurologic status who are cooperative and capable of protecting their airway should be offered a trial. In multiple studies, BiPAP ventilation has been shown to decrease the complications associated with ARF, primarily avoiding intubation and mechanical ventilation.

The findings in this study, that NPPV reduced the need for intubation, is compatible with the findings of most other studies on the use of BiPAP ventilation in acute respiratory failure. Brochard and coworkers found that only 1 out of 13 patients with COPD exacerbations required intubation when treated with NPPV as compared with 11 of 13 historically matched control patients Benhamou and coworkers reported.

In the present study there were three (3) patients (25%) who needed intubation during the course of noninvasive ventilation. Analysis showed, however, that there was no statistically significant difference in any variables compared to the patients who were successfully treated with BiPAP.

Several limitations of this study were noted. Firstly, as with other studies, this study examined a relatively small number of patients, increasing the likelihood of statistical errors. Secondly, the clinicians involved could not dictate how conventional medical therapy should be administered. Finally, respiratory muscle function was not directly monitored. Perhaps more sophisticated monitoring of respiratory muscle function would have determined better the lack of efficacy of NPPV and the need for endotracheal intubation.

In summary, the results demonstrated that BiPAP ventilation was well tolerated by COPD patients with acute hypercapneic respiratory failure and could be used safely with only a few complications. Most importantly, intubation and mechanical ventilation were deferred in 75% of patients.

A prospective randomized trial comparing patients on BiPAP and those on conventional medical treatment should be done to definitely conclude the beneficial effect of noninvasive mechanical ventilation using BiPAP to COPD patients in acute hypercapneic respiratory failure. Although this study was unable to determine predictors of success at the time of presentation, it still supports an interventional trial of BiPAP ventilation to COPD patients in acute hypercapneic respiratory failure. Any patient with ARF who is capable of cooperating with the respiratory therapist should be offered a trail of BiPAP ventilation. Failure to improve after 4-8 hours on stable BiPAP ventilation setting is an indication for its discontinuation and the initiation of conventional mechanical ventilation.

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Epidural Clonidine Infusion for Analgesia after Thoracotomy

ABSTRACT

Objectives

This study compared the efficacy and safety of epidural clonidine and morphine after thoracotomy.

Methodology

Using a randomized, prospective, double blind study design, 40 patients who were to undergo thoracotomy under general anesthesia were randomly allocated to receive epidurally one of two study drugs: clonidine 50µg/hour or morphine sulfate at 0.3 mg/hour.

Results

Comparison of pain scores using the Generalized Estimating Equations showed significantly higher values in the morphine group than the clonidine group (<0.05). Requirements for supplementary analgesia was lower in the clonidine group and the action was notably faster. Mean arterial blood pressures were lower in the clonidine group, although incidence of clinical hypotension requiring vasopressor therapy was low. Mean heart rate was reduced in the clonidine group, though pharmacological reversal was not necessary. There were no considerable differences between the two groups in emetic symptoms. Significantly higher number of patients in the morphine group ($p<0.05$) had urinary retention requiring catheterization.

Conclusion and Recommendation

The use of clonidine by continuous epidural infusion for post-thoracotomy analgesia has been shown to be effective, safe, and acceptable. However, it is recommended that further studies be done to determine appropriate dose based on body weight so as to lessen the incidence of hemodynamic effects.

Lateral thoracotomy incision is considered to be one of the most intense pain experiences[1] thus effective pain control is very important because severe pain can lead to splinting of the respiratory muscles, ventilatory restriction, and potentially dangerous arterial hypoxemia.[2] A wide range of analgesic techniques is currently being used in clinical practice for the treatment of post-thoracotomy pain. Frequently performed analgesic techniques include: systematic opioids, intercostal nerve blockade, intrapleural blockade, lumbar and thoracic epidural analgesia. Thoracic epidural analgesia, though technically demanding and requiring close postoperative observation has been shown to be very effective for pain management after thoracotomy.[3]

