Philippine Journal of Chest Diseases
Volume Fifteen Number One January - April 2012

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Philippine Journal of Chest Diseases

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EDITORIAL

The Mind of the College

On behalf of the Editorial Board and Reviewers, I take great pleasure in presenting this “resurrection” issue of The Philippine Journal of Chest Diseases (PJCD) to those seeking to publish their works in areas of or relating to pulmonology and those who wish to keep up with the latest findings in their respiratory spheres of interest.

While the College and its membership promotes and guards the respiratory health of the Filipino through its various activities and advocacies, the PJCD acts as the printed manifestation of its pedagogic ideals and ambitions. What we know, how we acquire this knowledge and which pieces of knowledge we retain or evolve with further personal or professional searching … all these are gleaned from the pages and print that come to the attention of the respiratory public in particular and the medical community in general. The Journal is the expression of the PCCP’s mind.

The growth of our professional knowledge is dependent partly on experience which is serendipitous and unpredictable and on our active impetus to acquire learning which is self-driven and directed. It is along the line of the latter that we do research. However, “…research, no matter how ‘good’, is incomplete, until it has been published. Publication also serves as a benchmark, indicative of having achieved a certain academic standard. Besides communication of a finalized piece of research, the published work also acts as a starting point for additional opinions, criticisms, refutations and discussion—all part and parcel of the scientific process—from fellow professionals and academics separated by time and distance.”(1)

With this issue of the PJCD, we institute the process of peer reviewing all articles submitted for publication. “Unbiased, independent, critical assessment is an intrinsic part of all scholarly work, including the scientific process. Peer review is the critical assessment of manuscripts submitted to journals by experts who are not part of the editorial staff.”(2).

All articles in this and forthcoming issues have passed through the editorial eyes of expert consultants (content review) and assistant editors (technical review) who evaluate manuscripts in a “blind” manner such that they are unknown to the authors and vice-versa. The review process strikes the conciliating balance between science and experience in a profession where data and proficiency dictate practice. Thus, as editors and publishers, we are of the same mind as the late 18th century French-Swiss political propagandist and writer, Madame Germaine de Stael, who declared that “the search for the truth is the noblest occupation of man; its publication is a duty.”(3)

With the publication of this issue, we hope to carry the torch for that noble occupation. This issue not only spans time and topic, it interestingly delves into different intellectual playgrounds of current day respirology.

Three original researches on lung infections affirm the strong affiliations we maintain with our colleagues in the Infectious Disease specialty. The work of Benedicto et.al. on the incidence of active tuberculosis in health workers with latent tuberculosis points to a potential infectious disease epidemiologic problem for tertiary hospitals on a small scale and possibly the country on a national perspective. While the figures resulting from the results are, as yet, small in comparison
with other Asian countries, they must be taken as a wake-
up call in the environment of a nation where tuberculosis
is a heavy (high incidence, high prevalence) health burden
and where, therefore, the probability of this number
increasing rapidly is not a far reality. This opens the
door for the meta-analysis of Pablo et. al. which provides
options to the diagnosis of multidrug resistant tuberculosis
strains.

In the section of Respiratory Inspirations, Lanzona’s
dissertation encourages readers to revisit the time-proven
“basics” of thoracic auscultation and to consider that, in
the fringe of the future, this may no longer invoke the use
of the heretofore-revered physician-image-validating
stethoscope. It is a provocative consideration: technology
allows diagnostic refinements but, in the course of utilizing
these 21st century developments, will we lose the age-old
art of hands-on medicine of Hippocrates and Laennec?

We welcome the interest and contribution of non (as yet)-
 pulmonologists who boldly go beyond the cemented
boundaries of their internal medicine training program to
do a commendable meta-analysis of yoga in asthma.
While literature in this region is sparse, the global
economic environment as well as the desire of many to
avoid what they perceive as the harmful effects of
chemical compounds is driving a growing interest in
nonpharmacologic interventions that we must be aware
of, if not totally knowledgeable about.

The process of this Journal’s rebirth has made this
current Editorial Board appreciate the formidably
herculean efforts if must have taken for the previous
editors of the PJCD to launch and nurture the past
issues. We hope that our work today continues to fan
the flames of scholastic curiosity, scientific enthusiasm
and exciting intellectual reform that they unflaggingly
championed.

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The Incidence of Active Tuberculosis Among Health Workers with Latent Tuberculosis Infection in Tertiary Hospital Settings

Jubert P. Benedicto, MD, FPCP, FPCCP\textsuperscript{1}, Roentgene Solante, FPCP, FPSMID\textsuperscript{2}, Ma. Teresa Benedicto, MD FPCR\textsuperscript{3}

\textbf{ABSTRACT}

\textbf{Background}

Tuberculosis (TB) poses a significant occupational risk among healthcare workers (HCWs) in a TB high burden country. No data exist documenting the prevalence of latent TB infection (LTBI) and incidence of active TB among HCWs in the Philippines.

\textbf{Methodology}

We conducted a cohort study involving HCWs assigned in the medical wards and medical intensive care units of ten tertiary hospitals. LTBI was documented using tuberculin skin test utilizing a 2 TU-dose of PPD RT23 and a cut-off of at least 10mm in induration. HCWs were followed up over an approximate two year period and were monitored for active TB. Possible risk factors associated with these conditions were likewise identified.

\textbf{Results}

Out of 337 HCWs monitored, a total of 286 HCWs had PPD reactions of at least 10mm during the study period. The prevalence of LTBI in this cohort was computed to be 84.87\% (95\% CI, 80.59\%-88.52\%). The incidence of PPD conversion among those who were non-reactive at baseline was 22.73\% (95\% CI, 13.31\%-34.70\%) after one year. Odds ratios (OR) were likewise calculated to possibly look at the risk of LTBI per number of years of employment in their current work status and age. For tenure, the OR was equivalent to 1.12 (95\% CI, 1.02-1.24) and for age, the computed OR was 1.03 (95\% CI, 0.99-1.08). Nurses and nursing attendants were found to be at greater risk for acquiring LTBI compared to medical residents. The incidence of active TB was 1.4\% (95\% CI, 0.4\%-3.5\%). There were no variables significantly associated with the development of active disease.

\textbf{Conclusions}

HCWs were found to have a high prevalence of LTBI and relatively low incidence of active TB. These findings might have implications in screening and employment policies among HCWs and infection control strategies that should be employed in these tertiary settings.

Keywords: latent tuberculosis, healthcare workers
healthcare workers (HCWs) are always at the forefront in the care of patients who may be afflicted with infectious diseases. This puts this particular sector at risk of acquiring these diseases especially when these individuals are admitted in the hospitals and various health facilities and are not identified and diagnosed promptly. This dreadful scenario is very possible when one considers a disease like tuberculosis (TB).

Nosocomial transmission of tuberculosis is a well-documented occupational hazard in the United States and other industrialized countries, although the transmission is generally low. However, the risk may be increased in health care facilities located in communities with a high prevalence of TB infection. (1) In a study by Geronimo and colleague in a tertiary government hospital setting, 50% of those treated for nosocomial TB were utility workers and physicians. (2) De Vries et al reported 42% of TB cases were acquired at work. (3) The American Thoracic Society (ATS) and the Centers for Disease Control and Prevention (CDC) recommend the targeted tuberculin testing to detect latent TB infection (LTBI) in high risk population and subsequent treatment to prevent the development of active disease. (4) This strategy is commonly employed among immigrants from high burden TB countries and healthcare workers residing in a low burden setting for TB.

Skin-test conversion rates among health care personnel after routine skin testing have ranged from 0.11% to 10%. Among health care personnel with known exposure to an infectious patient with TB, the skin-test conversion rates have ranged from 18% to 55%. (1) Persons with latent tuberculosis infection are considered at highest risk of developing active disease during the first two years of infection, during which approximately 5% to 10% develop active disease. (5) Of those, 54% developed active TB during the first year while 82% developed within two years of infection.

Data on risk of transmission of Mycobacterium tuberculosis and the figures of infected HCWs and those with actual TB disease may be more worrisome in high burden countries especially those which are considered to belong to low-middle income brackets. A recently published systematic review examined the evidence on the incidence and prevalence of LTBI and TB disease among HCWs in low and middle-income countries. (6) This review demonstrated the prevalence of LTBI was, on average, 54% (range 33% to 79%) with estimates of the annual risk of LTBI ranged from 0.5% to 14.3%, and the annual incidence of TB disease ranged from 69 to 5780 per 100,000. The attributable risk for TB disease in HCWs, compared to the risk in the general population, ranged from 25 to 5361 per 100,000 per year. Furthermore, working in the general medicine wards was associated with a higher risk of acquiring TB disease.

In the Philippines, occupational risk assessment using the tuberculin skin test (TST) among health care workers is complicated by the higher transmission of the disease and the widespread use of BCG vaccination. The country is ninth among the top 22 high burden countries globally with the TB burden estimated to be 520/100,000 in terms of prevalence and an incidence of 260/100,000 claiming about 30,000 deaths per year (7). According to the 1997 TB National Prevalence Survey, the estimated overall prevalence of tuberculous infection was 62.5% based on a TST cut-off of e” 8mm. (8) There was a tendency to increase in older age groups with the maximum rate of 92.2% in the age group 50-59 years for males and 81.8% in the 40-49 years age group in females. In a meta-analysis by Tee in 1999, the TST administered and interpreted as recommended by the ATS was not able to differentiate infection with TB from that due to a previous BCG vaccination in underdeveloped countries. (9) However, Justimbaste and Roa found no significant association between the history of previous exposure to BCG vaccination and TST result. (10) These data make the significance of a positive purified protein derivative (PPD) result, which indicates infection, quite challenging. In addition, the value of subsequent chemoprophylaxis administration in immunocompetent adults in this context remains unsettled. The protective effects of chemoprophylaxis may be questionable if the development of active TB among adults with LTBI residing in a high TB and low HIV burden country may be relatively low. Currently, the National TB Program (NTP) in the Philippines focuses on passive case finding and treatment of active cases which is logical considering these realities and the available marginal resources.

Significance of the Study

Latent TB infection has been well studied and is the major target for further elimination and prevention of active TB disease in developed countries. In Asia, particularly in the Philippines, which is one of the high burden countries for TB but has a low prevalence for HIV infection (7), there is limited data on latent TB infection especially among healthcare workers. Some centers routinely screen for LTBI with PPD testing and give chemoprophylaxis to employees entering their first year of training. However, there is a relative lack of documented local evidence to support this practice especially in the value of giving chemoprophylaxis in immunocompetent adults perceived to be at high risk of developing the disease due to their
results of this study as far as these particular practices are concerned.

**PPD testing and interpretation:**

A training workshop for the PPD administration and interpretation before study initiation was conducted to standardize administration, measurement, and interpretation. Representatives from the infectious disease practitioners, TB program administrator, and nurses were invited as the main resource persons and trainers as they are more adept in this aspect. Only one to two persons from each site performed the administration and reading of the PPD reaction. Likewise, spot checks were conducted during the monitoring per site by the core investigators during the study period. These steps hopefully ensured uniformity with the performance and interpretation of the PPD.

The Department of Health (DOH) provided the solution used for PPD testing. As recommended in the Philippines NTP, we performed TST using a 2-TU dose of PPD RT23 (Tuberculin PPD RT 23 SSI Statens Serum Institut, Copenhagen, Denmark). The injection was given intradermally in the middle third of the volar aspect of the forearm. The solution was slowly administered until a small papule (8-10mm in diameter) appeared and remained for about 10 minutes. The reaction was evaluated after 48-72 hours after the injection with the diameter of the induration size measured using a standardized ruler.

A positive reaction to Tuberculin PPD RT 23 SSI is defined as a flat, slightly raised induration having a diameter of at least 10mm, surrounded by a more or less defined area of redness. Only the induration was assessed. If the induration was less than 10 mm, a repeat PPD testing after 2 weeks was performed (2-step tuberculin skin test or TST procedure). If the induration was still less than 10 mm after the second TST then a repeat PPD after one year was done unless the individual presented with symptoms suggestive of active TB disease for which he or she was adequately evaluated by the site investigator.

**Main Study Flow**

All potential subjects were oriented on the study and were asked to sign an informed consent if they agree to participate. Those whose consent were obtained underwent history taking and physical examination (PE) at baseline with due emphasis on possible current or past history of TB disease. Each participant also provided demographic data, employment background, BCG vaccination, and symptoms. We also obtained information on direct contact with a potential TB-afflicted individual both in the workplace and in the household. This was defined as contact between two people that is
of sufficient distance to allow conversation between them. (11) Data on smoking and alcoholic beverage drinking status and other medical conditions were likewise taken. BCG vaccine scar was ascertained by inspection. Those with an unremarkable history and PE subsequently underwent a standard chest radiograph PA view (CXR-PA). This imaging study should be unremarkable for them to undergo TST as discussed above at baseline. Their PPD reaction was documented and measured in millimeters.

The included study participants were monitored every six months for the duration of the study using a standard history and PE form. The site investigator may subject these individuals to certain diagnostic procedures like sputum smear microscopy and chest radiograph at any time based on his discretion to rule out active TB disease. Those with possible active disease will be referred to a facility with directly observed treatment short-course (DOTS) services. Routine chest radiographs were taken one year from their baseline visits. Those who were assessed to have a PPD induration of less than 10mm at baseline also underwent a repeat TST after one year. Their reaction was likewise measured and documented.

Any possible adverse reaction to the PPD administration was documented. Participants could withdraw anytime during the study duration for whatever reason they implicate. Subject retention strategies included one-on-one as well as group discussion and assurances and contacting these persons through emails and telephone.

The study was approved by the technical and ethical review board of each participating institution.

Operational Definitions:
For the purpose of this particular study, the following operational definitions were employed:

**Latent TB infection (LTBI):** those who are reactive to PPD defined as having an induration of at least 10 mm 48-72 hours from the administration of Tuberculin PPD RT 23 SSI injected in an intradermal manner at the volar surface of the forearm

**Active TB disease:** symptomatic individuals with radiographic findings suggestive of PTB. This may be bacteriologic proven cases either by AFB microscopy (smear positive) or M tb culture of appropriate specimens. In instances of smear negative cases, they should have no documented response to symptomatic treatment which might include a trial of an antibiotic course *and* there has been a decision by the attending physician to initiate anti-TB treatment.

**Recent converters:** those who are initially PPD negative and found to be PPD positive (at least 10 mm induration) within one year from the baseline PPD test

This study was conducted over approximately two years.

All asymptomatic (based on history and physical examination) healthcare employees with informed consent and unremarkable or normal CXR (immunocompetent) assigned in the general medicine service areas (wards or intensive care unit). This included institutionalized workers (IW), registered nurses (RN), nursing attendants / aides (NA), and doctors (residents) and fellows-in-training in adult pulmonary and infectious diseases.

Sampling method employed was stratified random sampling with proportional allocation.

**Statistical Analysis:**
The following statistical methods were utilized for data analysis:

i) The estimation of the prevalence of LTBI among HCWs and its 95% confidence interval.

ii) The estimation of incidence of LTBI which developed into active TB among HCWs with LTBI and its 95% confidence interval.

iii) The estimation of incidence of PPD skin test conversion among PPD negative HCWs and its 95% confidence interval.

iv) Logistic regression analysis to relate risk factors to the evaluation of conversion of LTBI to active TB.

**RESULTS**

The study was conducted from September 2008 to April 2011. Of 741 potential participants, 495 (66.8%) agreed to be involved in the study. During the screening and monitoring period, there were a total of 159 (32.12%) drop-outs and 337 had complete data and were available for analysis (please see Figure 1). Subjects were followed up over an average of 22.27 months (range: 3.87-26.73 months).

As depicted in Table 1, majority of the included subjects were females and belong to the relatively younger age group (< 40 years old). Medical residents and nurses comprised more than sixty percent of the study population with almost three fourths being five years or less in their current occupation. Although all of the health workers told the site investigators
that they received BCG vaccination, only 63% of the participants had a BCG scar present on inspection. Most (83.4%) had contacts with a possible TB patient in the workplace while only 21 (6.23%) reported TB contacts in their household.

All of the ten centers that participated were from urban settlements and were tertiary hospital institutions. The University of the Philippines-Philippine General Hospital (UP-PGH), a government teaching hospital which caters to a vast indigent population in the heart of Manila, accounted for more than a quarter (26.11%) of the subjects. Fourteen percent came from Manila Doctors Hospital (MDH) while Veterans Memorial Medical Center (VMMC) in Quezon City and De La Salle University Medical Center in Cavite each contributed around 12% of the study population.

### LTBI and Active TB

A total of 286 HCWs had PPD reactions of at least 10mm during the study period. The prevalence of LTBI in this cohort was computed to be 84.87% (95% CI, 80.59%-88.52%).

The incidence of PPD conversion among those who were non-reactive at baseline was 22.73% (95% CI, 13.31%-34.70%) after one year. Odds ratios (OR) were likewise calculated to possibly look at the risk of LTBI per number of years of employment in their current work status and age. For tenure, the OR was equivalent to 1.12 (95% CI, 1.02-1.24) and for age, the computed OR was 1.03 (95% CI, 0.99-1.08).

The risks for having LTBI considering the profession of study participants were quantified by calculating the odds ratios using the medical residents as the reference group. The results are summarized in Table 2. Our data signify that being a nursing attendant conferred a seven fold increase in risk of having LTBI compared to a medical resident. Being a nurse was also associated with a higher (three fold increase) risk of acquiring LTBI when compared to a medical resident.

There were four subjects who were judged to have active TB disease (two NAs, one nurse, and one medical resident). All of them were PPD reactive at baseline and presented with new-onset cough of more than two weeks which were unresponsive to antibiotics and symptomatic treatment. They all had infiltrates on CXR-PA film suggestive of PTB which were not present in their baseline chest radiographs. All of them were negative on direct sputum smear microscopy and were placed on six months of anti-TB medications under DOTS setting. In this study, the incidence of active TB disease among HCWs with LTBI was 1.4% (95% CI, 0.4%-3.5%).

Table 3 correlates some variables with the risk of having active TB. This was based on the information gathered during history taking and physical examination at baseline from included individuals. In a majority of instances, the risk was not that substantial considering the relatively small number of active TB disease cases that was observed during the study period.

Factors like past history of any lung disease, alcoholic beverage drinking, smoking, nature of work, duration of employment, result of TST at baseline, and the size of the induration as a reaction to TST seem to have no significant risk as to developing active TB.

### DISCUSSION

This study was conducted over approximately two years in ten centers involving HCWs principally assigned in the medical in-patient service areas of these hospitals. To our knowledge, this is the first of such study in the Philippines to document the burden of TB infection and TB disease in adults whose occupations are considered at high risk for this particular affliction.
Table 1. Participant Characteristics (n =337)

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<tr>
<td>20 - 30</td>
<td>195 (57.86%)</td>
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<td>31 - 40</td>
<td>107 (31.75%)</td>
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<td>41 - 50</td>
<td>20 (5.93%)</td>
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<td>51 - 60</td>
<td>13 (3.86%)</td>
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<td>&gt;60</td>
<td>2 (0.60%)</td>
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<td>Sex</td>
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<tr>
<td>Male</td>
<td>107 (31.75%)</td>
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<tr>
<td>Female</td>
<td>230 (68.25%)</td>
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<td>Job Category</td>
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<tr>
<td>Nurse</td>
<td>103 (30.56%)</td>
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<td>Nurse Attendants (NA)</td>
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<td>Institutional Worker (IW)</td>
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<td>Medical Resident</td>
<td>105 (31.16%)</td>
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<td>Fellows/ Medical Staff</td>
<td>41(12.17%)</td>
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<tr>
<td>Years Served in Current Occupation</td>
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<tr>
<td>&lt;1 year</td>
<td>137 (40.65%)</td>
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<td>2 - 5</td>
<td>115 (34.12%)</td>
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<tr>
<td>6 - 10</td>
<td>38 (11.28%)</td>
</tr>
<tr>
<td>&gt;10</td>
<td>47 (13.95%)</td>
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<tr>
<td>BCG vaccine scar present</td>
<td>212 (63%)</td>
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<tr>
<td>Had direct contact w/ a TB patient in the workplace</td>
<td>281 (83.4%)</td>
</tr>
<tr>
<td>Lived in a household w/ an individual w/ TB</td>
<td>21 (6.23%)</td>
</tr>
</tbody>
</table>

Table 2. Correlation of Occupation and LTBI

<table>
<thead>
<tr>
<th>Occupation</th>
<th>With LTBI (n=286)</th>
<th>Without LTBI (n=51)</th>
<th>Odds Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>M. Resident</td>
<td>59</td>
<td>23</td>
<td>—</td>
</tr>
<tr>
<td>Fellow/M. staff</td>
<td>31</td>
<td>9</td>
<td>1.34 (0.55-3.25)</td>
</tr>
<tr>
<td>Institutional Worker</td>
<td>14</td>
<td>0</td>
<td>No OR</td>
</tr>
<tr>
<td>Nursing Attendants</td>
<td>57</td>
<td>3</td>
<td>7.41 (2.11-26.03)</td>
</tr>
<tr>
<td>Nurse</td>
<td>125</td>
<td>16</td>
<td>3.04 (1.50-6.19)</td>
</tr>
</tbody>
</table>

* Medical residents was used as the reference group

Our results indicate a high prevalence of LTBI at 84.87% (95% CI, 80.59%-88.52%) among HCWs in these tertiary hospital settings utilizing the TST. The incidence of PPD conversion was documented at 22.73% (95% CI, 13.31%-34.70%) after one year. Among those with LTBI, the incidence of active TB disease was 1.4% (95% CI, 0.4%-3.5%). It was also observed that nurses and nursing attendants had a significantly higher risk of acquiring LTBI compared to medical residents.

**LTBI Among HCWs**

In the current study, the incidence of LTBI was calculated to be 54.95 per 100 person-years. The prevalence of LTBI in our included population is relatively higher compared to the national figure of 62.5%. This is in agreement with studies conducted using the TST as the diagnostic tool among low to middle-income countries with high prevalence of TB. In a review by Joshi, HCWs from these areas had estimates ranging from 0.5% to 14.3% in terms of annual risk of LTBI which is significantly higher compared to the general population. (6) Nurses, ward attendants, and clinical officers were found to be more at risk for acquiring the infection and disease compared to other hospital occupations. Among healthcare workers in India, a TST cut-off of 10mm was found in 41% (95% CI, 38.5-45%). (11) This similar trend was demonstrated in other high burden countries which used TST as the diagnostic tool to document TB infection demonstrating the higher risk among these working individuals. (12-16)

All of our study population was assigned to the medical inpatient services areas of hospitals. This may mean more contact with TB cases, either suspected or confirmed, in the course of their daily patient responsibilities. In UP-PGH for example, based on the monthly medical ward census, there are approximately more than 300 cases with TB as part of the diagnosis being admitted to two general medical wards with a combined capacity of 110 beds and with isolation spaces allotted for four patients with positive sputum smears. On an eight hour shift, the staff complement for a ward is as follows: around five nurses, three nursing attendants, and three institutional workers. In a review by Menzies and colleagues, it was estimated that the risk of exposure of HCWs can be considered high in hospitals with over 200 admissions per year or a ratio of fewer than ten workers per admission for TB per year. (17)

The nursing staff were found to be at a greater risk (three to sevenfold) for acquiring LTBI compared to medical residents. This finding is similar to previous studies which demonstrated that occupations with greater time in terms of patient contact and those whose tasks involved closer encounters with patients had a higher risk of acquiring TB infection and disease. (6, 13, 15, 16) Nursing attendants, nurses, and paramedical students were generally found to be at increased risk. This can be explained by the observation that the medical staff, in general, has shorter contact times in the course of their duties per patient compared to the nursing personnel. In addition, there are around 9-10 medical staff (residents, fellows, medical students) on the average, which rotate in a general medical ward and they do not routinely see all of the confined patients. This means that the contact time and the pos-
<table>
<thead>
<tr>
<th>Variables</th>
<th>Number of Patients</th>
<th>Odds Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>with Active TB (n=4)</td>
<td>Without Active TB (n=333)</td>
</tr>
<tr>
<td>Age Mean (SD)</td>
<td>38.5 (15.7)</td>
<td>31.17 (8.7)</td>
</tr>
<tr>
<td>Past history of lung disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>0</td>
<td>60</td>
</tr>
<tr>
<td>No</td>
<td>4</td>
<td>273</td>
</tr>
<tr>
<td>TB Exposure (Multiple exposure possible)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Household</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>0</td>
<td>21</td>
</tr>
<tr>
<td>No</td>
<td>4</td>
<td>259</td>
</tr>
<tr>
<td>Not sure</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Workplace</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>4</td>
<td>277</td>
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<tr>
<td>No</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Not Sure</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Occupation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nurse</td>
<td>1</td>
<td>149</td>
</tr>
<tr>
<td>Nursing Attendant (NA)</td>
<td>2</td>
<td>59</td>
</tr>
<tr>
<td>Institutional Worker (IW)</td>
<td>0</td>
<td>14</td>
</tr>
<tr>
<td>Medical Resident</td>
<td>1</td>
<td>82</td>
</tr>
<tr>
<td>Fellows/ Medical Staff</td>
<td>0</td>
<td>53</td>
</tr>
<tr>
<td>Smoking (in pack years) Mean SD</td>
<td>6.65</td>
<td>3.21 (7.31)</td>
</tr>
<tr>
<td>Alcoholic Beverage Drinker</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>0</td>
<td>179</td>
</tr>
<tr>
<td>No</td>
<td>4</td>
<td>153</td>
</tr>
<tr>
<td>BCG scar</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>2</td>
<td>210</td>
</tr>
<tr>
<td>No</td>
<td>2</td>
<td>121</td>
</tr>
<tr>
<td>TST at baseline</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥10mm</td>
<td>4</td>
<td>267</td>
</tr>
<tr>
<td>&lt;10mm</td>
<td>0</td>
<td>66</td>
</tr>
</tbody>
</table>

* Medical residents was used as the reference group to quantify risk of occupation

There appears to be no significant interplay as to the risk for infection and the duration of employment and age. For tenure, the OR=1.12 (95% CI, 1.02-1.24) and for age, the OR=1.03 (95% CI, 0.99-1.08). This trend seem to be different from other studies which demonstrated that HCWs who were more senior in terms of age and years of employment were found to be more at risk of acquiring infection (14, 15). Rafiza and colleagues documented an odds ratio of 9.49 (95% CI, 2.22-40.50) for HCWs aged 35 years and older in Malay-
sia. (15) Pai et al found a threefold increase of the prevalence of LTBI among HCWs who were employed for at least 10 years compared to those who worked less than a year. (11) They attributed this to the longer cumulative exposure to patients with TB. In our study, the current results may be explained by the profile of the cohort included having a large percentage of younger individuals and with 40% being less than a year in their current occupation. The time spent in their respective occupations may still not be of significant duration to observe results similar to the mentioned studies.

Sixty-three percent of our study population had BCG scars verified on inspection. Concerns regarding the impact of BCG vaccination on the results of TST have previously been addressed by previous studies. (10,11, 18-20) These investigations have demonstrated that there are no significant interaction between BCG vaccination, especially given during the neonatal period, and subsequent reaction to TST. Reactions to tuberculin rapidly wane after this period. (18) Wang et al, in a meta-analysis, have shown that the effect of BCG on PPD skin test results was less after 15 years from vaccination. (19) Therefore, the TST reactions documented in the present study were likely the result of tuberculosis infection rather than BCG vaccination.

**LTBI and Active TB**

Our study estimates that the incidence of active TB among HCWs with LTBI is 9.04 per 1,000 person-years. The figure of 1.4% (95% CI 0.4%-3.5%) is relatively low compared to similar studies done among HCWs in a high TB burden setting. (3,6,14) TB prevalence was documented to be 6.7/1000 among medical staff in a cross-sectional study in Henan, China. (14) A recent literature review by Baussano and colleagues has estimated the incident ratio at 3.7 (95% CI, 2.9-4.5) among HCWs residing in countries with high TB incidence. (21) In addition, the median estimated population-attributable fraction for TB was as high as 0.4% making this sector at higher than average risk for TB. This was in agreement with a previous systematic review among low- to middle-income countries which showed that the attributable risk for TB disease in HCWs, compared to the risk in the general population, ranged from 25 to 5,361 per 100,000 per year. (6).

The relatively low number of active TB cases documented during the study period may be attributed to the average of about a two year follow-up which might be considered short to observe these cases from developing. Similar studies that were conducted over at least five years, estimated higher incidence values. In India, among medical residents, the incidence was computed to be 11.2 per 1,000 person-years. (22) Another potential explanation may be the optimal infection control practice of these institutions which prevent the acquisition of TB disease among their hospital staff. Delays in diagnosis and initiation of treatment and possible failures in identifying and isolating infectious cases contribute significantly to transmission risk. (22) Having a comprehensive infection control plan which addresses issues related to administrative, engineering, and personal protective devices is consistently regarded as an effective barrier in reducing the TB burden among HCWs. (3, 17, 21-24) A simple starting strategy of identifying TB suspects and segregating infectious TB patients may be more feasible in most settings. (14) The present study was not designed to examine the impact of infection control strategies employed and their effectiveness.

All the four TB cases captured in the current investigation presented with cough which persisted after appropriate empiric management with new upper lobe infiltrate on chest radiograph and had negative AFB smear results. They had variable demographic data with the youngest being 25 years of age and being less than two years employed in the institution. The oldest was sixty years old having spent 34 years at his current employment. Their TST induration ranged from 10mm to 21mm. All of them underwent a six month anti-TB regimen under DOTS conditions. They were all asymptomatic after the treatment period.

Effective screening for TB infection and active disease and subsequent management are always challenging among this particular workforce sector. It has been recommended that routine LTBI testing be done among HCWs and the possibility of offering preventive therapy in order to reduce the chances of developing active TB. (22) However, its effectiveness and feasibility may raise relevant issues when proposed in a high TB burden and marginal-resource setting. In a study in Netherlands with a cohort of all TB patients over a five year period, the median interval between infection and TB disease was 32 weeks. (3) There was also a relatively short interval between infection and disease for HCWs who presented with symptoms. However, three out of the eight individuals given isoniazid preventive treatment over six months still developed TB. Evaluation of the symptomatic healthcare
worker for active TB may be practical and may entail lesser costs. The health-seeking behavior of these hospital employees may be crucial in this regard as well as the high index of suspicion for TB of the physician doing the screening and evaluation. A responsive attitude among HCWs may be warranted to effectively implement such strategies. Educations as well as training of HCWs are practical starting points in resource-limited settings (14).

CONCLUSIONS

Our study documented the high prevalence rate of LTBI among HCWs assigned in the medical service areas of ten tertiary hospitals in the Philippines. Nurses and nursing attendants were relatively at higher risk of acquiring the infection compared to medical residents in this setting. There was a relatively low incidence rate of active TB disease among these infected HCWs over the two year study period. There was no significant risk factor that was identified to be associated with the development of active TB during the study duration. Our findings may have implications in terms of screening and employment policies and infection control strategies being employed in tertiary hospital settings.

Limitations

Participants in the study were followed up over around two years (average of 22.27 months with a range of 3.87-26.73 months). This might be perceived as relatively short to adequately capture those who may possibly develop active disease among those with LTBI. The study initiation and follow-up among these identified participants in these ten centers were quite challenging considering the very dynamic nature of the population. The final sample size of 337 was less compared to the calculated size of 380. Almost one-third (32.12%) of the population who consented dropped out during the study period. Majority of the reasons given revolved around the TST procedure and interpretation of results: that the results may have employment implications (hiring and retention), it might affect their employment chances abroad, and the perceived pain associated with the procedure. Majority of those who dropped out during the monitoring were nurses who resigned from their posts and sought employment abroad.

The figures here on infection prevalence and disease incidence may be underestimates considering the true burden of TB among HCWs. Senior staffs like consultants and nurse supervisors were not included but may have greater risks considering the relatively longer time they have spent in their respective institutions. On the other hand, the junior staffs like the medical and nursing students were also not included but may be at risk because their training requires them to be at closer contacts with patients at short intervals.

The study was not designed to distinguish if the infection was acquired from the community or the hospital. In addition, we also did not formally evaluate current infection control strategies and practices among the HCWs and institutions which might have interplay with the occurrences of LTBI and active disease.

Recommendations

The following may be viable options as a follow-up or offshoot of the current study:

• Extend the study observation/monitoring period to five years. This may capture other cases that may develop during this period.

• Compare newer diagnostic tools like IGRAs (interferon gamma release assays) among these HCWs. The performance of IGRA may be compared to TST especially in a high TB burden setting with high BCG vaccination rates.

• Do a similar study among DOTS center staff. This population may be considered at a higher risk because the factors identified may be doubly present in this set-up.

• Examine the value of chemoprophylaxis among this high risk sector. The incidence of active TB in our study was 1.4%. The cost effectiveness of giving preventive therapy in such a set-up should be closely investigated.

References


2. Geronimo, R et al. Tuberculosis among employees in Philippine General Hospital (unpublished)


9. Tee, ML. The role of mantoux skin test in the diagnosis (unpublished)


This study was accomplished with the help of the PCCP TB Council and the LTBI Study Group. It was mainly funded by the Philippine Council for Health Research and Development (PCHRHD) with partial funding from Philippine Tuberculosis Society, Inc (PTSI) and the cooperation of the Philippine College of Physicians (PCP).
Comparison of Bronchoscopy and Sputum Induction Techniques in the Diagnosis of Sputum Smear-Negative Pulmonary Tuberculosis: A Meta-Analysis

Maria Philina B. Pablo, MD, FPCP1, Norman Maghuyop, MD, FPCP, FPCCP2, Aileen David-Wang, FPCP, FPCCP3, Valerie Gilbert Ulep4

ABSTRACT

Introduction:
Sputum microscopy remains the initial test of choice for patients symptomatic of tuberculosis but this does not always reveal acid-fast bacilli. Such patients are recommended to undergo further tests including fiberoptic bronchoscopy and sputum induction. This study aims to compare the diagnostic test characteristics, sensitivity, specificity and accuracy of sputum induction and bronchoscopy techniques in the diagnosis of PTB among symptomatic, sputum smear-negative patients.

Methods:
Search was done through MEDLINE, the Cochrane Controlled Trial Register http://clinicaltrials.gov, and bibliographies of relevant trials to obtain studies meeting inclusion criteria. Two investigators independently extracted data and assessed for quality. Sensitivity and specificity, diagnostic odds ratios and their forest plots as well as the SROC curve and its area under the curve (overall summary of test performance) were determined for each test. Heterogeneity and publication bias were also analyzed. Analyses were performed using statistical software (Stata, version 10.0).

Results:
Five prospective studies were obtained. The pooled summary indices showed that for sputum induction, the sensitivity is 0.57 (95% CI, 0.51 to 0.63) and specificity is 0.99 (95% CI, 0.97 to 1.00). Whereas for bronchial lavage, the sensitivity is 0.42 (95% CI, 0.34 to 0.51) while specificity is 0.99 (95% CI, 0.97 to 1.00). The summary DOR for sputum induction was 43.32 meaning sputum induction test had a higher level of overall accuracy (95% CI, 291 to 634) while the summary DOR for bronchial lavage was 34.6 (95% CI, 5.85 to 204.62). Sputum induction showed more heterogenous results for sensitivity (chi-square=48.5, p=0.000) compared to bronchial lavage (chi-square=10.17, p=0.0172). There was no significant heterogeneity among the specificities for both sputum induction and bronchial lavage (chi-square=6.13, p=0.19).

Conclusions:
Sputum induction has better sensitivity, comparable specificity and higher level of overall accuracy compared to bronchial lavage in diagnosing sputum smear negative tuberculosis. It is our recommendation that sputum induction be used first if there is a need to further obtain sputum specimen for patients suspected of having tuberculosis that have negative spontaneous sputum smears or are unable to produce sputum spontaneously. Sputum induction is simpler, has lower cost and is a well-tolerated procedure with reduced risk of nosocomial transmission and thus be very helpful in a resource poor area.

Keywords: Sputum induction, Bronchoscopy, Pulmonary tuberculosis
uberculosis (TB), an important preventable and treatable cause of death, is a major health problem worldwide (1). It is the sixth leading cause of morbidity and mortality in the Philippines. The latter ranks ninth among 22 high TB burden countries and third in the Western Pacific region (2). The 2008 World Health Organization Report on Global Tuberculosis Control pegs the incidence of tuberculosis in the Philippines at 287 cases per 100,000 population per year while mortality is estimated at 45 deaths per 100,000 population per year (3). Early detection of active pulmonary tuberculosis (PTB) in affected patients is an essential and integral component of tuberculosis control, as consequent timely and appropriate treatment renders these patients noninfectious and interrupts the chain of disease transmission. Local clinical practice guidelines (CPGs) recommend sputum smear microscopy to detect acid-fast bacilli (AFB) as the screening laboratory examination of choice in the work-up of symptomatic patients suspected to have pulmonary tuberculosis. The test is easily taught to local health center personnel and the materials and equipment required are easily available, accessible and affordable. It is rapid, efficient, highly specific and does correlate well with infectiousness. All Filipino patients who present with cough of two weeks or more should preferably have three, but at the least two sputum AFB smear testing [Grade A Recommendation] (2).

However, the sensitivity of the AFB smear method is moderate at best; a local study reports a rate of only 51.8%, with the positive predictive value and negative predictive value at 76.3% and 93.0%, respectively (16). Furthermore, the diagnostic yield decreases with the number of sputum specimen submitted for examination. Mycobacterial culture, considered the gold standard in the diagnosis of tuberculosis, requires at least six to eight weeks of processing time and hence, is not useful as a screening test (2).

This study is a meta-analysis which aims to compare the diagnostic test characteristics of sputum induction and bronchoscopy techniques in the diagnosis of PTB among symptomatic, sputum smear-negative patients. Specifically, it aims to determine and compare the sensitivity, specificity and accuracy of sputum induced by hypertonic saline nebulization and bronchoalveolar lavage in detecting acid-fast bacilli and to draw and compare their summary receiver operating characteristics curves.

**Literature Search**

Publications containing the search terms “bronchoscopy”, “sputum induction” and “tuberculosis” were identified by searching the MEDLINE database, from January 1, 1966 to February 28, 2010, and the Cochrane Controlled Trial Register. Bibliographies of all relevant articles were reviewed to search for additional eligible studies. Likewise, references of review articles and observational studies were hand-searched. The search was limited to English-language studies. Only data accessible in peer-reviewed journals were included to minimize potential sources of bias and inaccuracy. Authors of studies published in abstract form were contacted. Clinical trials published with the U.S. National Institutes of Health were likewise screened via http://clinicaltrials.gov.

**Inclusion Criteria**

Studies were included in the analysis if they prospective studies which compared the diagnostic utility of sputum induction with fiberoptic bronchoscopy techniques. The study population should have included adult patients or mostly adult patients with symptoms of PTB who were unable to produce phlegm, or the spontaneously expectorated sputum smears were negative for AFB.

**Exclusion Criteria**

Studies were excluded if they focused only on children and if tests for obtaining sputum other than bronchoscopy and sputum induction were used.
Data Extraction

Studies were screened for inclusion by one author and final decisions on exclusion were made by consensus. Two investigators independently extracted the data, including patient characteristics, study design, study inclusion/exclusion criteria, setting, year of publication, country of origin, diagnostic technique description, sensitivity, specificity, positive predictive value, and negative predictive value. The diagnostic test characteristics were manually computed from the given data, if not explicitly stated.

Quality Assessment

Studies included in the meta-analysis were assessed for quality, as suggested by a previously reported standard by Whiting et al in 2003 (See Appendix 1). This was carried out by two authors, blinded to the identity of the study authors, their institution and journal name, working independently. Any disagreement was resolved by consensus. Data were recorded separately for the appropriate diagnostic group. Discrepancies were resolved by discussion until consensus was achieved for all data.