Clonidine is a centrally acting α_2 adrenergic agonist. Since the early 1970s it has been used successfully to treat patients with hypertension and patients withdrawing from long-term abuse of drugs and alcohol.[4] Recently, it has been extensively studied as an adjunct to general and regional anesthesia because of its analgesic, anxiolytic, and sedative properties.[4,5] It is administered through a variety of routes for long-term and short-term perioperative pain control.[4] Tshernko and Klepetko[7] reported that the addition of clonidine to local anesthetic for intercostal blockade enhances postoperative pain control and improves oxygenation on post-thoracotomy patients.[7] Castro et al.[6] assessed the physical properties, pharmacokinetics, and dynamics of clonidine after IV, epidural, and intrathecal administration in sheep and concluded that epidural administration was the most appropriate route of administration and continuous infusion was superior, when compared to bolus injection.[6] Epidural clonidine modulates anti-nociception by peripheral, supraspinal, and spinal cord mechanisms, including activation of post-synaptic α_2 receptors of descending noradrenergic neurons and the release of nitric oxide.[8]

Epidural analgesic with opioids, of which the gold standard is morphine, is currently the most popular analgesic regimen for post-thoracotomy pain management.[9] When compared with patients receiving parenterally administered opioids, those receiving neuraxial opioids have better pulmonary function and are more comfortable.[1]

Epidural opioids can decrease the ventilatory response to carbon dioxide, although significant respiratory depression and apnea are rare.[1] Other reported side effects associated with epidural opioids are pruritus, urinary retention, nausea, and vomiting. However, these are minor and are not significant reasons to seek for alternative drugs that can be given neuraxially.

METHODOLOGY

After obtaining permission from the institution's research committee and informed written consent from patients, 40 adult patients of ASA class I and II, aged 18-75 years old, scheduled for elective thoracotomy under general anesthesia, were divided into two groups (n=20 for group 1 and n=20 for group 2) in a randomized double-blind fashion. Patients were excluded if they had renal or hepatic dysfunction; (+) history of chronic use of opioids, anti-inflammatory, cardiovascular, or psychotropic drugs; a positive history of allergic reactions to any of the study drugs; and any contraindications to epidural block.

Patients were premedicated with oral midazolam 7.5mg 60 minutes prior to the operation. Upon arrival at the operating room, patients were connected to standard monitors (NIBP, electrocardiogram, pulse oximeter). Prior to induction of anesthesia, an epidural catheter was inserted at $T_7 - T_8$ or $T_8 - T_9$ level using a standard 18 gauge Tuohy needle using the loss of resistance technique. At least 3 cm of the catheter was threaded epidurally. Test dose with 2% lidocaine 3ml with epinephrine 1:200,000 was administered to exclude subarachnoid block or intravascular injection.

A standardized induction of general anesthesia was initiated using thiopental at 4mg/kg and fentanyl at 1.5µg/kg. Endotracheal intubation was facilitated with succinylcholine 1.5mg/kg. Neuromuscular block was provided by vecuronium 0.1mg/kg top up doses and anesthesia was maintained with isoflurane in oxygen titrated to desired level with controlled positive pressure ventilation to maintain normocapnea.

The moment the surgeons started suturing the skin (approximately 30 minutes before the end of surgery), patients were allocated randomly to receive either one of two treatments via the epidural catheter: clonidine 150 µg diluted to 10ml in 0.9% saline followed by an infusion of 50 µg/ml or morphine sulfate 1 mg diluted to 10 ml in 0.9% saline followed by an infusion of 0.3mg/cc. The rate of infusion was set at 1ml/hour, which started immediately after the bolus injection and continued for 48 hours after surgery.

In both groups, solution for the injections and infusions were prepared and administered by another operator who had no further role in the study.

At the end of the procedure, residual neuromuscular block was reversed if indicated and the patients were allowed to wake up spontaneously. Indwelling Foley catheter was removed simultaneously with endotracheal extubation.

Baseline vital signs were recorded 30 minutes after giving the bolus injection then at 15 minutes interval for the first two hours and at 4 hours interval thereafter for the succeeding 48 hours. Systolic blood pressure less than 85 mm Hg were treated with 5mg of ephedrine administered intravenously, repeated until acceptable blood pressure is obtained. A heart rate of less than 45 beats/minute was treated with atropine 0.3 mg of sulphate administered intravenously.