Quality assessment was particularly focused on whether the authors clearly enrolled the desired patient population; whether the two diagnostic tests were compared; whether all the techniques employed in the study meet current standards; whether Mycobacterial culture was used as the reference standard; whether test results were interpreted appropriately; and whether the report presented the results with sufficient detail so that the study could be replicated. Our study selection criteria required fulfillment of most of the quality standards.

Statistical Analysis

Sensitivity, specificity, and predictive values for each study were calculated from the original data by comparing the proportions of positive and negative AFB smears and mycobacterial cultures among subjects randomized to sputum induction or BAL. Sensitivity was defined as the percentage of patients with a diagnosis of tuberculosis by sputum induction or bronchoscopy AFB smear who were correctly found to be positive using culture. Specificity was the percentage of patients with negative sputum induction or bronchoscopy AFB smear results correctly identified by a negative result from sputum culture.

Two methods were used to summarize the data. Diagnostic odds ratio is a measure of overall diagnostic power of a test. It describes the odds of positive test results in participants with the disease compared with the odds of positive test results in those without the disease. The DOR has the advantage of allowing the inclusion of covariates to examine heterogeneity. It combines the strengths of sensitivity and specificity into a single number with the advantage of accuracy as a single indicator. The value of DOR ranges from 0 to infinity with higher values indicating better discriminatory test performance (i.e. higher test accuracy). The diagnostic odds ratio was independently combined for sputum induction and bronchoscopy across the studies by using a random-effects model.

As a complementary method to summarize the data, the summary receiver-operating characteristic (SROC) curve and its area under the curve present an overall summary of test performance and display the trade-off between sensitivity and specificity. An SROC curve plots the true-positive rate (sensitivity) on the y-axis against the false-positive rate (1 - sensitivity) on the x-axis for each study. Estimating mean sensitivity and specificity alone without looking at the area under the SROC curve may result in underestimation of test accuracy. The diagnostic test is constant throughout the studies, so the AUC reflects overall performance of that test. The perfect test will have an AUC of one. The SROC is reproducible and thus the AUC can be used to compare accuracy of different diagnostic tests. A fair test shows better than average accuracy and has an AUC above 0.5. To demonstrate excellent accuracy, the AUC should be in the region of 0.97 or above. An AUC
of 0.93 to 0.96 is very good; 0.75 to 0.92 is good. Less than 0.75 can still be reasonable (15).

Q is the intercept of the SROC and the antidiagonal line through the unit square. Its value indicates overall accuracy by finding where sensitivity and specificity are the same. The overall accuracy may be determined but it does not indicate the overall sensitivity which would be more useful clinically.

To detect heterogeneity, the likelihood ratios and diagnostic odds ratios (DORs) were graphically displayed using forest plots and were analyzed using chi-square test to detect heterogeneity. The F statistic was used to measure the percentage of variability among summary indices that were caused by heterogeneity rather than by chance. A study with $F > 50\%$ showed substantial variability. Publication bias was evaluated by visual inspection of funnel plots and statistically using Egger regression model. Analyses were performed using statistical software (Stata, version 10.0).

**RESULTS**

**Study Search Flow**

Extensive search made via Cochrane, registered clinical trials and MEDLINE database (January 1, 1966 to February 28, 2010) using Mesh search terms “bronchoalveolar lavage”, “sputum induction” and “tuberculosis” yielded 10 articles (See Figure 1). All of the studies were prospective, cross-sectional studies. There was no randomized controlled clinical trial obtained. Three studies were excluded because they involved sputum induction only while one study employed bronchoscopy only. One study compared spontaneous sputum with sputum induction. Another study was excluded because it was retrospective and another one involved only children. Additional search of the references cited by the studies included two more articles. The full text articles of the study by Conde et al. were obtained from PubMed. The other full text articles were obtained by correspondence with the authors/publishers. After an exhaustive search, a total of 5 prospective cohort articles involving mostly adult patients suspected of PTB but were either sputum smear negative or were unable to produce sputum spontaneously were included.

**Study/ Patient Characteristics and Study Quality**

The studies obtained were critically appraised by two independent authors, Rating differences were resolved by consensus. Table 1 shows the summary of the characteristics of the studies included in the meta-analysis. Five prospective studies fulfilled the inclusion criteria and were included in the analysis. The studies involved 579 patients, 61.8% are males, 38.3% are females. All patients were either unable to produce sputum spontaneously or have sputum AFB smears on spontaneous sputum production. Both sputum induction and bronchial lavage were used to obtain specimen for AFB smear and mycobacterial culture, the latter being the reference standard. The studies fulfilled most of the criteria in the quality assessment for studies of diagnostic accuracy (QUADAS) tool. The QUADAS score for each study are also shown in Table 1.
Table 1. Characteristics of studies included in the analysis

<table>
<thead>
<tr>
<th>Authors</th>
<th>Year</th>
<th>Country</th>
<th>Study Design</th>
<th>Participants N</th>
<th>Sex Age</th>
<th>AH Score</th>
<th>Mycoplasma spp. culture</th>
<th>Bronchoscopy technique</th>
<th>Quality Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Andrés, et al</td>
<td>1995</td>
<td>Canada</td>
<td>CRP</td>
<td>53</td>
<td>Adults</td>
<td>41</td>
<td>Ziehl-Neelsen staining</td>
<td>Middlesex agar, Bacter Coryne</td>
<td>70:30 ml 3% hypertonic saline via ultrasonic nebulizer</td>
</tr>
<tr>
<td>Casela, et al</td>
<td>2001</td>
<td>Brazil</td>
<td>CRP</td>
<td>251</td>
<td>Adults</td>
<td>37</td>
<td>Ziehl-Neelsen staining</td>
<td>Londerman-Jensen media</td>
<td>3% hypertonic saline via ultrasonic nebulizer</td>
</tr>
<tr>
<td>McWilliam, et al</td>
<td>2002</td>
<td>New Zealand</td>
<td>CRP</td>
<td>29</td>
<td>Adults</td>
<td>81</td>
<td>Ziehl-Neelsen staining</td>
<td>Bacteriolytic L. Jensen media</td>
<td>20 ml 3% hypertonic saline via ultrasonic nebulizer</td>
</tr>
<tr>
<td>Sazanka, et al</td>
<td>2005</td>
<td>Turkey</td>
<td>CRP</td>
<td>55</td>
<td>Mostly adults</td>
<td>35.8</td>
<td>Ziehl-Neelsen staining</td>
<td>Londerman-Jensen media</td>
<td>3% hypertonic saline via ultrasonic nebulizer</td>
</tr>
<tr>
<td>Gombytė, et al</td>
<td>2008</td>
<td>India</td>
<td>CRP</td>
<td>52</td>
<td>Adults</td>
<td>52</td>
<td>Ziehl-Neelsen staining</td>
<td>Londerman-Jensen media</td>
<td>55 ml 3% saline using jet nebulizer</td>
</tr>
</tbody>
</table>

CRP: cross-sectional prospective, NH: not indicated.
**Figure 2.** Forest plots of sensitivity and specificity of sputum induction for the diagnosis of sputum smear negative tuberculosis

- **Sensitivity (95% CI)**
  - Anderson: 0.18 (0.04 - 0.43)
  - Conde: 0.34 (0.23 - 0.47)
  - Ganguly: 0.74 (0.57 - 0.87)
  - McWilliams: 0.77 (0.67 - 0.85)
  - Saglam: 0.46 (0.27 - 0.67)

- **Specificity (95% CI)**
  - Anderson: 0.97 (0.91 - 1.00)
  - Conde: 1.00 (0.97 - 1.00)
  - Ganguly: 1.00 (0.77 - 1.00)
  - McWilliams: 0.97 (0.82 - 1.00)
  - Saglam: 1.00 (0.88 - 1.00)

- Pooled Sensitivity = 0.57 (0.51 to 0.63)
- Chi-square = 48.50; df = 4 (p = 0.0000)
- Inconsistency (I-square) = 91.8 %

- Pooled Specificity = 0.99 (0.97 to 1.00)
- Chi-square = 6.13; df = 4 (p = 0.1899)
- Inconsistency (I-square) = 34.7 %

**Figure 3.** Forest plots of sensitivity and specificity of bronchoscopy for the diagnosis of sputum smear negative tuberculosis

- **Sensitivity (95% CI)**
  - Anderson: 0.09 (0.00 - 0.41)
  - Conde: 0.38 (0.27 - 0.50)
  - Ganguly: 0.57 (0.37 - 0.75)
  - Saglam: 0.52 (0.33 - 0.71)

- Pooled Sensitivity = 0.42 (0.34 to 0.51)
- Chi-square = 10.17; df = 3 (p = 0.0172)
- Inconsistency (I-square) = 70.5 %

- **Specificity (95% CI)**
  - Anderson: 0.98 (0.91 - 1.00)
  - Conde: 1.00 (0.97 - 1.00)
  - Ganguly: 1.00 (0.85 - 1.00)
  - Saglam: 1.00 (0.87 - 1.00)

- Pooled Specificity = 0.99 (0.97 to 1.00)
- Chi-square = 4.65; df = 3 (p = 0.1991)
- Inconsistency (I-square) = 35.5 %
Quantitative Data Synthesis: Sensitivity and Specificity

Figure 2 shows the forest plot of the sensitivity and specificity of sputum induction on all the studies while figure 3 illustrates the forest plot of the sensitivity and specificity of bronchial lavage for four studies. The pooled summary indices showed that for sputum induction, the sensitivity is 0.57 (95% CI, 0.51 to 0.63) and specificity is 0.99 (95% CI, 0.97 to 1.00). Whereas for bronchial lavage, the sensitivity is 0.42 (95% CI, 0.34 to 0.51) while specificity is 0.99 (95% CI, 0.97 to 1.00). Heterogeneity was also demonstrated in the forest plots. Quantitative measurement of heterogeneity was made using chi square test. Sputum induction showed more heterogenous results for sensitivity (chi-square=48.5, p=0.000) compared to bronchial lavage (chi-square=10.17, p=0.0172). There was no significant heterogeneity among the specificities for both sputum induction (chi-square 4.65, p=0.1991) and bronchial lavage (chi-square=6.13, p=0.19).

The F² for the sputum induction sensitivity values was 91.8% while F² for specificity was 34.7%. On the other hand, the F for the bronchial lavage sensitivity values was 70.5% while F² for specificity was 35.5% These values reflect substantial statistical heterogeneity for the sensitivity of both diagnostic tests.

Quantitative Data Synthesis: DORs and sROCs

The summary DOR for bronchial lavage was 3.27 (95% CI, 2.17 to 3.92) while the summary DOR for sputum induction was 43.32 meaning sputum induction test had a higher level of overall accuracy (95% CI, 12.74 to 147.26). The DOR values for both tests are illustrated in Figure 4.

**Figure 4.** Summary of Diagnostic Odds Ratio for sputum induction (A) and bronchoscopy (B)

**Diagnostic OR (95% CI)**

- **A**
  - Anderson: 7.82 (1.20 - 51.17)
  - Conde: 144.89 (8.64 - 2,429.94)
  - Ganguly: 78.71 (4.30 - 1,440.09)
  - McWilliams: 92.52 (11.93 - 717.60)
  - Saglam: 50.86 (2.81 - 920.46)

  Random Effects Model
  - Pooled Diagnostic Odds Ratio = 43.32 (12.74 to 147.26)
  - Cochran-Q = 5.12; df = 4 (p = 0.2755)
  - Inconsistency (I-square) = 21.8%
  - Tau-squared = 0.4272

- **B**
  - Anderson: 3.95 (0.33 - 47.59)
  - Conde: 158.35 (9.50 - 2,639.76)
  - Ganguly: 58.33 (3.24 - 1,050.64)
  - Saglam: 56.66 (3.15 - 1,017.40)

  Random Effects Model
  - Pooled Diagnostic Odds Ratio = 34.60 (5.85 to 204.62)
  - Cochran-Q = 4.97; df = 3 (p = 0.1743)
  - Inconsistency (I-square) = 39.6%
  - Tau-squared = 1.3018
The SROC curves for each test is shown in figures 5 and 6. Our data for sputum induction showed an AUC of 0.9677 and Q’ point of 0.0162. On the other hand, the data for bronchial lavage showed an area under the curve value (AUC) of 0.9812 and Q’ point of 0.9394. Based on this analysis, bronchial lavage has better overall accuracy than sputum induction.

Publication Bias Measurement

The result of the Egger regression test for publication bias was not significant for both bronchial lavage (p=0.919) and sputum induction (p=0.515) indicating no small-study effects and insignificant publication bias. The funnel plots for both tests, as represented in figure 7, showed symmetry.

The funnel graph plots the log of the DOR against the SE of the log of the DOR. The dashed line indicates 95% confidence limits of the log of the DOR. The funnel plots show approximate symmetry. The result of the Egger test for publication bias was not significant both for sputum induction (0.515) and bronchial lavage (p =0.919).

DISCUSSION

The results of this systematic review and meta-analysis indicate that sputum induction is comparable to bronchial lavage in diagnosis of sputum negative tuberculosis. Overall sensitivity of sputum induction was higher than that of bronchoscopy while specificity was the same for both.

The study of Anderson et al. in 1995 reported low sensitivity of direct AFB smear of specimens from both techniques (6). Conde et al in 2000, concluded in their study that sputum induction had a high diagnostic yield and was in
agreement with the results of fiberoptic bronchoscopy for the diagnosis of PTB in both HIV seronegative and HIV-seropositive patients (7). The study of McWilliams et al in 2002 showed that bronchial lavage had no positive AFB smear yield hence sensitivity was 0 for this test (5). The forest plot for bronchial lavage thus did not include this study. The study of Saglam et al, in 2005 concluded that sputum induction has a higher sensitivity rate than spontaneous sputum for the detection of tuberculosis, and fiberoptic bronchoscopy is useful for the early diagnosis of tuberculosis when AFB are not detected in spontaneous or induced sputum specimens (9). Lastly, Ganguly et al in their study in 2008, showed that the yield of sputum induction were significantly more than that of bronchoalveolar lavage for the diagnosis of PTB (4). The reported sensitivities of the induced sputum and bronchial lavage techniques differ greatly from one report to another. In this context, a metaanalysis can provide an overall summary of diagnostic accuracy.

The low yield of bronchoscopy in the study of McWilliams was attributed to the possibility that less trained bronchoscopists led to the underdiagnosis of TB. Moreover, since lidocaine can inhibit the growth of Mycobacterium in vitro, the use of more lidocaine may have led to apparent false negative rates in McWilliam’s study although the amount used in the study was not mentioned. It was just suggested that less experienced bronchoscopists used more anesthesia. But note that in the study of Saglam, more local anesthesia was used compared to that of Anderson’s but the latter showed less sensitive bronchial lavage findings. The actual effect of lidocaine on the yield of bronchoscopy may warrant further investigation.

Another explanation offered for the decreased sensitivity of bronchial lavage in McWilliams’ study was that the volume of lavage fluid used was 40 ml per segment whereas Anderson et al used 50-60 ml. Conde et al having done bronchoalveolar lavage supposedly used substantially larger volumes. Such differences in technique may explain the heterogeneity more significantly noted in the bronchoscopy results in all the included studies (5).

Other factors which may have contributed to the differences in results include the use of different nebulizers in sputum induction. Ganguly used a Jet nebulizer while Conde and Anderson used ultrasonic nebulizer. Mycobacterium culture was done using solid medium in the study of Ganguly.
whereas both solid and liquid media were used in Conde and Anderson’s studies (4).

However, McWilliams indicated that rather than bronchoscopy causing underdiagnosis of TB, it may have been that there was underestimation of the diagnosis of TB in the study of Anderson et al and Conde et al since they used only single induced sputum test whereas McWilliams obtained three induced sputum specimens (5).

The disadvantage of sputum induction include the risk of transmission of TB but this is lesser compared to bronchoscopy where there conduct of the procedure would require the presence for more medical personnel (5). The adverse effects noted with sputum induction in the studies were mostly minor and these included minimal, short-lived and rarely persistent cough, headache, dizziness and dyspnea (4) (10).

On the other hand, bronchoscopy is a more invasive procedure and often would require sedation. The risk for nosocomial infection, although low, is present in bronchoscopy. Adverse events noted with this procedure include persistent cough, headache and dyspnea (4) (10).

On the other hand, the advantage of bronchoscopy is that specimens can be obtained from specific area of the lung (12).

In terms of cost, cost-analysis done by McWiliams showed that the cost of bronchoscopy alone per case diagnosed is tenfold greater compared to three sputum inductions. Anderson also showed that direct costs of induced sputum was substantially lower than the costs of bronchoscopy. The time spent in the hospital was also significantly more for bronchoscopy (about half day on average) than sputum induction (about one hour) (9). Indirect costs such as lost wages were also greater for bronchoscopy where patient may lose half of a working day for the procedure.

This meta-analysis shows that there is a significantly greater diagnostic yield for TB with induced sputum testing than with bronchoscopy. The overall diagnostic power of sputum induction is greater compared to bronchoscopy as reflected by the diagnostics odds ratio. The AUC showed that bronchoscopy has better test accuracy but this is not reliable since the SROC had less than 10 study points.

Sputum induction also proves to be more cost-effective and convenient to use. It is our recommendation that sputum induction be used first if there is a need to further obtain sputum specimen for patients suspected of having tuberculosis that have negative spontaneous sputum smears or are unable to produce sputum spontaneously. This is particularly since sputum induction is simpler, has lower cost and is a well-tolerated procedure with reduced risk of nosocomial transmission. It would thus be very helpful in a resource poor area.

Bronchoscopy may still be used if investigation for other pathologies included in the differential diagnosis is called for. And in certain instances such as clinical suspicion of lung cancer or other non tuberculous conditions, sputum induction certainly can not replace bronchoscopy.

Limitations of the Study

Although other tests have been proposed for further evaluation of sputum smear-negative tuberculosis, this study aims to compare sputum induction and bronchoscopy as means of obtaining specimen for diagnosing pulmonary tuberculosis. All studies included were prospective, cohort studies as no randomized controlled trial on the subject has been published as of the time of literature search. It was assumed that all of the techniques used for each study followed current standards and are similar (thus comparable). However, our results are limited by the lack of formal RCTs and by the heterogeniety of the data. This can be attributed to the differences in the techniques in each study (e.g. duration of sputum induction, amount of anesthesia , amount of BAL fluid, expertise of the bronchoscopist).
In terms of AUC, bronchial lavage has better overall accuracy. However, in this study, there are several limitations of SROC (from which AUC was derived). According to literature, ten or more data points are needed to make the assumption that the data points are normally distributed in the SROC. And for SROC to be valid, there should be similarity of study methodology and quality, diagnostic threshold, study end points and test variables. There are some differences in the methodologies of the studies included albeit study endpoints and test variables are the same. Still, the small number of data points/studies used in this analysis makes the SROC analysis not very reliable. Moreover, the probability of the disease associated with test outcomes was not computed in the study.

Microbiologic confirmation of PTB among symptomatic patients whose spontaneously expectorated sputum smear is negative has become increasingly important because of the emergence of drug-resistant strains and the need for timely treatment.

CONCLUSION

This systematic review of 5 prospective studies showed that sputum induction technique has greater sensitivity, comparable specificity and higher level of overall accuracy, compared to BAL, in detecting active PTB.

Thus, sputum induction – a less invasive, cheaper and easily performed test – can be recommended for adult patients with symptoms of PTB but are unable to produce phlegm or are sputum smear negative, in lieu of more invasive and expensive methods. This is particularly relevant in resource poor countries, like the Philippines. Accepted standard techniques in sputum induction should be followed to ensure adequate sputum production and prevention of disease transmission.

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This research paper was presented orally in the Asia Pacific Society of Respiratory Medicine Convention held November 2010, Manila, Philippines.
A Two-Year Post-Treatment Follow-up of Multi-Drug Resistant Tuberculosis Cases Completing a Programmatic MDR-TB Management (DOTS-Plus) at the Lung Center of the Philippines: a Preliminary Report

Maria Victoria Lucas – Legaspi, MD¹ and Joven Roque V. Gonong, MD²

ABSTRACT

Purpose
There is a rising global rate of multidrug-resistant tuberculosis (MDR-TB). Little is known however, about the long-term follow-up of patients treated for MDR-TB, including rates of relapse, the factors associated with failure and success of treatment and chronic disability among cured persons. The purpose of this study is to establish the clinical outcomes including relapse rate of MDR-TB cases, and factors associated with relapse of patients who have completed the Programmatic Multi-drug Resistant Tuberculosis Management at the Lung Center of the Philippines.