Sedation levels were assessed on a three-point scale: 1 – awake, 2 – drowsy, 3 – asleep, at 30 minutes interval for the first two hours then at four hours interval for the succeeding 48 hours. Pain scores were assessed using the 10 cm visual analogue scale (VAS): 0-1 no pain, 2-3 mild pain, 4-5 moderate pain, 6-7 severe pain, 8-9 very severe pain, and 10- worst pain imaginable, at 30 minutes interval for the first two hours then at four hours interval for the next 48 hours. Patients with VAS score of 5 or more were provided by infusion with a rescue analgesia using 50 mg of meperidine. The time for the first analgesia demand and the number of analgesia demands were noted. The incidence of nausea, vomiting, urinary retention requiring catheterization, and any spontaneously volunteered side effects were recorded. All assessments of sedation levels and pain scores were done by a recovery room nurse who was unaware of the nature of the epidural infusion.

Quantitative data were described as mean, median, and standard deviation and qualitative data were described as frequency and percentages. Pain scores were compared using the Generalized Estimating Equations. The number of rescue demand and the time of demand were compared using the Mann-Whitney U test. Sedation levels at two hours and side effects were compared using the Fischer's exact probability test. The level of significance considered was 5%.

RESULTS

The two groups were comparable with respect to age, weight, height, ASA physical status, and the duration of surgery (Table 1). Both groups had more male patients. The placement of the epidural catheter was easy and successful at the first attempt in all patients.

Table 1. Demographic characteristic of patients

	Clonidine (n = 20)	Morphine (n = 20)
Age (Mean, SD)	42.4 13.7	42.05 12.48
Sex (M: F)	13:7	15:5
Weight (kg) (Mean, SD)	57.6 12.48	59.6 11.22
Height (cm) (Mean, SD)	160.66 7.60	162.75 7.49
ASA physical status (n, %)	I:11 (55%) II:9 (45%)	I:12 (60%) II:8 (40%)
Duration of surgery (min) (Mean, SD)	263.90 88.89	267.50 88.62

Mean arterial blood pressure was noted to be lower among the clonidine group, with seven patients requiring vasopressor therapy (Figure 1). Two patients had persistent hypotension for 24 hours, thus repeated doses of ephedrine were given to correct the hypotension (Table 2). No episode was noted during the first two hours of the study period. The incidence of persistent hypotension was not

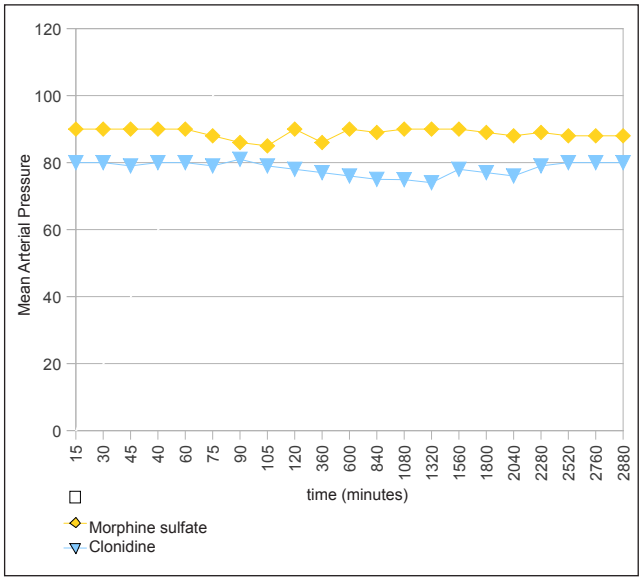

Figure 1. Mean arterial pressure (Clonidine vs Morphine sulfate)