Methods
This was designed as an observational and analytical prospective cohort study involving all diagnosed and enrolled MDR-TB patients from January 1, 2005 to December 31, 2005 at the Lung Center of the Philippines who completed the 2-year programmatic management of multi-drug resistant tuberculosis and were considered bacteriologically cured. The study excluded those who defaulted for at least 2 months while on treatment, and those who had completed the course but were still culture positive. Patients were followed up until 18-24 months after completion of MDR-TB therapy with the following evaluations: physical examination every 3 months; smear microscopy, culture, chest radiography every 6 months for the next 2 years; blood chemistries as the case required; and clinical evaluation for any episode of potential TB symptoms. Data analysis was done by calculating descriptive statistics, such as percentages, mean and standard deviation.

Results
There were 34 (77%) patients who were alive at the time of completion of MDR-TB therapy. There were 19 males (55.9%) and 15 females (44.1 %), mostly at age range of 35-54 years. They were followed up for a mean of 19.21 months after initiation of treatment and 1 year after completion of treatment. The most common regimen was Kanamycin, Ofloxacin, Prothionamide, Cycloserine, Vit B6 (KmOfxPtoCsB6) given to 10 patients (29.4%) with Isoniazid, Rifampicin, Pyrazinmaide, Ethambutol, and Streptomycin (HRZES) being the most common resistance pattern. Among the 34 patients included in this study, 4 patients died (2 died of massive hemoptysis, 1died of heart failure, 1 died of sepsis), and 9 patients dropped out. There were no cases of relapse by the end of the observation period after completing the programmatic MDRTB management.

Conclusions
Although MDR-TB presents a major challenge to TB control, effective treatment can result in cure. In this study, no relapse was noted due to the small sample size. This study needs to be completed with the computed sample size to be able to reach a definite conclusion.

Keywords: Multi-Drug Resistant Tuberculosis, DOTS-Plus
Rising global rates of multidrug-resistant tuberculosis (MDR-TB) has led to a concerted international effort to confront this disease, particularly in countries with a high incidence of TB (1-3). There have been concerns that the WHO re-treatment regimen could be exacerbating the MDR-TB problem, particularly where there are failures in the National Tuberculosis Program. Therefore, the WHO considered a strategy of supervised treatment of MDR-TB – the so called DOTS-PLUS program, to try to contain it. Nonetheless, despite cure rates of greater than 80% in some programs, MDR-TB patients tend to have a chronic disease and require prolonged therapy. Little is known about the long-term follow-up of patients treated for MDR-TB, including rates of relapse, the factors associated with failure and success of treatment and chronic disability among cured persons. Among patients treated for pan-susceptible TB, pulmonary sequelae and malnutrition can be substantial (4). Given the prolonged nature of MDR-TB, one might expect higher rates of chronic disability among patients with drug-resistant TB compared with those with pan-susceptible TB.

To explore these questions, we conducted a follow-up at the end of treatment, in line with the WHO recommendation, of MDR-TB patients who received individualized therapy at the Public Health Domiciliary Unit of the Lung Center of the Philippines (1).

The main objective of the study is to establish the relapse rate of MDR-TB cases who were enrolled and who have completed a programmatic MDR-TB management (DOTS-PLUS) from January 1, 2005 to December 31, 2005 at the Public Health Domiciliary Unit (PHDU) of the Lung Center of the Philippines. It also aims to describe the post-treatment clinical and microbiological outcomes of multi-drug resistant tuberculosis cases at the Lung Center of the Philippines as well as to determine the factors associated with relapse and the success of treatment.

**METHODS**

This is an observational and analytical prospective cohort study. The study protocol was evaluated and approved by the institution’s Technical Review Board and Ethics Review Committee. An informed consent was made and explained to all of the patients meeting the inclusion criteria. We included patients diagnosed and enrolled MDR-TB patients at the Lung Center of the Philippines DOTS-PLUS Clinic who completed the 2-year programmatic management of multi-drug resistant tuberculosis were included in the follow-up study from July 2006-June 2008. Specifically, we included all patients MDR-TB patients considered cured on completion of the 2-year programmatic MDR-TB Management (DOTS-PLUS), all MDR-TB patients with DST revealing resistance to at least Isoniazid and Rifampicin and subjects who have signed and dated written informed consent to participate in the study. We excluded patients enrolled at the PHDU-LCP DOTS Clinic who defaulted for at least 2 months while on treatment and patients enrolled at LCP DOTS-PLUS PHDU Clinic, who had completed the course but were still bacteriologically positive at the end of the treatment.

We followed up the patients who have completed the programmatic management of MDR-TB at the DOTS-Plus Clinic of the Lung Center of the Philippines. Each was assigned a registration and identification number, and was...
provided with an individual checklist for monitoring and recording of findings. Clinic visits were done every 3 months with routine physical examination and review of systems (with option to do health check during the first 2 months of the quarter at their respective health centers and the 3rd month at LCP-DOTS Clinic thereafter). TB culture and AFB smear exam as well as chest radiography every 6 months. This study was planned to be completed for a minimum of 2 years following treatment completion. (Fig 1.1)

Data analysis was done by calculating descriptive statistics such as percentages, mean and standard deviation.

### RESULTS

The study involved the remaining 34 (77%) patients who were alive at the time of stopping the MDR-TB therapy. Among the cohort were 19 males (55.9%) and 15 females (44.1 %), mostly at age range of 35-54 at 55.9%. All were of Asian ethnicity, 41.2% had primary residence within the catchment area in Quezon City, and 76.5% belonged to the class C social status (Table 1). Twenty three were referred from the public sector, and 31 (91.2 %) patients claimed that they had at least two or more prior Non - DOTS but completed treatments. The total duration of treatment was not taken into account. Fifty two percent were cigarette smokers and alcohol beverage drinkers. The most common co-morbidity was diabetes. The baseline susceptibility testing showed (HRZES) being the most common resistance pattern (23.5 %), signifying loss of response to both the main bactericidal drug and the main sterilizing drugs, hence the need for lengthening the treatment duration.

These patients were followed up for a median of 19.21 (+/- 1.15) months after initiation of treatment and 1 year after completion of treatment. The most common regimen given was KmOfxPtoCsB6 (Kanamycin, Ofloxacin, Prothionamide, Cycloserine, Vit B6) given to 10 patients (29.4%) as shown in Table 3.

Among those who were considered cured at the time of treatment completion, 21 patients (61%) are currently clinically stable. Two patients died before the start of scheduled follow up due to asphyxia secondary to massive hemoptysis. Likewise, two other cured (culture-negative) patients later died (heart failure and sepsis) as shown in

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**Table 1** Characteristics of evaluable patients with MDR-TB (n=34) who completed the LCP programmatic MDRTB Management.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Number</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>19</td>
<td>55.9</td>
</tr>
<tr>
<td>Female</td>
<td>15</td>
<td>44.1</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
</tr>
<tr>
<td>15-34 years old</td>
<td>13</td>
<td>38.2</td>
</tr>
<tr>
<td>35-54 years old</td>
<td>19</td>
<td>55.9</td>
</tr>
<tr>
<td>≥55 years old</td>
<td>2</td>
<td>5.9</td>
</tr>
<tr>
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<tr>
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<td>Married</td>
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<tr>
<td>Others</td>
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<td>8.8</td>
</tr>
<tr>
<td>Social Status</td>
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</tr>
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<td>Class A</td>
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</tr>
<tr>
<td>Class B</td>
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<td>14.7</td>
</tr>
<tr>
<td>Class C</td>
<td>26</td>
<td>76.5</td>
</tr>
<tr>
<td>Class D</td>
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<td>0</td>
</tr>
<tr>
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<td>Smoking History</td>
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<td>Amphetamine use</td>
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<td>Pulmonary other than TB</td>
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<tr>
<td>Cardiac</td>
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<td>0</td>
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<tr>
<td>Diabetes</td>
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<td>26.5</td>
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<tr>
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<tr>
<td>Combination &gt;2 co-morb</td>
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<td>11.8</td>
</tr>
<tr>
<td>Number of Previous TB treatment</td>
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<tr>
<td>1</td>
<td>3</td>
<td>8.8</td>
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<tr>
<td>≥ 2</td>
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<td>Status of previous treatment</td>
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<td></td>
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<td>Completed treatment</td>
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<tr>
<td>Incomplete treatment</td>
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<td>8.8</td>
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<td>Strategy of previous treatment</td>
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<tr>
<td>DOTS</td>
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<tr>
<td>Non- DOTS</td>
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<td>exposure to TB</td>
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<tr>
<td>22</td>
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<td>exposure to MDRTB</td>
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<tr>
<td>Private sector</td>
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<td>67.6</td>
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<tr>
<td>Data Not Available</td>
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<td>2.9</td>
</tr>
<tr>
<td>Residence</td>
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<td></td>
</tr>
<tr>
<td>14</td>
<td>41.2</td>
<td></td>
</tr>
<tr>
<td>Catchment area (within QC)</td>
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<td>32.4</td>
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<tr>
<td>Other areas of Metro Manila</td>
<td>9</td>
<td>26.5</td>
</tr>
<tr>
<td>Outlying provinces</td>
<td></td>
<td></td>
</tr>
<tr>
<td>17</td>
<td>50.0</td>
<td></td>
</tr>
</tbody>
</table>

Table 4. Of the surviving patients who were supposed to be observed, 5 were lost and 4 had incomplete follow-up until they totally abandoned the post treatment program (see Figure 1.2).
Thus, among the entire cohort of 34 patients enrolled during the study period, favorable long-term microbiological outcome was observed among 61%, although clinically most of them experienced persistent coughing and some with long-term sequelae of hemoptysis and exertional dyspnea. The economic impact of the disease was evident as nearly everyone who was employed before starting MDR-TB treatment have not regained their jobs nor have resumed school because of work disruption caused by their TB therapy and physical limitation. Many, however, have reported to still participate in family roles as parents and caretakers.

However, a retrospective of patients who received individualized, community-based MDR-TB therapy by Shin et al., emphasized that effective treatment can result in cure. Among 86 patients treated in Peru for multidrug-resistant tuberculosis (MDR-TB) followed-up after completion of treatment, there was favourable outcome with 97% remaining healthy. Long-term follow-up therefore is important for understanding the long-term efficacy of treatment and the overall impact of this disease both on patients’ physical and socioeconomic well-being (11).

Similarly, in the background of strongly functioning and well espoused unit, this study showed favourable outcome among our cases who have completed the program and 61.76% were successfully followed up, remained stable and with no evidence of relapse.

The World Health Organization, together with the Global TB Alliance, and along with several partners around the world, including the Lung Center of the Philippines, ensured that TB patients adhere to the full course of the treatment. This approach requires a sustainable and functioning national TB programme, drug availability at a reasonable cost, wide DOT provision and a good infrastructure for monitoring and delivery of treatment. Its effectiveness in the community-based outpatient treatment can yield high cure rates even in resource-poor settings (7).

It is still poorly understood why some MDR-TB patients were lost to follow-up after treatment. Personal stresses, such as the need to earn money, alcoholism, pessimism, poor previous experiences with TB treatment, and family migration may play a role in deterring adherence. Misclassification and loss to follow-up may also lead to underestimates of the true impact of MDR TB on the population. Knowledge of factors associated with patient not adhering to the programme of study could assist healthcare workers and may serve to improve patient retention and thus close the gap between the potential high efficacy of standardized MDR TB treatment and but its low effectiveness.

With access to laboratory results to guide individualized therapy for persons with MDR-TB in the context of a well-supported program, the outcomes observed are encouraging. These outcomes favor the full implementation of similar MDR-TB treatment programs especially in the Philippines.

Table 2. Baseline MTB susceptibility pattern

<table>
<thead>
<tr>
<th>Drug Resistance to:</th>
<th>N = 34</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR</td>
<td>3</td>
<td>8.8</td>
</tr>
<tr>
<td>HR + FQ</td>
<td>0</td>
<td>0</td>
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<tr>
<td>HRZ</td>
<td>1</td>
<td>2.9</td>
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<tr>
<td>HRZ + FQ</td>
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<td>0</td>
</tr>
<tr>
<td>HRE</td>
<td>4</td>
<td>11.8</td>
</tr>
<tr>
<td>HRE + FQ</td>
<td>1</td>
<td>2.9</td>
</tr>
<tr>
<td>HRZE</td>
<td>2</td>
<td>5.9</td>
</tr>
<tr>
<td>HRZE + FQ</td>
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</tr>
<tr>
<td>HRZS</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>HRZ + FQ</td>
<td>1</td>
<td>2.9</td>
</tr>
<tr>
<td>HRES</td>
<td>4</td>
<td>11.8</td>
</tr>
<tr>
<td>HRES + FQ</td>
<td>3</td>
<td>8.8</td>
</tr>
<tr>
<td>HRS</td>
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<td>2.9</td>
</tr>
<tr>
<td>HRS + FQ</td>
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<td>0</td>
</tr>
<tr>
<td>HRZES</td>
<td>8</td>
<td>23.5</td>
</tr>
<tr>
<td>HRZES + FQ</td>
<td>4</td>
<td>11.8</td>
</tr>
<tr>
<td>HRZES + FQ + KN</td>
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<td>5.9</td>
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Table 3. Most Common MDRTB therapeutic regimens

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<th>Regimen</th>
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<tbody>
<tr>
<td>ZESOfxPtoCsB6</td>
<td>3</td>
<td>8.8</td>
</tr>
<tr>
<td>ZSOfxPtoCsB6</td>
<td>4</td>
<td>11.8</td>
</tr>
<tr>
<td>EKmMfxPtoCsPasB6</td>
<td>1</td>
<td>2.9</td>
</tr>
<tr>
<td>ZKmOfxPtoCsB6</td>
<td>5</td>
<td>14.7</td>
</tr>
<tr>
<td>ZKmMfxPtoCsPasB6</td>
<td>4</td>
<td>11.8</td>
</tr>
<tr>
<td>ZEKmOfxPtoCsB6</td>
<td>1</td>
<td>2.9</td>
</tr>
<tr>
<td>KmOfxPtoCsB6</td>
<td>10</td>
<td>29.4</td>
</tr>
<tr>
<td>KmMfxPtoCsPasB6</td>
<td>5</td>
<td>14.7</td>
</tr>
<tr>
<td>CmMfxPtoCsPasBs</td>
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<td>2.9</td>
</tr>
<tr>
<td>Total</td>
<td>34</td>
<td>100%</td>
</tr>
</tbody>
</table>
DISCUSSION

Drug-resistant tuberculosis has been reported since the early days of the introduction of chemotherapy. However, most of the evidence was limited to developed countries. In 1992, the Third World Congress on Tuberculosis concluded that there was little recent information on the global magnitude of multidrug-resistant tuberculosis, defined as resistance to at least isoniazid and rifampicin. Through the WHO/IULTD (World Health Organization and the International Union Against Tuberculosis and other Lung Diseases) Global project on Drug-Resistance Surveillance launched in 1994, a large number of reliable and accurate data have allowed us to understand the magnitude of the problem of MDR-TB (7). And in 1997, the first standardized information on drug resistance was reported from surveys or surveillance systems and confirmed what many has feared: DRUG RESISTANCE. Thus DOTS-Plus was coined to face MDR-TB programmatically, meaning, no longer solely through individual practitioners efforts but through wider DOTS-Plus pilot projects, implemented by, or in collaboration with, the National Tuberculosis Programs (8).

A study by Masuhiro Narita et al. in 2001, compared treatment outcome of MDRTB treated or who received specialized treatment, than those solely on an out-patient basis during part or all of their regimen. The specialized TB case group had a higher completion rate than the community care group despite data suggesting that they were a more difficult group to treat. This may reflect the factor that few clinicians have had specialized training in the treatment of multi-drug resistant tuberculosis or extensive experience in its complex management (10).

Figure 1.2 Flow Chart of the significant clinical events on the first year following treatment completion

CONCLUSIONS

Although MDR-TB presents a major challenge to TB control, effective treatment can result in cure. Long-term follow-up is important for understanding the long-term efficacy of treatment and the overall impact of this disease on patients’ physical and socioeconomic well-being. An interesting finding was noted in this study such that unlike previous reports of high death rates associated with MDR-TB, most of our patients met the definition of cure. There was no relapse reported on the first year post treatment and they remained sputum and culture negative with few having long-term sequelae.

We recognize the limitations of this study. In this study, no relapse was noted due to the small sample size. This preliminary study needs to be completed with the computed sample size to be able to reach a definite conclusion. Since there were no cases of relapse, the factors associated with relapse and the success of treatment cannot be determined.

Longer follow-up would be useful in determining if these indicators of physical and social recovery are sustained. Several patients were lost to follow-up; thus, the outcome of these patients was not well characterized. Finally, these results may not be applicable to other situations, where the socioeconomic situation determines, in large part, the ability of a patient to resume work and studies.
References:


Presented in the European Respiratory Society Annual Congress, September 2009, Vienna, Austria.
Risk Factors Associated with Multi-Drug Resistant Pathogens among Patients with Hospital Acquired Pneumonia Admitted at the Philippine General Hospital

Ruby T. Nolido MD, FPCP¹, Lenora C. Fernandez MD, FPCP, FPCCP²

ABSTRACT

Purpose:
The aim of this study is to identify the risk factors associated with multi-drug resistant pathogens among patients with hospital acquired pneumonia admitted at the Philippine General Hospital.

Methods:
All adult patients admitted either in the ICU or Pay/Charity Wards exhibiting a clinically and bacteriologically documented HAP were included in the study. The patient’s chart is reviewed and the data collected includes the patient’s baseline characteristics on admission. The potential factors for the development of hospital acquired pneumonia will then be subdivided into: patient-related, procedure-related, and pharmacologic-related factors. The patients were monitored until the day of discharge.

Results:
137 cases of HAP were included, 95 (69%) developed HAP secondary to multi-drug resistant pathogen. The mean age was 56, predominantly females 80 (58%). Nosocomial pneumonia is highest in the ICU (75%). Among 155 organisms, 115 pathogens were MDR pathogens. The three most common MDR pathogen isolated were: Acinetobacter baumanii, Pseudomonas aeruginosa and Klebsiella pneumonia – ESBL. Risk factors identified with the use of logistic regression included: (1) > 5 days hospital admission prior to HAP, \( P=0.03 \); (2) length of intubation or mechanical ventilation of > 5 days prior to the diagnosis of HAP, \( P=0.006 \); (3) antibiotic use within three months prior to the diagnosis of HAP, \( p-value=0.032 \). Among patients with HAP, the involvement of more than one lobe based on chest radiograph has significantly greater risk of developing HAP with MDR pathogens.

Conclusions:
The length of hospital stay, duration of mechanical ventilation and recent antibiotic use prior to the onset of HAP, and involvement of more than one lobe based on chest radiograph have greater risk of developing HAP with MDR pathogens. Early recognition of these risk factors and prevention intervention such as: early weaning from invasive mechanical ventilation, and adequate empiric antibiotic coverage for suspected multi-drug resistant organisms may help decrease morbidity and length of hospital stay. In future studies, it is suggested to develop an algorithm to evaluate these risk factors for HAP and prospectively test this algorithm in a validation cohort.

Keywords: Hospital-acquired pneumonia, multidrug resistant organisms
Hospital-acquired pneumonia (HAP) is a significant public health issue. It is associated with significant morbidity and mortality. The high in-hospital mortality rates for patients with HAP is correlated with inadequacy of initial empiric antibiotic treatment secondary to resistance of causative bacteria to the prescribed antibiotics. Antimicrobial resistance is an important variable in patient’s mortality and utilization of Intensive Care Unit. Thus antimicrobial-resistant pathogens pose a significant challenge to the successful treatment outcomes.

In order to reduce the incidence of inadequate antimicrobial treatment, strategies to reduce the emergence of antibiotic-resistant pathogens should be developed. This study aimed to identify the risk factors associated with multi-drug resistant pathogens among patients with hospital acquired pneumonia admitted at a tertiary care institution, the Philippine General Hospital. Specifically, the clinical characteristics of patients with hospital-acquired pneumonia with multi-drug resistant pathogens were identified. The multi-drug resistant pathogens were likewise searched for. From these data, an antibiogram susceptibility pattern of the most common multi-drug resistant pathogens isolated would be determined.

**METHODS**

We conducted a prospective observational cohort study involving patients diagnosed to have hospital acquired pneumonia and confined at the Philippine General Hospital’s intensive care units (Central Intensive Care Unit, Medical Intensive Care Unit, Neurology Intensive Care Unit, Neurosurgical Intensive Care Unit, and Surgical Intensive Care Unit) as well as its Pay and Service/Charity Wards. The study was conducted from December 2009 - July 2010.

A diagnosis of hospital acquired pneumonia was based on the 2005 American Thoracic Society (ATS) Guidelines which included clinical evidence which included radiologic and bacteriologic parameters.

After obtaining approval from the hospital’s technical and ethical review boards, consent for study participation was also obtained from attending physicians and identified subjects.

We collected the patients’ baseline characteristics on admission including age, gender, underlying medical conditions, indication/s for admission and length of hospital stay prior to hospital acquired pneumonia.

Potential factors for the development of hospital acquired pneumonia were noted. The patient related risk factors for HAP included were immunosuppression, diabetes, chronic lung disease, chronic neurologic diseases, congestive heart failure, chronic renal disease, chronic liver disease, aspiration, HIV infection and AIDS. Procedure-related HAP risk factors were endotracheal tube placement, number of endotracheal changes, tracheostomy, invasive ventilation, and invasive procedures (bronchoscopic and endoscopic procedures, central line insertion and hemodialysis or hemofiltration). Pharmacologic related risk factors for HAP included gastric acid suppression therapy, sedative drugs, corticosteroids, inotropics and all antimicrobial agents used in the preceding 3 months or 90 days prior to occurrence of hospital acquired pneumonia except for the antimicrobials used for prophylaxis during surgical procedures. We observed and monitored the patients until the day of discharge to identify those who developed multi-drug resistant (MDR) causative organisms based on culture and sensitivity.

Multi-drug resistant pathogens were identified based on resistance to at least 3 or more classes of antibiotics. The following pathogens are considered as multi-drug resistant pathogens: *Pseudomonas aeruginosa* (with resistance to carbapenems, fluoroquinolones, antipseudomonal penicillins and cephalosporins), Extended-spectrum beta-lactamase (ESBL) producing Enterobacter, *E. coli* and *Klebsiella pneumoniae* (to include: KPC or Carbapenem-resistant strain). All *Stenotrophomonas maltophilia*, *Bukholderia cepacia* and *Acinetobacter* species are considered as antimicrobial resistant bacteria whatever their antimicrobial susceptibilities.

**Statistical analysis:**

To determine the risk factors associated with multi-drug resistant pathogens among patients with hospital acquired pneumonia, we compared the characteristics of patients diagnosed with non-MDR HAP to those who developed MDR HAP. We used logistic regression analysis to determine significant risk factors.
RESULTS

There are many factors that contribute to a patient's susceptibility to multi-drug resistant organisms. This prospective, observational, cohort study was formulated to determine such factors in a Tertiary Government Hospital.

Patient Characteristics

During the study period, we included a total of 137 cases of nosocomial pneumonia. Of whom 95 (69%) developed hospital acquired pneumonia secondary to multi-drug resistant pathogens. Two or more causative organisms were isolated in 59 (62%) of these cases.

The mean age was 56 years old; there were 57 (42%) males and 80 (58%) females. Nosocomial pneumonia is highest in the intensive care unit (103, 75%) predominantly in the Central ICU (52, 38%), followed by Medical ICU (20, 15%) as shown in Table 1.1. Of these cases, the most common indication for intensive care unit admission is respiratory failure secondary to hospital acquired pneumonia followed by neurologic diseases secondary to cerebrovascular accident.

As shown in Table 1.2, the duration of hospital stay was as follows: Non-MDR HAP: 9-51 days, and MDR HAP: 5-123 days. The mortality was 11 (28.9% of all Non-MDR HAP), 26 (40.6% of all MDR HAP) and 37 (36.2% of all HAP cases). Septic shock was the most common cause of mortality. The total number of N for mortality here does not correspond to the total N for the HAP event as one patient may have 2 or more HAP events and may have both MDR and Non-MDR events. Patient having 2 events are counted as one for each mortality and patients having both events of Non-MDR and MDR are excluded.

<table>
<thead>
<tr>
<th>Patient’s Characteristics</th>
<th>NON-MDR HAPN (%)</th>
<th>MDR-HAPN (%)</th>
<th>TOTALN (%)</th>
<th>p - value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (median, yr)</td>
<td>56.21</td>
<td>56.01</td>
<td>137</td>
<td>0.9528</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>21 (15)</td>
<td>36 (27)</td>
<td>57 (42%)</td>
<td>0.1850</td>
</tr>
<tr>
<td>Female</td>
<td>21 (15)</td>
<td>59 (43)</td>
<td>80 (58%)</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>42 (30%)</td>
<td>95 (69%)</td>
<td>137</td>
<td>0.1913</td>
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<tr>
<td>CENICU</td>
<td>13 (9%)</td>
<td>39 (28%)</td>
<td>52 (38%)</td>
<td></td>
</tr>
<tr>
<td>MICU</td>
<td>09 (7%)</td>
<td>11 (8%)</td>
<td>20 (15%)</td>
<td></td>
</tr>
<tr>
<td>NICU</td>
<td>03 (2%)</td>
<td>10 (7%)</td>
<td>13 (9%)</td>
<td></td>
</tr>
<tr>
<td>NSSCU</td>
<td>01 (0.7%)</td>
<td>04 (3%)</td>
<td>05 (4%)</td>
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<tr>
<td>PACU</td>
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<td>0</td>
<td>01 (0.7%)</td>
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<tr>
<td>SICU</td>
<td>04 (3%)</td>
<td>08 (6%)</td>
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<td>Wards</td>
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</tr>
<tr>
<td>W1</td>
<td>02 (1%)</td>
<td>07 (5%)</td>
<td>9 (7%)</td>
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</tr>
<tr>
<td>W3</td>
<td>0</td>
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<td>7 (5%)</td>
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</tr>
<tr>
<td>W5</td>
<td>03 (2%)</td>
<td>02 (1%)</td>
<td>05 (4%)</td>
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</tr>
<tr>
<td>W10</td>
<td>0</td>
<td>01 (0.7%)</td>
<td>01 (0.7%)</td>
<td></td>
</tr>
<tr>
<td>Pay</td>
<td>06 (4.4%)</td>
<td>06 (4.4%)</td>
<td>12 (9%)</td>
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<table>
<thead>
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<th>Indications for ICU admission</th>
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<td>Infectious diseases</td>
<td>05 (4%)</td>
<td>06 (4.4%)</td>
<td>11 (8%)</td>
<td>0.6554</td>
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<td>Respiratory failure</td>
<td>11 (8%)</td>
<td>29 (21%)</td>
<td>40 (29%)</td>
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<td>Neurologic disturbances</td>
<td>12 (9%)</td>
<td>19 (14%)</td>
<td>31 (23%)</td>
<td>0.7545</td>
</tr>
<tr>
<td>Shock</td>
<td>04 (3%)</td>
<td>07 (5%)</td>
<td>11 (8%)</td>
<td>0.8257</td>
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<td>Metabolic disturbances</td>
<td>0</td>
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Antibiogram:
We isolated one hundred fifty-three causative organisms from respiratory specimens (sputum and endotracheal aspirate) and two from blood cultures. Among these organisms, 115 pathogens (75.16%) were multi-drug resistant pathogens predominant among which were Acinetobacter baumanii (n=50), Klebsiella pneumoniae – ESBL (n=16) and Pseudomonas aeruginosa (n=16). The other organisms isolated included Klebsiella pneumoniae (n=8), Enterobacter cloacae (n=6), Klebsiella ozanae (n=4), Stenotrophomonas maltophilia (n=4), Achromobacter species (n=3), Pseudomonas putida (n=3), Enterobacter aerogenes (n=2), Burkholderia mallei (n=1), Escherichia coli-ESBL (n=1), methicillin-resistant Staphylococcus aureus (n=1) and Sphingomonas paucinobilis (n=1).

Figures 1-3 show the antibiograms for the three most common multi-drug resistant pathogens isolated namely: Acinetobacter baumanii (n=50), Pseudomonas aeruginosa (n=16) and Klebsiella pneumoniae – ESBL (n=16). Acinetobacter baumanii had the highest resistance rates to ciprofloxacin, ceftiraxone cefepime, and gentamicin, 93%, 90%, 78%, and 75% respectively. It had a susceptibility rate of 45% for ampicillin-sulbactam as compared to meropenem, imipenem and ceftazidime (44% each). This demonstrates an increasing resistance of Acinetobacter baumanii to these commonly used antibiotics. However, ampicillin-sulbactam, meropenem and imipenem could still be used as along as the isolate is susceptible.

Pseudomonas aeruginosa has the highest resistance rate to ceftazime, ceftazidime and ciprofloxacin. As stated by the Asian HAP Working group, local susceptibility data should guide the decision of whether or not to use fluoroquinolone in the antibiotic regimen because some studies have reported a decrease sensitivity of these agents. This study clearly showed a decreased susceptibility of Pseudomonas to ciprofloxacin (29%).

Klebsiella pneumoniae-ESBL isolates had the highest resistance rate to ceftiraxone and ampicillin-subactam (100%) followed by ceftazidime and aztreonam (92% and 91% respectively). These figures support the recommendations by the Asian HAP working group to use meropenem or imipenem as first-line treatment.

<table>
<thead>
<tr>
<th>Risk Factors for MDR Pathogens in HAP</th>
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</thead>
</table>
| We classified the risk factors for the development of HAP into patient-related, pharmacologic-related and procedure-related risk factors as shown in Table 2.0. We identified the following significant risk factors on univariate analysis: (1) five days or more hospital admission prior to hospital acquired pneumonia (p=0.03); (2) length of intubation or mechanical ventilation of five days or more prior to the diagnosis of hospital acquired pneumonia, (p= 0.006); (3) antibiotic use within three months or 90 days prior to the diagnosis of hospital acquired pneumonia, (p= 0.032). Among the antibiotics used, the beta-lactam/beta-lactamase inhibitor combination posed the most significant risk (p= 0.015). The patient’s area of confinement during diagnosis of hospital acquired pneumonia (p=0.19); and suspected aspiration (p=0.89), were not significant risk factors.

Among patients with hospital acquired pneumonia, the involvement of more than one lobe based on chest radiograph has significantly greater risk of developing hospital acquired pneumonia with multi-drug resistant organisms, p-value of 0.04 (Table 2.0).
Figure 1. Antibiogram of *Acinetobacter baumanii* (n=50)

Figure 2. Antibiogram of *Pseudomonas aeruginosa* (n=16)
Antimicrobial resistance continues to pose as a major problem and significant challenge in the successful treatment of patients with hospital acquired or ventilator-associated pneumonia. At the same time, the rate of hospital acquired pneumonia due to multi-drug resistant pathogens have increased dramatically especially among patients admitted at the intensive care unit. As documented in this study, nosocomial pneumonia was highest in the intensive care unit predominantly in the Central Intensive Care Unit followed by the Medical Intensive Care Unit. This increasing trend is reflected in increasing resistance of respiratory isolates from hospital acquired pneumonia, especially in late-onset VAP which accounted for 61 (46%) of cases.

Many risk factors for colonization and infection with multi-drug resistant pathogens have been published by the ATS/IDSA guidelines. These include: antimicrobial therapy in preceding ninety days; current hospitalization of five days or more; high frequency of antibiotic resistance in the community or in the specific hospital unit presence or risk factors for HCAP; and immunosuppressive disease and/or therapy. We identified similar significant risk factors namely: (1) five days or more hospital admission prior to hospital acquired pneumonia; (2) antibiotic use within three months or ninety days prior to the diagnosis of hospital acquired pneumonia. We identified additional risk factors namely: (1) length of intubation or mechanical ventilation of five days or more prior to the diagnosis of hospital acquired pneumonia; and (2) involvement of more than one lobe based on chest radiograph upon diagnosis of hospital acquired pneumonia. Similarly, Trouillet and coworkers demonstrated a close correlation between previous use of broad-spectrum antibiotics and the potential development of Antibiotic Resistant-Ventilator Associated Pneumonia. Occurrence of VAP due to potentially-resistant pathogens such as Pseudomonas aeruginosa or Acinetobacter baumannii has also been correlated with prolonged hospital stay, duration of MV >7 days, invasive devices and underlying patients condition (COPD, neurosurgery, large-volume aspiration, head trauma). Other similar studies by Grossman and Chastre also stated that the longer a patient is in hospital, the wider the spectrum of likely pathogens and the more likely they are to be multiple drug resistant. We noted similar findings in this study wherein in patients with hospital acquired pneumonia secondary to multi-drug resistant pathogens have prolonged hospital stay (Non-MDR: 9-51 days, MDR: 5-123 days) and a 12% difference in mortality. However, we were not able to note the significance of the underlying patient’s condition and use of invasive devices in this study as shown in Table 2.0.

The microbiologic agents responsible for hospital acquired pneumonia have been elucidated in numerous studies and included: gram negative bacteria, including Pseudomonas aeruginosa, Enterobacter, Acinetobacter, and enteric Gram-negative rods and are implicated in 55 to 85% of HAP cases;
Gram-positive cocci (particularly Staphylococcus aureus) account for 20 to 30%; and 40 to 60% of cases are polymicrobial. In critically ill patients requiring prolonged mechanical ventilation (MV) in ICUs, P aeruginosa and Acinetobacter (eg, Acinetobacter calcoaceticus and Acinetobacter baumannii), which are resistant to many antibiotics, account for 30 to 50% of HAP; these pathogens are uncommon in non-ICU settings.

Likewise, we noted that among critically ill patients, multi-drug resistant hospital acquired pneumonia account for 69% of HAP cases with 62% being secondary to polymicrobial agents. The antimicrobial resistance patterns in Asia may be quite different from those found in the United States and other Western countries, with markedly higher incidences of methicillin-resistant Staphylococcus aureus (MRSA) and MDR pathogens. Only one case of methicillin-resistant Staphylococcus aureus (MRSA) was identified in our study. In the review of data by the ASIAN HAP Working Group, Acinetobacter was found to be emerging in several countries: Malaysia, Thailand, and India, where it was one of the most common pathogens being isolated in cases of HAP and VAP. In Taiwan, it represented the second-most common pathogen. However in China and the Philippines (1999 HAP and VAP study), Pseudomonas aeruginosa was the most common pathogen causing HAP. However, our study has showed that Acinetobacter baumannii is the most common pathogen causing HAP. As previously mentioned, we identified Acinetobacter baumannii (50, 43%), gram negative rods: Pseudomonas aeruginosa (16, 14%) and Klebsiella pneumonia (16, 14%) as the three most common pathogens causing multi-drug resistant-HAP. These are some of the most serious pathogens (multidrug- or pandrug-resistant Pseudomonas aeruginosa and Acinetobacter strains) which are resistant to most available treatments. This increasing resistance trend continues to pose as a challenge in the appropriate antimicrobial treatment.

<table>
<thead>
<tr>
<th>Table 2. Risk factor for HAP secondary to Multi-Drug Resistant Organism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk Factors for HAP</td>
</tr>
<tr>
<td>----------------------</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td><strong>Patient-Related Factors</strong></td>
</tr>
<tr>
<td>Immunosuppression (&lt;1000/ul)</td>
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<tr>
<td>Active Cancer</td>
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<tr>
<td>Diabetes Uncontrolled</td>
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<td>COPD</td>
</tr>
<tr>
<td>Pulmonary Tuberculosis</td>
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<tr>
<td>Bronchial Asthma</td>
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<tr>
<td>Congestive Heart Failure</td>
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<tr>
<td>Unstable Coronary Artery Disease</td>
</tr>
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<td>Hypertension</td>
</tr>
<tr>
<td>Neurologic Disease</td>
</tr>
<tr>
<td>Suspected Aspiration</td>
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<tr>
<td>Chronic Renal Disease</td>
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<tr>
<td>Chronic Liver Disease</td>
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<tr>
<td>Chronic Steroid Use</td>
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<tr>
<td>HIV infection</td>
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<tr>
<td>AIDS</td>
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<tr>
<td><strong>Time of Onset of HAP</strong></td>
</tr>
<tr>
<td>&lt; 5 days from admission</td>
</tr>
<tr>
<td>≥ 5 days from admission</td>
</tr>
<tr>
<td>&lt; 5 days from start of mechanical ventilation</td>
</tr>
<tr>
<td>≥ 5 days from start of mechanical ventilation</td>
</tr>
<tr>
<td>Chest radiograph involvement</td>
</tr>
</tbody>
</table>

Nolido and Fernandez
#### Table 2. Risk factor for HAP secondary to Multi-Drug Resistant Organism

<table>
<thead>
<tr>
<th>Risk Factors for HAP</th>
<th>NON-MDR</th>
<th>MDR-HAP (%)</th>
<th>MDR-HAP (N%)</th>
<th>HAPN (%)</th>
<th>TOTAL (%)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Procedure-related factors</strong></td>
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<tr>
<td>Endotracheal tube</td>
<td></td>
<td>36 (26%)</td>
<td>80 (58%)</td>
<td>116 (85%)</td>
<td>0.74</td>
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</tr>
<tr>
<td>Reintubation</td>
<td></td>
<td>15 (11%)</td>
<td>33 (24%)</td>
<td>48 (35%)</td>
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<tr>
<td>Tracheostomy</td>
<td></td>
<td>13 (9%)</td>
<td>38 (28%)</td>
<td>51 (37%)</td>
<td>0.34416</td>
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</tr>
<tr>
<td>Invasive MV</td>
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<td>36 (26%)</td>
<td>82 (60%)</td>
<td>118 (86%)</td>
<td>0.74</td>
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<tr>
<td>Bronchoscopic procedures</td>
<td></td>
<td>03 (2%)</td>
<td>07 (5%)</td>
<td>10 (07%)</td>
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<tr>
<td>Nasogastric tube</td>
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<td>39 (28%)</td>
<td>87 (64%)</td>
<td>126 (92%)</td>
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<td>Endoscopic procedures</td>
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<tr>
<td>Coloscopy</td>
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<tr>
<td>Central line insertion</td>
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<td>09 (7%)</td>
<td>23 (17%)</td>
<td>32 (23%)</td>
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<tr>
<td>Invasive monitoring of BP</td>
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<td>Hemodialysis or hemofiltration</td>
<td></td>
<td>03 (2%)</td>
<td>09 (7%)</td>
<td>12 (09%)</td>
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<tr>
<td>Intracranial pressure control</td>
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<td><strong>Pharmacologic-related factors</strong></td>
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<td>H2 Blockers</td>
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<td>06 (4%)</td>
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<td>33 (24%)</td>
<td>83 (61%)</td>
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<td>Sedative drugs</td>
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<td>13 (09%)</td>
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<tr>
<td>Corticosteroids</td>
<td></td>
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<td>34 (25%)</td>
<td>44 (32%)</td>
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<tr>
<td><strong>Inotropic drugs</strong></td>
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<td>Dopamine</td>
<td></td>
<td>09 (7%)</td>
<td>28 (20%)</td>
<td>36 (26%)</td>
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<td>Dobutamine</td>
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<td>03 (2%)</td>
<td>08 (6%)</td>
<td>11 (08%)</td>
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<td>Norepinephrine</td>
<td></td>
<td>04 (3%)</td>
<td>17 (12%)</td>
<td>21 (15%)</td>
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<td><strong>Prior antibiotic use (within 90 days prior to diagnosis of HAP)</strong></td>
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<td>Penicillin</td>
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<td>06</td>
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<td>Cephalosporin</td>
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<td>Beta Lactamase Inhibitor Combination (BLIC)</td>
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<td>Macrolides</td>
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<td>08</td>
<td>20</td>
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<td>Fluoroquinolones</td>
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<td>02</td>
<td>12</td>
<td></td>
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<tr>
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</table>

**Limitations of the Study**

The limitations of our study included: (1) the method used to assess the etiologic agent was not all quantitative cultures but rather semi-quantitative cultures of sputum or endotracheal aspirate for charity patients; (2) due financial constraints, not all patients with suspected hospital or ventilator-acquired pneumonia had blood cultures collected in order to identify the presence of either pneumonia or extrapulmonary infection; and (3) our study population was limited only to those that were identified during chart rounds or those who were referred to the Pulmonary Section during our study period.