Table 2. Incidence of persistent hypotension

	+	–
Morphine	0	20
Clonidine	2	18
Fisher's exact probability = 0.487		

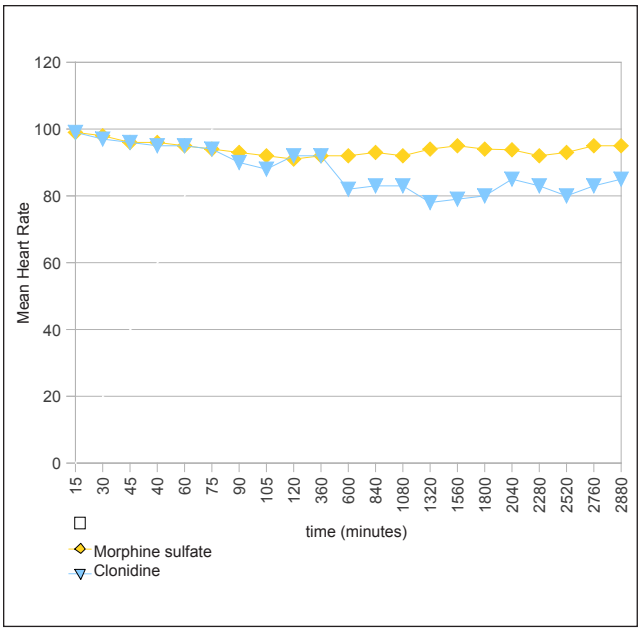

Figure 2. Mean heart rate (Clonidine vs Morphine sulfate)

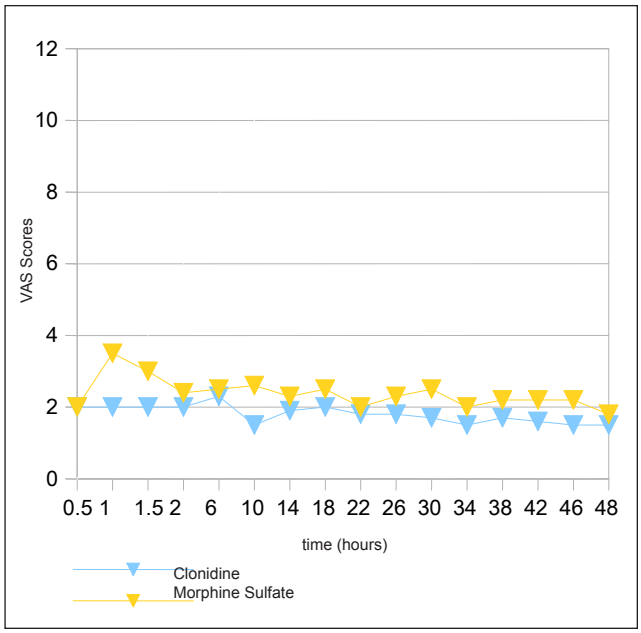

Figure 4. Mean VAS scores (Morphine sulfate vs Clonidine)

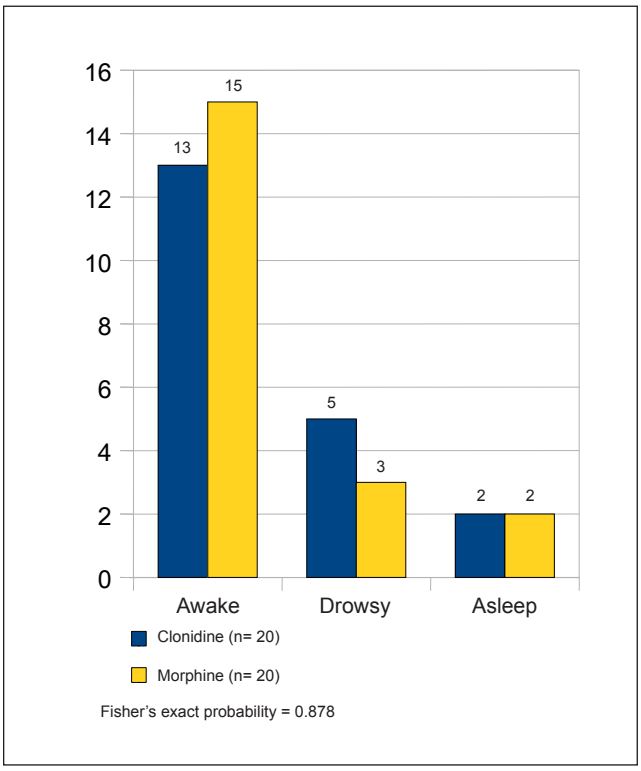

Fig 3: Sedation status at two hours

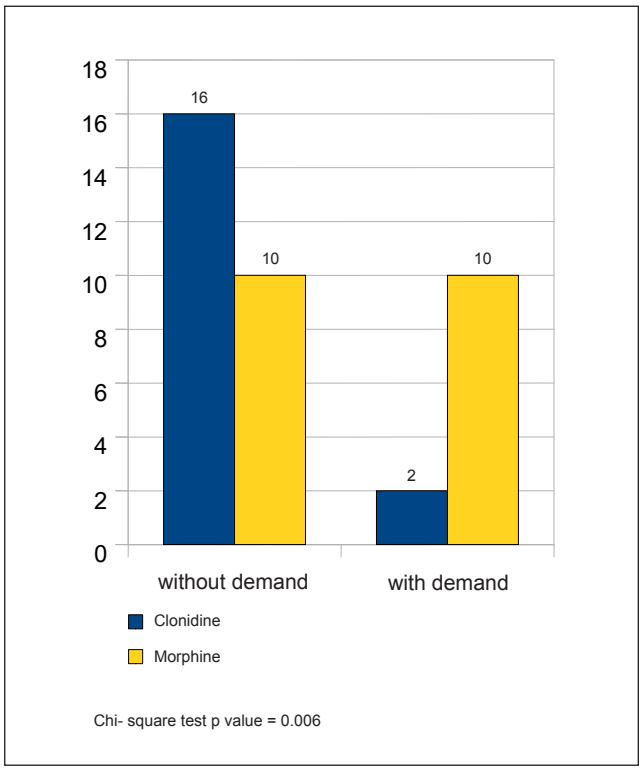

Figure 5. Number of patients requiring Meperidine

significant between the two groups (p=0.487). The values for heart rate were lower in the clonidine group (Figure 2). No patient required treatment for bradycardia. No significant differences were noted with regard to sedation status on both groups. Majority of the patients were fully awake within two hours after surgery (Figure 3). VAS scores were significantly higher in the morphine group (Figure 4). Fifty percent of the patients in the morphine

group had moderate pain requiring additional analgesia (Figure 5). Three patients in the morphine group required several doses of additional analgesia (Table 3). Comparison of VAS scores using the Generalized Estimating Equations showed significantly lower VAS scores in the Clonidine group than the Morphine group (Table 4).

Table 3. Number of Demerol demands

Number of demands	Morphine sulfate	Clonidine
0	10	18
1	7	2
2	2	0
3	1	0

Table 4. VAS Scores: Morphine sulfate vs Clonidine (values computed as mean and median)

	Time (hours)															
	0.5	1	1.5	2	6	10	14	18	22	26	30	34	38	42	46	48
Clonidine	1.9 1	2 1	1.9	2.1 1	1.75 1	1.85 1	2 1	1.6 5 1	1.8 1	1.7 1	1.35 1	1.2 1	1.55 1	1.5 1	1.25 1	1.3 1
Morphine sulfate	2.35 1	3.4 3	2.95 3	2.7 1	2.65 3	2.8 3	2.25 2	2.6 2.5	2 1.5	2.2 2	2.65 2	1.75 1	2.25 2	2.25 1.5	2.2 2	1.5 5 1
Generalized Estimating Equations p value = 0.0001																

Table 5. Incidence of side effects

	Morphine sulfate	Clonidine	p value
Nausea and vomiting	5	1	0.182
Urinary retention	6	2	0.007
p value computed using the Fisher's exact probability test			

There were no significant differences between the groups in the incidence of emetic symptoms (Table 5). A significantly higher number of patients in the morphine group had urinary retention requiring catheterization.

No other side effects were reported in both groups.