**CONCLUSIONS**

This prospective, observational, cohort study on 137 cases of hospital acquired pneumonia of whom 95 developed hospital acquired pneumonia caused by multi-drug resistant pathogens...
at Philippine General Hospital reveals that the length of hospital stay, duration of mechanical ventilation and recent antibiotic use (within three months or 90 days) prior to the onset of hospital acquired pneumonia, and involvement of more than one lobe based on chest radiograph have greater risk of developing hospital acquired pneumonia with multi-drug resistant organisms such as Acinetobacter baumanii, Pseudomonas aeruginosa and Klebsiella pneumonia-ESBL. Early recognition of these risk factors and prevention intervention such as: early weaning from invasive mechanical ventilation, and adequate empiric antibiotic coverage for suspected multi-drug resistant organisms may help decrease morbidity and length of hospital stay.

As the Asian HAP working group previously recommended, that national and multinational surveillance data is needed to provide better information on the incidence of etiologic pathogens of HAP and VAP and the resistance patterns. Our study proves to be fruitful as it has shown that Acinetobacter is indeed the primary pathogen of MDR-HAP as previously suspected by the group.

We also recommend that further prospective studies with larger population be conducted to test other significant variables identified as risk factors for the development of hospital acquired pneumonia caused by multi-drug resistant organisms. We suggest that similar studies be conducted on a periodic basis to identify temporal variations in bacterial flora and antibiogram. Thereby, providing a rational basis for selection of initial antibiotic therapy for patients with hospital acquired pneumonia while waiting for culture results. In future studies, we recommend to build an algorithm to evaluate these risk factors for hospital acquired pneumonia secondary to multi-drug resistant pathogens and prospectively test this algorithm in a validation cohort. The algorithm will allow patient stratification and may decrease unnecessary use of antimicrobial agents thus help prevent in emergence of MDR pathogens.

References:


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10. Ranes, Justin, et. al., Hospital Acquired, Health Care Associated, and Ventilator-Associated Pneumonia, Cleveland Clinic Meded.com


This research paper has been presented in the poster presentation of the Asia Pacific Society of Respirology Convention held November 2010, Manila, Philippines.
Comparison of the Flutter Device (Lung Flute) to Active Cycle Breathing Technique (ACBT) in Hospitalized Patients with Bronchiectasis: A Pilot Study

Ruth DC. Babalo, M, FPCP¹, Vincent Balanag Jr., MD, FPCP, FPCCP², Glynna Ong-Cabrera, , FPCP, FPCCP²

ABSTRACT

Purpose:
Stasis of secretions in bronchiectasis leads to chronic infection, inflammation, and lung destruction. Thus, airway clearance techniques are important in routine care of bronchiectasis patients. We compared the efficacy of Lung Flute to the standard Active Cycle breathing Technique (ACBT) among hospitalized patients with a clinical diagnosis of bronchiectasis in improving the amount of expectorated sputum and level of relief after expectoration.

Methods:
Sixty two (62) patients with bronchiectasis took part in this open label, randomized 3 day control trial. Thirty-one (31) patients received ACBT and the other 31 patients used Lung Flute. We instructed each patient to collect sputum from 7am to 12 noon after each session using standard measuring cup and rate the level of relief and ease of expectoration after 3 days.

Results:
Improvement in sputum expectoration was observed in Lung Flute group (58.1%) compared to 41.9% in ACBT group. Marked relief after expectoration was reported by 16 patients using Lung Flute (51.6%) while moderate relief only for patients (13/31) who received ACBT (41.9%). Data analysis regarding improvement in sputum expectoration (p=0.4400) and relief (p=0.4885) showed no significant statistical difference between two techniques. Eight (8) patients in ACBT and 1 patient in Lung Flute complained of discomfort of breathing and 1 patient experienced minimal hemoptysis after using Lung Flute.

Conclusions:
Increase amount of sputum expectoration and relief was achieved using Lung Flute device and is efficacious as ACBT in improving airway secretions in bronchiectasis patients. It appears safe with less adverse reactions in patients undertaking this therapy.

Keywords: Lung Flute, Active Cycle Breathing Technique, Bronchiectasis
INTRODUCTION

Impaired clearance of sputum results in a vicious cycle of colonization and infection of bronchi with pathogenic organisms, dilation of bronchi, and further production of sputum. Techniques for augmenting, when necessary, the normal mucociliary and cough clearance mechanisms are not new, but, in more recent years, techniques have been developed which are effective, comfortable, and can be used independent of an assistant in the majority of bronchiectatic patients.

Bronchiectasis consists of abnormal, permanent, and irreversible dilatation of bronchi with recurrent infections, inflammation, hypersecretion and a reduction of mucus clearance. Clinical Manifestations are chronic cough, fever, and voluminous expectoration, with a fetid odor. Thus, Airway Clearance Techniques are important component of the routine care together with antibiotics for most patients with Bronchiectasis.\(^1\)

Considering that Respiratory Physiotherapy lack scientific evidence to support its application in the treatment of several obstructive diseases, this investigation was designed to evaluate the hypothesis that Lung Flute can improve the airway clearance of hypersecretive Bronchiectatic patients and detect a clinically important difference between the Standard Active Cycle Breathing Technique (ACBT) and Lung Flute using sputum volume as the primary outcome measure.\(^2\)

The Lung Flute described as a hand-held disposable device is used to help loosen, mobilize, and obtain sputum sample. It can also be used to clear mucus lung congestion to improve patient’s condition.

The Lung Flute, which is shaped like a flute, creates a specific low frequency sound when the user blows into it. The sound vibrates the airways and lung secretions which causes the deep lung secretions to thin and be expelled. Currently, the standard method for obtaining lung secretions for testing uses hypertonic saline which is breathed into the lungs through a mask. This method is very uncomfortable for the person being tested and often causes bronchial spasm and inflammation and cannot be done more frequently than every 48 hours.\(^3\)

The Lung Flute is a small self-powered audio device that generates 18 to 22Hz with an output of 110 to 115dB using 2.5cm H2O of pressure. This sound wave, when generated at the mouth by mild exhalation, travels retrograde down the tracheobronchial tree and vibrates tracheobronchial secretions. This device consist of a mouth piece and a reed inside a tube.

The Lung Flute which simply requires the person being tested to blow into the device as though they were blowing out a candle, can be performed every 20 minutes, enabling to monitor inflammatory biomarkers during an asthma attack or at various stages of obstructive or restrictive pulmonary events.

A study by Akira et al (Dec 2007) evaluated the use of Lung Flute for sputum induction in patients suspected of Tuberculosis and concluded that patients expectorated sputum within 10 to 20 minutes after using Lung Flute. It provides a rapid and effective method of sputum induction and the diagnostic yield of pulmonary tuberculosis using the device was positive in 7 out of 15 cases with treatment started immediately without the need for other examinations such as gastric juice sampling or Bronchoscopy.\(^4\)

Lastly, Sanjay Sethi\(^5\) studied Lung Flute in University of Buffalo for 20 COPD patients in terms of efficacy and safety in sputum induction compared with hypertonic saline and saliva. It was concluded that there was no statistical difference between Lung Flute and hypertonic saline but was statistically better than saliva. It was also noted that many patients (10/20) experienced bronchospasm using hypertonic saline compared to only one patient using the Lung Flute device.
**METHODS**

This is an open label, randomized control trial where patients admitted at Lung Center of the Philippines with clinical diagnosis of bronchiectasis came in due to fever, dyspnea, and with physical examination findings of wheezes and crackles on auscultation supported by CXR compatible with Bronchiectasis who requires use of bronchodilators, steroids and antibiotics on admission.

**Individuals** 18 years old and above admitted at the Lung Center of the Philippines with clinical diagnosis of bronchiectasis and signed an informed consent and willing to participate were considered for inclusion into the study.

**Exclusion Criteria:** Subjects not available to perform the procedure, with untreated pneumothorax, Diffuse Interstitial Lung Disease, Acute Coronary Syndrome, Third Stage Hypertension, Advanced Cancer, Severe heart, liver, renal, blood system, and endocrine system dysfunction, non-invasive mechanical ventilation and extubation within 48 hours and with active hemoptysis were excluded from the study.

Upon admission at the ward, patients were randomized after informed consent, duly approved by the Technical Review Board and the Ethics Review Committee of the Lung Center of the Philippines, has been signed. A computer generated randomization schedule were prepared for the study. Treatment were given within 24 hours after admission.

**A. Lung Flute Technique**

We ordered patients using Lung Flute to sit up straight and away from the back of the bed. Tilt head slightly downward so throat and windpipe are wide open. Inhale a little deeper than normal. Place lips completely around mouthpiece and mimic blowing out like a candle. Vigorously blow out twice (2) in succession through the device for 20 sets of two(2) blows each. The patient should concentrate in making fluttering noise produced by the reed. The harder and faster, the more sound is produced for Lung Flute to work better. In between blows, remove the device from the mouth to breath in. Wait for 5 seconds while taking a couple of breaths. We supervised the procedure and instructed the patients to collect sputum after nebulization from 7am to 12 noon for 3 consecutive days. After each session, sputum volume was measured using the standard measuring cup.

**B. Active Cycle Breathing Technique**

Patients were instructed to do Active Cycle Breathing Technique (ACBT) supervised by the Physical Therapist-on-duty. The Active Cycle Breathing Technique is a cycle of techniques of breathing control (tidal breathing at the patient’s own rate and depth, encouraging use of the lower chest with relaxation of the upper chest and shoulders), thoracic expansion exercises (deep breathing exercises emphasizing inspiration with or without a breath hold; expiration is quiet and relaxed) and the forced expiration technique (one or two huffs combined with periods of breathing control). Huffing to low lung volumes will assist in mobilizing and clearing the more peripherally situated secretions and, when secretions have reached the larger more proximal upper airways, a huff or cough from a high lung volume can be used to clear them. After the procedure, patients were also instructed to collect sputum after nebulization from 7am to 12 noon daily for 3 days. Sputum volume after each session was measured using the standard measuring cup.

Patients were also instructed to rate the level of relief and ease of expectoration.

- Grade 0 - no improvement
- Grade 1 - slight improvement
- Grade 2 - moderate improvement
- Grade 3 - marked improvement
Patients were monitored for occurrence of symptoms and complications like hypoxemia, pneumothorax and hemoptysis.

**Sample Size:** Assuming that 90% of patients will improve using Lung Flute against 60% in ACBT, 31 participants were needed in each group using the power of 80%, Alpha of 0.05 and Beta of 0.20

**Statistical Analysis:** Descriptive analysis was done by calculation of percentages and means. Differences between the 2 groups were tested using Chi-square test for categorical variables and T-Test for continuous variables. A p value of < 0.05 was considered significant.

**RESULTS**

A total of sixty-two (62) subjects were recruited in this study. Complete clinical history and information were gathered from the patients and diagnosis of Bronchiectasis was made based on the presenting signs and symptoms, radiographic findings, and medications given on admission. The population was randomized to receive for treatment either the Lung Flute or the Active Cycle Breathing Technique.

General demographic profile of the study population is described in Table 1. There was male predominance in both groups and majority of the population were non-smokers (35/62). Most often, subjects in both groups were in their 5th to 6th decade of life.

Graphical representation of the comorbidities in Lung Flute group are illustrated in Figure 2. Hypertension and Diabetes were among the most frequent condition noted.

Demonstration of the common diseases among patients who received ACBT are depicted in Figure 3. Hypertension was the most common comorbid condition.

<table>
<thead>
<tr>
<th>Table 1. Patient Characteristics</th>
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<td><strong>Patients Characteristics</strong></td>
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<td>Age</td>
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<td>16-35</td>
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<td>36-55</td>
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<td>76-95</td>
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<td>Sex</td>
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<td>Male</td>
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<tr>
<td>Female</td>
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<tr>
<td>Smoking History</td>
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<tr>
<td>Smoker</td>
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<td>Non-Smoker</td>
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Outcome Measures

The total expectorated sputum per day as illustrated in Figure 4 was relatively higher among patients who use Lung Flute (69.75±66.08 ml) compared to subjects who received Active Cycle Breathing Technique (54.95±49.30 ml). We analyzed the data using t-test which showed no statistical difference between 2 treatment groups (p=0.3214).

We have also documented that use of Lung Flute (2503.5ml) was able to generate voluminous amount of sputum for 3 consecutive days compared to ACBT (1355.5ml). This study also demonstrates that 64.5% (20/31) of the study population who used Lung Flute noted improvement after expectoration against 51.6% (16/31) of the patients who received Active Cycle Breathing Technique. We analyzed the data using Chi-square 2-tailed test which showed no statistical difference between 2 groups (p=0.44).

Figure 5 showed that majority of the subjects who used Lung Flute experienced marked relief after expectoration (51.6%) while most of the patients who received Active Cycle Breathing Technique noted moderate relief only (41.9%). We analyzed the data using Chi-square test and still showed no statistical difference between the 2 treatment groups (p=0.4885). However, cross-tabulation of the total volume of sputum expectorated to the grade of relief noted by the patients was statistically significant (p=0.0001).

Eight patients (25.8%) who received Active Cycle Breathing Technique complained discomfort of breathing after the procedure as it requires deep inhalation and expiration technique. One (1) patient was noted to have minimal hemoptysis and another with discomfort of breathing after using Lung Flute.
DISCUSSION

A number of airway clearance techniques has been introduced in the last decades. The use of Flutter device was initially proposed for the treatment of children with Cystic Fibrosis (Lindemann, 1992). There is not enough evidence about its utilization in patients with Bronchiectasis. The effect of Flutter device on respiratory mechanics of patients with Bronchiectasis have been evaluated by Forced Spirometry (Pryor e cols,1994; Gondor e cols,1999;Thompson e cols,2002). This approach, however, does not allow the characterization of mucus transportation along the airways.

Respiratory diseases are still increasing in older population and conventional respiratory physiotherapy, using clearance maneuvers, is a very commonly used resource in the treatment of Bronchiectasis, as the consequence of the disease’s chronic nature is retention of mucous, increases airflow resistance and gas exchange difficulties, which makes the work of expiratory muscles excessive and facilitates re-infection, thereby highlighting the necessity of bronchial hygiene.

Since then, different airway clearance techniques have developed independently in different parts of the world, evidence as to the optimal modality. In this study, both Lung Flute and ACBT were assessed in random order as part of pilot diagnostic evaluation over a period of 3 days in 62 patients (mean age of 60 years) with clinical diagnosis of Bronchiectasis. Both techniques were well accepted and tolerated by patients.

Demographic profile of each patient were reviewed. Detailed clinical history and information were taken from all the subjects and evaluated for 3 days based on expectorated sputum volume and relief after expectoration. Bronchiectasis was seen more often in males and prevalent among non-smokers. Some of the patients had associated comorbid condition with hypertension being the most frequent disease identified.

The amount of sputum expectorated per day by the subjects were quantified. This study confirms that using Lung Flute as mucus clearing device was more than two to three times the amount of expectorated than Active Cycle Breathing Technique. Although the mean quantity expectorated for the 2 treatment groups did not give statistical significance, this implies that the effectiveness of Lung Flute has equaled the standard Active Cycle Breathing Technique.

There was a significant improvement in relief after expectoration using Lung Flute, but this did not achieve a clinically meaningful change. While most patients experience marked ease in release of sputum secretions at 51.6%, comparison with the standard ACBT did not show considerable difference (p=0.4885).However, correlation of the total volume expectorated per day significantly influence the degree of relief felt by the subject(p=0.0001) suggesting that this device can be an acceptable alternative to standard ACBT during in-hospital care for patients with bronchiectasis.

<table>
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<tr>
<td>Discomfort of Breathing</td>
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<td>Hemoptysis</td>
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</table>
Taking into consideration both the patient’s and professional views, an airway clearance regimen should be effective, efficient, easy to use and easy to teach, capable of being done independently from the assistant, should improve lung function and should neither cause complications nor make patient uncomfortable. But while accomplishing these goal of therapy, it should be realized that these techniques have important adverse reactions to monitor. Some of the patients were noted to have discomfort of breathing and minimal hemoptysis after the treatment was done but inspite of this, majority of the patients stated they felt clinically better, were able to expectorate sputum easier and felt more relief after expectoration.

There continues to be a widespread debate as to which airway clearance regimen should be used and when. Like other studies, Lung Flute was found to have high level of patient acceptability as many of the patients commented on the ease of its use. A recent review of airway clearance techniques in adults has suggested that, if the objective differences are small between the different techniques, then individual preferences are likely to play an important part in compliance with treatment. Furthermore, it is proven in this report that Lung Flute is as effective in aiding sputum clearance in individuals with Bronchiectasis as the Active Cycle Breathing Technique and therefore suggest a trial of its utilization, and if preferred by the patients, should be recommended for regular use.

**CONCLUSION**

In general, the use of Lung Flute enables bronchiectasis patients to expectorate voluminous amount of sputum and provide relief after 3 days of therapy suggesting that this device can be a suitable alternative to standard ACBT during in-hospital care for patients with bronchiectasis. There was no overall difference in improvement between 2 treatment groups. It is therefore deduced that such techniques are equally efficacious in removal of secretions from patients with bronchiectasis.

**Recommendation**

A larger clinical trial and longer duration of the use of this device comparing with other respiratory devices and techniques will be necessary in the future to define its place among the current therapies available. This is just a preliminary study and some patients reported improvement only after 5-7 days of its daily use. Once benefit is justified through further research, the use of Lung Flute could improve patient’s compliance with mucus clearing therapy and result in reduced costs of care.

**References**


This research paper won first place in the PCCP Annual Research Paper Presentation during the PCCP 30th Annual Convention, March 2011
Efficacy Of Yoga In Improving Clinical Outcomes Among Patients With Asthma: A Meta-Analysis

Joanne Marie Balbuena, MD¹, Joye M. Cabradilla, MD¹, Janellen L Quiambao, MD¹, Ma. Bella Siasoco, MD, FPCP, FPCCP², Nolido MD, FPCP¹, Lenora C. Fernandez MD, FPCP, FPCC¹

ABSTRACT

Purpose:
This study aims to determine the efficacy of yoga as an added treatment to conventional asthma management in improving pulmonary function and controlling symptoms.

Methods:
Study selection and data abstraction were done in duplicate. Meta-analysis of mean change of PEFR, FEV1 and FEV1/FVC expressed as percent predicted was performed. Study quality through reporting of allocation concealment, blinding, outcome measures and follow-up of each of the studies was assessed.

Results:
Four randomized control trials were included in the review. For the primary outcome, 2 RCTs had comparable results, percent predicted of PEFR, FEV1 and FEV1/FVC at 4 and 8 weeks, representing 177 subjects. For the secondary outcome, 2 RCTs had comparable results, the evaluation of 4 domains of quality of life expressed as mean at 4 weeks, representing 182 subjects.

Yoga was able to show a progressive improvement in pulmonary function. The mean change in PEFR showed marked improvement in airway narrowing and airway limitation at four weeks (1.78 [1.18, 2.38]). The effect of yoga on PEFR was more evident at 8 weeks (5.90 [3.61, 8.18]). Mean change in FEV1 also showed improvement in airway resistance at 4 weeks (5.90 [5.43, 6.37]) and at 8 weeks (12.19 [9.85, 14.54]). The Mean change in FEV1/FVC at 4 weeks is 2.65 [2.06, 3.24] and 3.02 [0.90, 5.15] at 8 weeks. The yoga group scored higher in the Asthma Quality of Life Questionnaire compared to the control group (0.34 [0.21, 0.47]).