DISCUSSION

The results of the present investigation demonstrate that epidural clonidine is more effective than epidural morphine in providing analgesia for post-thoracotomy patients. There was a lower demand for supplementary analgesia and a greater number of patients with lower pain scores in the clonidine group. Although, Motsch et al. have suggested that analgesia attributable to α2 adrenergic agonist alone is insufficient and that its role lies in reducing the dose requirement of the other agents[10] this study proves otherwise. Clonidine at 50 µg/hour administered by continuous epidural infusion is sufficient to provide postoperative analgesia after thoracotomy. This is further supported by the study of De Koch et al. who confirmed the efficacy of epidural clonidine as a sole analgesic agent for patients undergoing abdominal surgery.[11] Moreover, Carrabine and Milligan investigated the use of epidural clonidine on patients undergoing hip arthroplasty and concluded that clonidine at 50 ug/hour given by continuous infusion was adequate in providing analgesia.[9]

Epidural clonidine infusions appear to provide excellent analgesia even in the early postoperative period as demonstrated by the very low rate of rescue analgesia demands and the good VAS scores. This is not the same with morphine infusion. Sixty percent of the patients in the morphine group who required additional analgesia had higher pain scores during the first two hours. This can be explained by the fact that morphine sulfate is a hydrophilic agent, thus it takes time before it could diffuse to the cerebrospinal fluid causing the delay in its onset of action, as compared to that of clonidine which is a lipophilic agent.[1]

Significant hemodynamic effects have been reported with clonidine use. Although epidural clonidine causes hemodynamic alterations, Rockemann, et al. showed that under stable filling pressures, these were within physiologic limits and no interventions were needed for restoration of normal heart rate or blood pressure.[12] The lower arterial blood pressure could be due to several factors: 1. Epidural clonidine decreases blood pressure at the brainstem level, thereby inhibiting sympathetic spinal cord outflow,[8] 2. The site of injection of intraspinal clonidine is important in determining its cardiovascular effect,[13] and the lower blood pressures noted in this study might have been related to the high thoracic

administration of the drug. The reduced heart rate observed in the clonidine group could have been caused by direct and central mechanisms.[14] Although there was no significant bradyarrythmias noted in this study requiring pharmacological intervention, precautions should be observed in patients with resting bradyarrythmias or on medications to slow the heart rate.

For more than a decade α_2 agonist have been used to provide preoperative sedation and anxiolysis and to decrease intraoperative anesthetic requirement.[4] Recently, this property has been explored for patients requiring postoperative sedation. This action of clonidine results from its effect on the locus ceruleus, the predominant noradrenergic nucleus in the brain.[15] This effect, however, was not evident in this study. This could be due to the fact that the degree of sedation correlates with systematic clonidine levels and is usually less with epidural administration due to reduced dose requirements.[16]

The incidence of side effects like respiratory depression and emetic symptoms were comparable in both groups. One of the concerns associated with use of epidural opioids is the relatively high incidence of urinary retention that requires catheterization. As expected, incidence of catheterization was significantly lower in the clonidine group.

The use of Clonidine by continuous epidural infusion for post-thoracotomy analgesia has been shown to be effective, safe, and acceptable. However, it is recommended that further studies be done to determine appropriate dose based on body weight so as to lessen the incidence of hemodynamic effects. Furthermore, intraspinal administration can be given at a lower level to minimize hypotensive episodes. Lastly, it is recommended that studies be made to determine the cost effectiveness of the use of clonidine.

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ORIGINAL ARTICLE

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Profile of Bronchiectasis at Lung Center of the Philippines

ABSTRACT

Objective

This study determined the clinical profile of patients with bronchiectasis at the Lung Center of the Philippines (LCP).

Methodology

This is a retrospective, descriptive study that reviewed charts of 80 patients at the LCP diagnosed to have bronchiectasis, from 2000 to 2002. Information gathered were plain or high-resolution computed tomography (HRCT) scans of the chest with their corresponding bronchiectasis protocol, as well as data on clinical presentation and severity based on clinical parameters. These materials were analyzed using descriptive statistics.