Conclusions:
Yoga breathing exercises have the potential to improve lung function and quality of life in persons with persistent asthma.

Keywords: Asthma, Yoga
Asthma and Yoga

INTRODUCTION

The World Health Organization (WHO) estimates that 300 million people currently suffer from asthma and this number is rising. Worldwide rates of asthma are, on average, rising by 50% every decade. In developing countries where the prevalence of asthma has been much lower, there is a rising incidence that appears to be associated with increased urbanization (1). In the Philippines, asthma affects approximately 5.5 million people (2).

The increasing global prevalence of asthma, the large burden it now imposes on patients, and the high health care costs have led to extensive research into its mechanisms and treatment (1). However, it has proved very difficult to discover novel pharmaceutical therapies, particularly as current therapy with corticosteroids and B2-agonists is so effective in the majority of patients.

In the 2009 Global Initiative for Asthma (GINA) guidelines, it is recognized that complementary and alternative medicine may have a role in the treatment of asthma. However, its use in adult asthma treatment is limited because these approaches have been insufficiently researched and their effectiveness is largely unproven (3). This study will concentrate on one of the non-pharmacologic treatments of asthma which is YOGA. The article, Therapeutic Importance of Yoga Practices by Dr. M.V. Bhole, discussed the benefits of yoga in the treatment of diseases. The yoga practices used in therapy are Asanas, Pranayamic breathing and Kriyas. Asanas are postures or postural patterns. These postures could give physio-therapeutic measures to develop coordination in different groups of muscles, to adjust the tonic disturbances in the body and to work on different joints and ligaments with a view to increase their flexibility and to influence local circulation. The various postures are Suryanamaskara (Figure 1), Matsyasana (Figure 2), Bhujangasana (Figure 3), Dhanurasana (Figure 4), Ushtrasana and Shavasana (Figure 5) (4).

Pranayama is yogic breathing. It increases ventilation, oxygen consumption and washes carbon dioxide in the body. Dr. Bhole outlined six channels of action of pranayama: 1) Due to increased airway resistance, the
normal pressure changes in the thoracic cavity are augmented and this has beneficial effect on circulation. 2) Prolonged phase of exhalation has a tranquilizing effect on the nervous system. 3) Slightly contracted pelvic and abdominal muscles help keep the thoracic diaphragm at a higher level, thereby reducing the dead-space volume. 4) Ten cycles of the same type of breathing helps establish a new rhythm at the higher level, which in turn will influence various psycho-neuro-endocrine mechanisms. 5) After about six or seven rounds of Pranayamic breathing, the level of carbon-dioxide in the expired air increases. 6) As the mind is attached to the breathing it becomes calm and quiet. Kriyas or “cleansing process” developed to prepare oneself for the effective practice of Pranayama and to intensify the events taking place in Pranayama (5).

There are currently conflicting results from randomized controlled trials investigating the impact of yoga in bronchial asthma management. In the clinical study of PK Vedanthan, pulmonary functions did not vary significantly between yoga and control groups (6). The study of S Cooper showed that Buteyko breathing techniques can improve symptoms and reduce bronchodilator use but does not appear to change bronchial responsiveness or lung function (7). Based on the pilot study of A Sabina (8), Iyengar yoga conferred no appreciable benefit in mild-to-moderate asthma.

There were RCTs which showed improvement in lung function of asthmatics after yoga training. According to the study of R Nagarathna (9), there were highly significant improvements in the yoga group compared with controls. In the study of R Manocha (10), Sahaja yoga does have...
Asthma and Yoga

limited beneficial effects on some objective and subjective measures of the impact of asthma. Based on the trial by R Vempati, adding a comprehensive yoga-based mid-body intervention to the conventional treatment improves several measures of pulmonary functions in subjects having mild to moderate asthma. Yoga also improves the quality of life and reduces rescue medications (11). In the study of C Sodhi, yoga breathing exercises used adjunctively with standard pharmacological treatment significantly improves pulmonary functions in patients with bronchial asthma (12). Since there are a growing number of clinical trials giving conflicting results as to what extent yoga is of benefit for asthma, it is the authors’ goal to find clinical trials focused on yoga as an additional treatment to conventional asthma management. Further, we want to determine if yoga has an impact on control of asthma symptoms, pulmonary function and the prevention of asthma exacerbations.

METHODS

Randomized controlled trials with adult patients diagnosed with mild to moderate Bronchial Asthma (based on the American Thoracic Society spirometry criteria, 1994 update) using conventional treatment with yoga were compared to those receiving conventional treatment only. Primary outcome was mean change of PEFR, FEV1 and FEV1/FVC. Secondary outcome is mean change in Asthma Quality of Life Score (AQOL) which evaluates the 4 domains (symptoms, activity limitation, emotional function and environmental stimuli).

Articles were searched for in Cochrane, Pubmed, Medline and Medscape. Search terms were “Yoga” and “Asthma”. “Asthma” [Mesh] AND “Yoga” [Mesh] were the final search terms in Pubmed. Search was also done in Clinical Trials.gov. The International Association of Yoga Therapist has a website which features the following journals: International Journal of Yoga Therapy, Yoga Therapy Today and Yoga Studies Online. Ms. Trisha Lamb of the said association compiled a list of articles on Yoga and Asthma which was revised last May 7, 2004. Google was also searched with the same search terms. Several duplicates were noted. There were also 2 yoga websites devoted to yoga research. The YOGA SITE (The Online Yoga Resource Center) (12) and SYVASA Higher Learning in Yogic Sciences and Research (14). A thorough search was also done in the two websites. Two duplicates were noted.

Three studies were available in Clinical Trials.gov. The first is on Bikram Yoga and Asthma, however the study is not yet recruiting. The second is Integrative Medicine Approach to the Management of Asthma in Adults, with a clinical question: Among patients 18-80 years old with mild persistent, moderate persistent and severe persistent asthma, what is the efficacy of healthy eating, yogic breathing exercises and journaling sessions in the quality of life of asthmatics. It is not yet published and investigators could not be located. The third trial is on Asthma and Mindfulness-Based Stress Reduction (MBSR). The study

Data extraction was done independently by three reviewers, using a standardized data extraction form. Data extracted was recorded using Revman. Abstraction included information on characteristics of the participants, the verification of diagnosis, the specific yoga program instituted and the outcomes assessed (e.g. PEFR, FEV1 and FEV1/FVC).

All of the studies were examined for validity. Three reviewers working independently determined the adequacy of randomization, allocation concealment, blinding, outcome measures, intention-to-treat and follow-up of each of the studies.

Meta-analysis of the randomized controlled trials was done by three authors. Data from the extraction forms was used. The mean change in percent predicted of PEFR, FEV1 and FEV1/FVC, and mean change in AQQL were computed. The results were plotted in a forest plot wherein each individual trial intervention effect is shown with its confidence interval. A tool to assess heterogeneity was used.

Articles were searched for in Cochrane, Pubmed, Medline and Medscape. Search terms were “Yoga” and “Asthma”. There were a total of 43 articles on “Asthma” [Mesh] AND “Yoga” [Mesh] in Pubmed. No articles were found in Cochrane. There were 34 documents in Medline. Fourteen journal articles were retrieved from Medscape. The listing compiled by the International Journal of Yoga therapy comprised of 351 articles. Google was also searched with the same search terms. Several duplicates were noted. There were also 2 yoga websites devoted to yoga research. The YOGA SITE (The Online Yoga Resource Center) (13) and SYVASA Higher Learning in Yogic Sciences and Research (14). A thorough search was also done in the two websites. Two duplicates were noted.
is active but not yet recruiting. A talk with experts in yoga here in the Philippines was attempted; however no known local studies are available.

A total of 455 citations were retrieved. Four hundred twenty three citations were excluded, including the 3 trials from Clinical Trials.gov, 5 articles in foreign languages, 4 articles where abstracts were unavailable and several duplicates. Most of the excluded citations were editorials or descriptive studies. Thirty-two articles with abstracts and full texts were left to be reviewed. Each of the studies was broadly screened based on the inclusion criteria for types of participants, types of interventions and outcomes. Twenty-four were excluded for reasons mentioned in the flow chart. A total of 8 RCTs were retrieved for full scrutiny.

Three trials representing 239 subjects were included in this review. Table 1 lists the characteristics of these studies. For the primary outcome, only 2 RCTs have comparable results, mainly the percent predicted of PEFR, FEV1 and FEV1/FVC at 4 and 8 weeks, representing 177 subjects. For the secondary outcome, only 2 RCTs have comparable results, which are the evaluation of 4 domains of quality of life expressed as mean at 4 weeks, representing 182 subjects.

**RESULTS**

Table. 1 shows the characteristics of the included studies.

Articles were searched for in Cochrane, Pubmed, Medline and Medscape. Search terms were “Yoga” and “Asthma”. There were a total of 43 articles on “Asthma” [Mesh] AND “Yoga” [Mesh] in Pubmed. No articles were found in Cochrane. There were 34 documents in Medline. Fourteen journal articles were retrieved from Medscape. The listing compiled by the International Journal of Yoga therapy comprised of 351 articles. Google was also searched with the same search terms. Several duplicates were noted. There were also 2 yoga websites devoted to yoga research. The YOGA SITE (The Online Yoga Resource Center) and SYVASA Higher Learning in Yogic Sciences and Research. A through search was also done in the two websites. Two duplicates were noted. Three studies were available in Clinical Trials.gov. The first is on Bikram Yoga and Asthma, however the study is not yet recruiting. The second is Integrative Medicine Approach to the Management of Asthma in Adults, with a clinical question: Among patients 18-80 years old with mild persistent, moderate persistent and severe persistent asthma, what is the efficacy of healthy eating, yogic breathing exercises and journaling sessions in the quality of life of asthmatics. It is not yet published and investigators could not be located. The third trial is on Asthma and Mindfulness-Based Stress Reduction (MBSR). The study is active but not yet recruiting. A talk with experts in yoga here in the Philippines was attempted; however no known local studies are available.

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![Flowchart](image-url)
A total of 8 RCTs were retrieved for full scrutiny. Three trials representing 239 subjects were included in this review. For the primary outcome, only 2 RCTs have comparable results, mainly the percent predicted of PEFR, FEV1 and FEV1/FVC at 4 and 8 weeks, representing 177 subjects. For the secondary outcome, only 2 RCTs have comparable results, which are the evaluation of 4 domains of quality of life expressed as mean at 4 weeks, representing 182 subjects.

Risk of Bias in included studies

Both studies randomly allocated their subjects. Baseline characteristics of subjects in the two studies were comparable. Allocations, analysis and drop outs were not stated. Subjects were not blinded.

Effects of Intervention

Yoga as an adjunctive therapy was able to show a progressive improvement in pulmonary function. The mean change in PEFR shows marked improvement in airway narrowing and airway limitation at four weeks (Fig 8), 1.78 [1.18, 2.38]. The effect of yoga on PEFR is more evident at 8 weeks (Fig 9), 5.90 [3.61, 8.18]. However, a wide variation was noted. The PEFR varies at different times of day. It is also dependent on the severity of the disease and patient characteristics like age, gender, height and socio-economic status. Mean change in FEV1 also showed improvement in airway resistance at 4 weeks (Fig 10) 5.90 [5.43, 6.37] and at 8 weeks (Fig 11), 12.19 [9.85, 14.54]. The Mean change in FEV1/FVC at 4 weeks (Fig 12) is 2.65 [2.06, 3.24] and 3.02 [0.90, 5.15] at 8 weeks (Fig 13). The yoga group had a higher mean change 0.34 [0.21, 0.47] in the Asthma Quality of Life Questionnaire (Fig 14) scored compared to the control group at 4 weeks.
DISCUSSION

Significant, steady and progressive improvement in key objective variables such as FEV1 and FEV1/FVC in the yoga group but not in the control group indicates the efficacy of yoga. This is further supported by the significant greater improvement in quality of care in the yoga group than in the control group. The results of Asthma Quality of Life questionnaire revealed that the yoga subjects had better sense of well-being than the control group.

While the methodology was thorough, the main limitation of our study is the small number of randomized controlled trials available. Randomization, concealment, small sample size and funding are common issues in the methodology of primary studies.

In this meta-analysis, the efficacy of yoga as adjuvant therapy for asthma was evaluated. It is important to note that the role of yoga was assessed as adjunctive treatment in addition to the benefits of conventional treatment such as inhaled corticosteroids and bronchodilators. It is not the objective of this review to test the role of yoga as a replacement for conventional treatment.

Learning yoga and practicing it requires time commitment and schedule, and can be even be more costly than conventional medications during the initial period of instruction. However, once learned, yoga can be practiced at home with no associated costs.

Yoga breathing exercises have the potential to improve lung function and quality of life in persons with persistent asthma. However, due to the small number of high quality randomized controlled trials currently available, it is not possible to make strong associations and conclusions regarding the efficacy of yoga in controlling asthma attacks. Better constructed randomized controlled trials with strict methodological quality are needed.

CONCLUSION

Yoga breathing exercises have the potential to improve lung function and quality of life in persons with persistent asthma. However, due to the small number of high quality randomized controlled trials currently available, it is not possible to make strong associations and conclusions regarding the efficacy of yoga in controlling asthma attacks.

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<th>Mean Difference</th>
<th>N, Fixed, 95% Cl</th>
<th>Mean Difference</th>
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Table 1. Study Characteristics of Yoga and Asthma

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<td>Group C</td>
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<td>Group D</td>
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<th>Intervention</th>
<th>Postures: Beginners, Intermediate, Advanced</th>
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<tr>
<td>Week 1</td>
<td>Beginner: Cat-Cow, Downward Dog, Warrior I</td>
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<tr>
<td>Week 2</td>
<td>Intermediate: Sun Salutations, Warrior II</td>
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<tr>
<td>Week 3</td>
<td>Advanced: Chair, Triangle, Warrior III</td>
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References:

4. Therapeutic Importance of Yoga Practices. Dr. MV Bhole, MB, BS, MD. Deputy Director of Scientific Research, Lonavla Institute, India.

This paper was presented as a poster presentation during the 16th Congress of the Asian Pacific Society of Respirology
Theme: Asia-Pacific Respirology: Symbiosis in the 21st Century
## CME Calendar

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<td>ACCP Mid Year Convention</td>
<td>April 12 - 13, 2012</td>
<td>Bacolod, Phil</td>
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<td>ACCP (Philippine Chapter)</td>
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<tr>
<td>American Thoracic Society 2012 International Conference</td>
<td>May 18 - 23, 2012</td>
<td>San Francisco Ca., USA</td>
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<tr>
<td>55th Annual Thomas L. Petty Aspen Lung Conference</td>
<td>June 6 - 9, 2012</td>
<td>Aspen Colorado, USA</td>
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<tr>
<td>COPD 8</td>
<td>June 20 - 22, 2012</td>
<td>Birmingham, UK</td>
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<tr>
<td>PCCP Midyear Convention</td>
<td>August 2-4, 2012</td>
<td>Palawan, Phil</td>
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<tr>
<td>27th Annual Meeting American Association of Cardiovascular Pulmonary Rehabilitation</td>
<td>Sept. 6 - 8, 2012</td>
<td>Florida, USA</td>
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<tr>
<td>Chest 2012 (ACCP)</td>
<td>Oct. 20 - 25, 2012</td>
<td>Atlanta, Georgia, USA</td>
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<tr>
<td>6th Forum on Respiratory Tract Infection</td>
<td>Nov. 28 - 30, 2012</td>
<td>Barcelona Spain</td>
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BONE CONNECTION:
A Case of Klippel-Feil Syndrome with Spinal TB Osteomyelitis

Irenee Faustina Casino, MD, FPCP; Myla M. Castillo, MD, FPCP; Rhea Louela Jusi, MD, FPCP; Irene Villanueva-Felipe, MD, FPCP; Rommel Bayot, MD, FPCP, FPCCP; Fernando Ayuyao, MD, FPCP, FPCCP; Teresita de Guia, MD, FPCP, FPCCP

ABSTRACT

This is a case of a 30 year-old man, noted to have stooped posture since birth, who was admitted due to difficulty of breathing and productive cough. Treatment for pulmonary tuberculosis was ongoing at this time, but he was non-compliant with his medications. Physical examination revealed a low hairline and short neck with a limited range of motion. Crackles were auscultated on both lower lung fields, and the patient was in cardiopulmonary distress. Work-up revealed chronic respiratory acidosis on arterial blood gas analysis, pulmonary tuberculosis of both upper lobes seen on chest radiograph, and narrowing of the C4-C5 disc space, fusion of the posterior diameter of multiple cervical vertebra, and blocked bodies of C5-C7. A Gibbus deformity and synostosis in the upper thoracic spine were also appreciated. He was thus diagnosed as having Klippel-Feil syndrome with concomitant spinal TB osteomyelitis, combined obstructive and restrictive lung defect, bronchiectasis, obstructive sleep apnea, and pulmonary hypertension. He was managed with antibiotics, quadruple anti-TB medications, non-invasive ventilation, nightly CPAP administration, and other supportive therapies, and was later discharged improved.

CASE PRESENTATION

A 30-year-old male was admitted with a chief complaint of difficulty of breathing. He was previously well until three months prior to admission, when he started experiencing exertional dyspnea and cough productive of yellowish phlegm. These were not accompanied by fever, weight loss, edema, hemoptyisis, nor chest pain. He was diagnosed to have Pulmonary Tuberculosis at a local health clinic and advised to start quadruple anti-tuberculosis medications but was non-compliant with treatment.

One week prior to admission, there was worsening cough and progressive difficulty of breathing. No further complaints were noted. Due to the persistence of symptoms, he was admitted.

The patient been noted to have a stooped posture with limitation of neck movement since 2 years of age. Motor and sensory developmental milestones were at par with age but he complained of hearing loss on the right ear since eight years ago. There were no other co-morbid conditions such as hypertension, diabetes mellitus, heart disease or asthma.

The patient previously worked as a drummer in a musical band. He is a 7-pack-year smoker who stopped 3 months prior to admission, but still drinks alcohol occasionally. He denied illicit substance abuse.
n physical examination, the patient was noted to be conscious, coherent, and in cardiorespiratory distress. He was ambulatory, with a stooped posture, a low hairline, a short neck with limited neck motion on all planes (Figure 1), and a prominent right scapula. Chest examination revealed supraclavicular and intercostal retractions, with crackles auscultation on both anterior and posterior lower lung fields. Neurologic examination revealed a positive Weber test with bone conduction greater than air conduction on the right ear. Muscle strength and sensation were intact on both left and right sides, and bilaterally normoreflexive DTRs with no pathologic reflexes were observed.

At this point, the working diagnosis was that of acute respiratory failure secondary to Community-Acquired Pneumonia Moderate Risk, Pulmonary Tuberculosis, and Congenital Kyphosis.

On admission, arterial blood gas testing revealed acute on top of chronic respiratory acidosis with more than adequate oxygenation. Chest radiography showed pulmonary tuberculosis on both upper lobes, hyperaerated lungs, and narrow upper thoracic intercostal spaces (Figure 2). Sputum culture and sensitivity did not reveal any significant pathogens while sputum AFB results for 3 days were negative. Cervical radiography showed a fusion of the posterior diameter of multiple cervical vertebra, blocked bodies of C5-C6 and probably C7, and narrowing of the C4-C5 disc space likely congenital in origin (Figure 3-A). Cervical MRI showed exaggerated kyphosis of the upper thoracic spine with a Cobb’s angle of 70 degrees with an unsegmented or blocked C5-C6 vertebra, and narrowing of other intervertebral disc space (Figure 3-B). A subsequent chest CT scan revealed a Gibbus deformity, synostosis in the upper thoracic spine, pleuroparenchymal fibrosis, volume loss, tubular and cystic bronchiectasis, blebs, bullae and pleural thickening in the right upper and middle lobe (Figure 4). Whole abdominal ultrasound was normal. Echocardiogram revealed moderate pulmonary hypertension but with no septal defect seen. Polysomnography results showed moderate sleep-disordered breathing. Pulmonary function test revealed an obstructive lung defect with no significant bronchodilator response, a concomitant restrictive lung defect, hyperinflation, and a reduced DLCO.