Results

The subjects' ages ranged from 14-74 years old with the highest frequency seen in the age distribution between 51-60. There was equal sex distribution. Thirty-four percent were lifetime nonsmokers. The most common childhood diseases were measles and rhinitis. The most common antecedent etiologic causes in adults were PTB, COPD, and aspergillosis. The most common symptoms were chronic sputum production, hemoptysis, and recurrent pneumonia. The usual physical examination finding was crackles. The most common radiologic findings were multiple cystic densities and atelectasis. All the subjects were classified as mild in terms of sputum years, volume, character, dyspnea grade, limitation in activity, and number of exacerbations. Half of the subjects had an abnormal acid-base balance. The most common spirometry finding was obstructive ventilatory pattern.

Conclusions

This retrospective study described the clinical presentation of bronchiectasis at LCP. Chronic sputum production in a previous history of pulmonary tuberculosis is the classic presentation of bronchiectasis at the Lung Center of the Philippines. HRCT of the chest is a reliable tool for a definite diagnosis.

Bronchiectasis refers to chronic irreversible dilatation of the diseased bronchi, and usually causes chronic sputum production, hemoptysis, or in a few instances may not cause any symptom at all. It has been described as cylindrical, varicose or cystic in type. The theories for the pathogenesis include obstruction, infection, and traction.[1] Before the advent of antibiotics, clinical features of patients with bronchiectasis usually reflected severe disease with persistent production of large volume of purulent sputum, recurrent hemoptysis, frequent infective exacerbations, finger clubbing, and obvious bronchiectatic changes on chest radiography.[2] Fewer patients now manifest such severity and the clinician may be presented with a few clinical clues to point to the diagnosis of bronchiectasis. In the absence of an underlying cause for the bronchiectasis, the most frequent past medical history presenting with idiopathic bronchiectasis is one with wheezy bronchitis early in life and with apparent remission around adolescence. Almost abruptly, a nonspecific respiratory or viral infection heralds a period of chronic purulent sputum production.[3] Because most patients now present with relatively mild bronchiectasis and few physical signs, the diagnosis can be made by a combination of medical history, chest radiography, and HRCT scan examination. Knowledge of the clinical profile of patients with bronchiectasis based on history, radiographic findings, and HRCT scan examination may help formulate a characteristic clinical picture, which will help us define a set of typical findings enabling prompt diagnosis of bronchiectasis.[4]

This study aimed to determine the clinical profile of patients with bronchiectasis at the LCP. Specifically, data on presenting signs and symptoms, common comorbidities, and severity of the disease were studied.

METHODOLOGY

This is a retrospective study where all patients diagnosed with bronchiectasis, either admitted or seen at the Outpatient Department of the LCP from the years 2000-2002 were included. The subjects were identified from their charts in the medical records. Bronchiectasis patients were identified by plain CXR or HRCT scan with a corresponding bronchiectasis protocol.

Data on the following were extracted from the medical chart: presenting signs and symptoms, sputum volume, sputum color and character, dyspnea grade, activity limitation, number of exacerbations, and spirometry results.

Data regarding clinical severity during stable conditions based on clinical parameters were analyzed using descriptive statistics.

RESULTS

Included were 80 subjects with ages ranging from 14 to 74 years old. The age distribution of subjects revealed the highest frequency in the 51- to 60-year-old age group. There was almost equal sex distribution. Thirty-four percent of the subjects were lifetime nonsmokers (Table 1). The two most common childhood diseases were measles (26.25%) and rhinitis (26.25%) (Table 2). PTB (77.5%) was the most common antecedent etiologic cause identified in adults, followed by COPD (21.25%) and Aspergillosis (11.25%) (Table 3).

The most common symptom was chronic sputum production (93.75%) followed by hemoptysis (73.75%)

Table 1. Profile of subjects

Charateristics	Frequency (%)
No. of patients	80
Sex	
Male	39 (51%)
Female	41 (49%)
Smoking history	
Smoker	9 (7.2%)
Ex-smoker	20 (16%)
Never	42 (33.6%)
No data	9 (7.2%)

Table 2. Associated childhood respiratory diseases

Childhood respiratory diseases	Frequency (%), n=80
Measles	21 (26.25%)
Rhinitis	18 (22.5%)
Recurrent pneumonia	5 (6.25%)
Asthma	1 (1.25%)
Tuberculosis	1 (1.25%)
Pertussis	0

Table 3. Associated adult respiratory diseases

Adult respiratory diseases	Frequency (%), n=80
PTB	62 (77.5%)
COPD	17 (21.25%)
Aspergillosis	9 (11.25%)
PTB 3	2 (2.5%)
Recurrent pneumonia	2 (2.5%)
Destroyed lung	1 (1.25%)
CA	1 (1.25%)

and recurrent pneumonia (20%). Usual findings on physical examination were crackles (58.57%) followed by clear breath sounds (32.5%). Radiographic review showed that multiple cystic densities (28.75%) and atelectasis (28.75%) were the most common findings (Table 4).

In determining severity, most of the subjects were classified as having mild bronchiectasis in terms of sputum volume, character, dyspnea grade, limitation in activity, and number of exacerbations (Table 5).

Table 4. History, PE, and radiographic findings

History, PE, and radiographic findings	Frequency (%), n=80
Symptoms	
Chronic sputum production	75 (93.75%)
Number of years	mean = 3.79
Recurrent pneumonia	16 (20%)
Recurrent hemoptysis	59 (73.75%)
Signs	
Crackles	47 (58.57%)
Clubbing	8 (10%)
Foul-smelling breath	4 (5 %)
Clear breath sounds	26 (32.5%)
Radiographic findings	
Multiple cystic densities	23 (28.75%)
Atelectasis	23 (28.75%)
Tram line or ring shadows	2 (2.5)
Fibrosis	2 (2.5%)
Infiltrates	2 (2.5%)
Normal	0

Table 5. Distribution of grading severity of clinical parameters

Clinical variables	Mild	Moderate	Severe
Sputum volume	54	20	1
Sputum color	52	23	4
Dyspnea grade	63	14	2
Limitation in activity	65	11	2
Number of exacerbations	43	27	9
Sputum years	40	25	13

Table 6. PFT and ABG results

PFT results	Frequency (%), n=80
Normal	3 (4%)
Obstructive	11 (14%)
Restrictive	20 (25%)
Obstructive with restrictive	19 (23%)
No data	27 (34%)
ABG results	**Frequency (%), n=80**
Normal	29 (36%)
Abnormal	40 (50%)
No data	11 (14%)

Obstructive ventilatory pattern, with or without a restrictive component, was the most common finding in spirometry. Half of the subjects had abnormal acid-base balance (Table 6).

DISCUSSION

Bronchiectasis as a pulmonary disease seems to be a common disease. There was a high incidence of post tuberculosis bronchiectasis in the ederly. Chronic sputum production and hemoptysis were seen in the majority of cases and crackles was the most frequent PE finding. Similar results were noted by Carter et al. on the most commonly observed signs and symptoms. In an article by Rivera et al., pneumonia was the most frequent etiology for childhood disease, followed by genetic disease, pertussis, and granulomatous disease. For the adult group, PTB was still the most common antecedent injury. Agrill stated that 50% of cases were idiopathic while in a study of Pastuer who evaluated 150 adults, 47% of cases had specific etiology and 29% were due to respiratory infection. The profile for this study, however, showed that pulmonary tuberculosis was the most common disease associated with bronchiectasis.

Being a retrospective study, many issues remain unsettled. Majority of the cases in the elderly population were associated with prior TB infection. In the younger age group, specific etiologies were not investigated. A thorough evaluation and investigation of the underlying genetic or acquired disease is recommended especially in the young. The advent of widespread antibiotic use has altered the presentation of the disease such that there are now only subtle and less severe clinical clues to suggest the presence of bronchiectasis. HCRT evaluation is a reliable and sensitive tool to diagnose bronchiectasis in a patient with chronic sputum production.

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World Health Organization. Hospital infection control guidelines for severe acute respiratory syndrome. April 16,

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