Considering his short webbed neck, limited neck motion and low hairline, coupled with cervical fusion, Gibbus deformity, and synostosis as seen on imaging, the patient was diagnosed to have both Klippel-Feil syndrome and spinal TB osteomyelitis.

He was initially provided with non-invasive ventilation for the acute respiratory failure, and was started on antibiotics and quadruple anti-TB therapy with Isoniazid, Rifampicin, Pyrazinamide and Ethambutol. Once stabilized, he was started on nightly CPAP, and other supportive treatments. He gradually improved and was eventually discharged on low-flow home oxygen treatment with plans for rehabilitation and continuous follow-up.

The final diagnosis for the patient was Acute on top of Chronic Respiratory Failure Type 2, Klippel-Feil Syndrome, Pulmonary Tuberculosis, Spinal Tuberculosis Osteomyelitis, Bronchiectasis, moderate Obstructive Sleep Apnea, and Pulmonary Hypertension Class 3, Functional Capacity 2.
DISCUSSION

Klippel-Feil Syndrome (KFS) is a rare disease presenting with congenital fusion of the cervical vertebral segments (Klippel). The infrequency with which it is encountered makes it a formidable diagnostic challenge, especially in the Philippines where it can often be confused with Pott’s disease. In the case of our patient, he had both.

Klippel-Feil Syndrome (KFS) was first described by Maurice Klippel and Andre Feil in 1912. Its true incidence is unknown because no one has ever studied a cross-section of healthy people to determine it (1). Thus, the incidence of KFS in the Philippines is also unknown. However, Gjorup et al determined an incidence of 0.2 cases per 1000 people in a review of radiographs from a single hospital (2), while Brown et al found an incidence of 0.71% from a review of skeletons at the Washington University School of Medicine. A male predominance was also noted by Smith (4).

In KFS, there is bilateral failure of vertebral segmentation, which leads to the formation of a block vertebra. It is due to the mutation on the long arm of chromosome 8 and is inherited as an autosomal dominant disorder with limited penetrance. Subsequently, KFS has been classified into 3 types: Type I, in which there is massive fusion of the cervical spine; Type II, in which there is fusion of one or two cervical vertebrae, and Type III, in which there is involvement of the thoracic or lumbar vertebrae. Our patient was classified to have Klippel-Feil Syndrome Type II. Aside from cervical vertebral fusion, other orthopaedic findings in KFS that may be present in 60% of patients include scoliosis, kyphoscoliosis, and kyphosis (1, 5).

Klippel-Feil Syndrome may also be associated with a constellation of anomalies: renal anomalies in 33%; renal agenesis; impaired hearing in 30%; synkinesia, or mirror movement in 18%; cardiovascular anomalies such as septal defects in 14% of patients, and obstructive sleep apneas (6). In our patient, pulmonary hypertension and obstructive sleep apnea were also documented.

Plain radiography is the basis of the diagnosis of KFS, showing the fused segments. CT scanning is more useful at the spinal level. Magnetic resonance imaging (MRI) is indicated in patients with neurologic deficits. Other diagnostic tests that can be done to screen other associated anomalies include ultrasonography of the kidneys to rule out renal anomalies and 2D echocardiography for cardiac involvement (1). Urologic and/or cardiac evaluation may be indicated based on the results of the imaging studies. An audiologist or otologist should also evaluate all patients suspected to have the syndrome (1).

Patients with KFS usually manifest during childhood but may present later in life. Patients with upper cervical spine involvement tend to become symptomatic at an earlier age than those whose involvement is lower in the cervical spine. Irrespective of the time of presentation, a decreased range of motion of the cervical spine is the most frequent clinical finding. Rotational loss is usually more pronounced than is the loss of
flexion and extension of the cervical spine(7). In the case of our patient, he presented with a stooped posture and decreased range of motion of the neck since childhood, however, considering that tuberculosis is endemic in our setting, and the fact that the Klippel-Feil syndrome may render the affected bone to be a site of predilection for infection and trauma, a concomitant Pott’s disease was also considered.

Pott’s disease is an extrapulmonary tuberculosis that affects the spine, and it is the least common manifestation of musculoskeletal tuberculosis. According to Park et al (8), among adults, the lower thoracic vertebrae are the most common area of involvement (40-50%), followed closely by the lumbar spine (35-45%), and then by the upper thoracic spine. Only 10% of Pott’s disease cases involve the cervical spine (9).

The duration of symptoms ranges from days to months, and includes localized pain, soft tissue swelling that may be accompanied by low grade fevers, weight loss and malaise. Regional lymphadenopathy and abscess formation are common, and disease progression may result in collapse of one or more vertebrae. Loss of anterior column support results in kyphotic deformities, which may occur in both the active and healed phases of the disease with or without surgical arthrodesis. Progression of kyphosis is most common in children with multiple levels of involvement in the thoracic spine (10).

Imaging is suggestive of the disorder; however, if feasible, biopsy is recommended. Tuberculin skin test (purified protein derivative [PPD]) results are positive in 84-95% of patients with Pott’s disease who are not infected with HIV(11).

The management of Klippel-Feil syndrome is based on treating the most common patient complaints. The cervical fusion may be asymptomatic, and may only be discovered when radiographs are done for unrelated reasons. Alternatively, they may present with decreased range of motion of the neck, radicular pain, cosmetic concerns, or problems related to other organs. Treatment of these symptoms includes modification of activities, bracing, pain relievers, and traction. Patients are also advised periodic flexion-extension of the neck, cervical spinal radiographs, and avoidance of contact sports, as these patients are prone to neurologic compromise.

Indications for surgery include pain, progressive cervical instability or neurologic symptoms, which were not present in the patient. Thus, conservative treatment was recommended. However, consideration had to be given to the fact that the patient has concomitant Pott’s disease (12).

The cornerstone of treatment for both pulmonary and bone and joint tuberculosis remains to be chemotherapy. The standard regimen of two months of Isoniazid, Rifampicin, Pyrazinamide, and Ethambutol, and four months of Isoniazid and Rifampicin is recommended. However, both the latest Philippine and WHO tuberculosis guidelines suggest extending the continuation phase for 7 months for cases of bone and joint tuberculosis because of the difficulties in assessing treatment response (10,11,13,14).

Opinions also differ as to whether the treatment of choice should be chemotherapy alone or combined chemotherapy and surgery. The 2010 WHO tuberculosis guidelines confirm that surgery is reserved for neurologic involvement from Pott’s disease. Lastly, two randomized controlled trials comparing chemotherapy alone plus surgery versus chemotherapy alone for treating Pott’s disease had too few participants to conclude that routine surgery may be beneficial. Surgical approaches to bone and joint tuberculosis include anterior corpectomy, shortening of the posterior column, posterior instrumentation, and anterior and posterior bone grafting (12).
The patient also initially presented with dyspnea and respiratory acidosis. He met the indications for non-invasive positive pressure ventilation (NPPV), and was alert and cooperative, both important predictors for the success of NPPV. Once the acute symptoms were relieved, attention was turned to the management of the patient’s chronic respiratory failure. In such cases, options include non-invasive positive- and negative-pressure ventilation.

Long-term nocturnal or continuous NPPV has been shown to improve lung volumes, respiratory function, and arterial blood gases. On the other hand, negative pressure ventilators have significant disadvantages and are thus infrequently used. In a study comprising 7 patients suffering from respiratory failure secondary to kyphosis, nocturnal non-invasive ventilation led to a decrease in symptoms, improvement of physiologic abnormalities, and prolonged survival (14).

Kyphosis with minimal respiratory impairment has a good prognosis and only requires supportive care, while patients with severe kyphosis and cor pulmonale have a life expectancy of less than one year. Our patient already had signs of cor pulmonale, thus supportive treatment was maximized (14).

The patient was also diagnosed to have Obstructive Sleep Apnea. According to the American Academy of Sleep Medicine, CPAP should be offered to all patients with a Respiratory Distress Index (RDI) greater than 15 events per hour, and those with an RDI of only 5 to 14 events per hour but presenting with symptoms. Our patient had an RDI of 24.1 events per hour indicative of Moderate Sleep-Disordered Breathing, thus qualifying him for CPAP. CPAP provides a pneumatic splint to the airway, and its beneficial effects include a decrease in frequency of respiratory events, a decrease in daytime sleepiness, improvement in sleep quality, reduction of nocturnal hypertension, prevention of driving accidents, and improvement in quality of life (15). After undergoing a therapeutic sleep study, it was recommended that the patient use nightly CPAP at 8 cm water. On follow-up testing, it was noted that his RDI improved to 4.4 per hour.

In this patient, the cervical fusion secondary to KFS and the kyphosis caused by the spinal TB affected the biomechanics of the spine and body, causing a clinically significant cosmetic disfigurement, notably the hypoventilatory type of respiratory failure.

For normal respiration to occur, the respiratory muscles, the bony structure of the rib cage, the spine, and the soft tissues must be effectively functioning (9). Disorders in these fundamental parts with or without other diseases may interfere with inspiratory pump function and lead to respiratory failure. For example, an abnormality of the thoracic vertebra due to tuberculous osteomyelitis of the spine would result in the distortion of the chest configuration and impaired respiratory function. The existence of structural abnormalities of the thoracic cage, such as in kyphosis and cervical fusion, would also interfere with the action of the respiratory muscles, including the major and secondary muscles.9

In patients with thoracic deformity like kyphosis, scoliosis or kyphoscoliosis, the respiratory system compliance is reduced due to the decreased chest wall compliance and, to a lesser degree, decreased lung compliance. The stiffened chest wall places the resting position of the respiratory system at a lower lung volume, further reducing compliance by shifting tidal breathing to a flatter portion of the volume-pressure curve. Although in kyphosis, the chest wall may be greatly deformed but remaining symmetrical, respiratory compliance is lessened due to the increase in the elastic load placed on the respiratory muscles, thereby increasing the work of breathing (9).

Ventilatory failure may also be affected by the Cobb’s angle. An angle more than 100 degrees leads to ventilatory failure; however, in the case of the patient, the measured Cobb’s angle of kyphosis was only 70 degrees (12).

Ventilatory failure secondary to the kyphosis of spinal tuberculosis has been noted to develop only 43 to 61 years after the kyphosis is noticed, suggesting that it may be precipitated by changes associated with aging, such as a reduction in respiratory drive (12).

Characteristically, these patients have decreased total lung capacity (TLC) and vital capacity (VC) (9). An obstructive pattern has also been reported, mainly because of small airway obstruction. In fact, studies have shown that these patients may exhibit a reduced FEV1 and FEV1/FVC ratio, and a RV/TLC ratio as high as 50%. Kyphosis increases the risk of airway obstruction by more than three times, independent of other conditions that may lead to this abnormality, such as chronic bronchitis and asthma. Although further study is needed in order to better understand the pathophysiology of ventilatory abnormalities, it is hypothesized that the distortion of the large airways, which are forced to follow the abnormal curvature of the kyphotic spine, may lead to the obstructive lung defect. These mechanisms may help explain the severe restrictive and obstructive pattern seen in our patient (9).

The increase in the chest wall and lung elastic load caused by...
the chest deformity, and the decrease in the neuromuscular competence secondary to the depressed drive in obstructive sleep apnea result to hypercapnic respiratory failure leading to chronic hypoxemia (16). The chronic hypoxemia from hypoventilation results in the hypertrophy of the pulmonary arterial muscle and to subsequent pulmonary hypertension (9) abnormality, such as chronic bronchitis and asthma. The widened alveolar-arterial gradient observed in the patient confirms the presence of ventilation-perfusion mismatch which is easily correctable by oxygen supplementation. The ventilation-perfusion mismatch may have been brought about by bronchiectasis and pulmonary tuberculosis, leading to airway obstruction and the destruction of lung parenchyma. The resulting deficiency in oxygen supply further aggravates the hypoventilation leading to the hypoxemia and respiratory failure observed in the patient (9).

## CONCLUSION

The collection of evidence points to an extraordinary juxtaposition of events - that of an acquired deformity on top of a congenital abnormality. It is a combination so rare that it has never been reported thus far in the Philippines, and has only been documented once in literature: in the exhumation of Cardinal Carlo de’ Medici, former Dean of the College of Cardinals, who lived from 1595–1666. Of course, we can only speculate who among our countless patients with spinal tuberculosis may actually have concomitant Klippel-Feil’s syndrome, or congenital spinal fusion masquerading as Pott’s disease.

However, our role as pulmonologists when encountering patients with significant spinal abnormalities is to prevent and treat the respiratory complications that invariably arise in these cases. In the case of our patient, who presented with hypoventilatory respiratory failure, restrictive and obstructive lung defects, obstructive sleep apnea, and pulmonary hypertension, perhaps some of his respiratory problems may have been delayed or attenuated had they been anticipated at an early stage.

In conclusion, although Klippel-Feil Syndrome and Pott’s disease present primarily with a cosmetic deformity, a high index of suspicion should always be maintained for the coexistence of respiratory problems which can be managed accordingly in order to improve the patient’s quality of life.

## References

Ten individuals are responsible for the development of modern physical diagnosis: Hippocrates, Vesalius, Morgagni, Sydenham, Auenbrugger, Corvisart, Laennec, Louis, Mueller, and Osler (1). Of this elite group, Auenbrugger, Corvisart, and Laennec forged the basis of chest examination. The story of these three physicians illustrates how medical traditions links older knowledge with innovations and thus allows science to evolve (2).

Since ancient Egyptian and Mesopotamian times, chest inspection and palpation have been the basis for examination of the respiratory system. Immediate auscultation (performed by laying one ear directly on the patient’s chest to listen to lung and heart sounds) gained relevance only in 1761. Credits belonged to an Italian physician, Giovanni Battista Morgagni, who described the correlation between some alterations of normal body sounds with pathologic states. Morgagni contributed enormously to pathologic anatomy by correlating autopsy findings with the clinical history. He described many pathologic states like pneumonia with consolidation of the lungs (3).

But Morgagni’s contributions had little value in the face of the inability of the physician to ascertain the state of diseased organs inside the patient (1). It was an Austrian physician, Leopold Auenbrugger (1722-1809) who conferred this ability upon the physician by introducing percussion to the physical examination of the chest (4). He conceived the method of percussion of the chest in order to be able to judge the condition of the underlying organs (normal or pathologic) on the basis of the sound produced. By striking the chest he can distinguish four percussion notes: normal, tympanitic, dullness, and flatness (5). He associated the different percussion notes with various lung diseases. For seven years he devoted himself to the study of comparing necropsy findings with what he had “observed” by percussion in terminal patients. In 1761 he published his work in a 95-page book: Inventum novum ex percussion e thoracishumanis (6).

Auenbrugger’s book received unfavorable and even hostile reviews. It was apparently little noticed until Maximilian Stoll became the leader of the Old Vienna School and used percussion in the clinics (7). One of Stoll’s pupils, Josef Eyerel, wrote a paper on percussion that serendipitously was noticed by the French clinician Corvisart.

Jean Nicolas Corvisart (1755–1821) was France’s greatest clinician in his time. His fame and ability were such that he became Napoleon Bonaparte’s personal physician. He recognized the value of Auenbrugger’s work and applied it on the wards (8). After 20 years’ experience with percussion, he published his findings in 1808 together with an unabridged translation of Inventum Novum to French. Years later, Corvisart became the mentor of a young French physician, Théophile Laënnec (1781-1826) (9). Corvisart introduced Laënnec to immediate auscultation and to the concept of chest percussion. In so doing, he acted as a link between the senior Auenbrugger and his young pupil.

Rene Théophile Hyacinthe Laënnec invented the stethoscope in 1816 (10, 11). As recounted by a friend the great discovery was due to chance…

“One day walking in the court of the Louvre, he saw some children, who, with their ears glued to the two ends of some long pieces of wood which transmitted the sound of the little blows of the pins, struck at the opposite end. … He conceived instantly the thought of applying this to the study of diseases of the heart. On the morrow, while asked to examine a young fat lady (in whom direct auscultation will not yield useful information), at his clinic at the Necker Hospital, he took a sheet of paper, rolled it up, tied it with a string, making a central canal which he then placed on a diseased heart. This was the first stethoscope.” (3, 12)
Lung Sounds

Laënnec did more than discover auscultation. It was he who first sought and found the confirmation of the clinical diagnosis at the autopsy table and united pathologic anatomy by an inseparable bond (13). To his credit, Laënnec had a mind that has been prepared for the discovery of “mediate auscultation” (listening to the body through another object, such as the stethoscope). He tried many designs before he adopted one that consisted of a light wooden tube, four centimeters wide and 30 centimeters long, one end of which was funnel-shaped. He named his invention, stethoscope, from the Greek stethos—the chest and scope—to view, because it enabled the physicians to “see” the inside of the chest.

In 1819, he published his observations in a book entitled: *Traité de l’auscultation mediate* (14). It was the product of three years of the most intensive work with his new stethoscope and also of more than 18 years of close study of problems in pathology and clinical medicine. His book was far more than a manual on the use of the stethoscope. It was also a treatise on diseases of the lungs and heart (14, 15). He was creator of a large number of words now currently used in physical diagnosis, such as rales, bronchopony, pectoriloquy, and egophony. It was immediately accepted as an epochmaking work, and auscultation was soon used in medical clinics throughout the world (3). John Forbes published the first English translation of *Traité de l’auscultation mediate* in 1821 (15).

**Origin of vesicular and bronchial breath sounds**

The origin of the lung sounds remains unclear. Laënnec described the normal lung sound as “a slight but extremely distinct murmur answering to the entrance of air into and its expulsion from the air cells of the lungs” (14). However, increased information on pulmonary function especially mechanics of breathing paved the way to a better understanding of lung sound production. Forgacs believed that the source of the lung sounds is primarily from the turbulence of the airstream flowing through the pharynx, glottis and large airways (trachea and major bronchi) (16). As air passes through the larger airways and segmental bronchi, it now goes to the peripheral airways. In the peripheral airways, the total airflow is now divided among hundreds or thousands of tubes and the volume of air is now spread out. As a result, the airflow becomes slower, less turbulent, and laminar.

Therefore, on auscultation, bronchial breath sounds are generated by turbulent airflow in the trachea and proximal bronchi. However, the origin of the vesicular breath sounds is less clear since airflow in the peripheral airways is laminar and less turbulent. It is then assumed that vesicular breath sounds may come from filtered bronchial breath sounds.

In general, the normal air-filled lung acts as a “low-pass” filter to sound. It will cause sounds to decrease in intensity and pitch as such sounds waves travel through the alveoli. However, changes in lung tissue density caused by disease or pneumonia (less air in the lungs) will cause a change in the filtering properties of the lungs. This will make us appreciate bronchial breath sounds (replacing vesicular breath sounds) at most areas of the lungs depending on the site of the pathology consistent with consolidation. On the other hand, in patients with emphysema (more air in the lungs) there will be a larger variability in the transmission of low frequency sounds, which is quantitatively consistent with the common auscultatory findings of decreased breath sounds (17).

**Respiratory sounds nomenclature**

Lung-sound nomenclature has been confusing and imprecise. The lung sounds were originally derived from the description by Laënnec and from the translation by Forbes into English (14). This caused confusion among pulmonologist. Even medical textbooks in physical diagnosis were ambiguous coining terms such as wet, coarse, sibilant in the nomenclature. In 1971 an American Thoracic Society Ad Hoc Committee on Pulmonary Nomenclature suggested to follow the schema by Robertson and Coope for general use. Robertson and Coope recommended dividing the adventitious sounds into 2 major categories—continuous sounds or wheezes and discontinuous sounds or crackling noises (18). In 1985, at the 10th meeting of the International Lung Sounds Association, an Ad Hoc committee reviewed all detail all aspects of pulmonary nomenclature. Continuous and discontinuous sounds were maintained (19, 20).

**Advances behind the stethoscope**

Pulmonary auscultation is widely utilized at the bedside. It is cheap, quick, easy to carry out and to repeat, noninvasive and totally innocuous (21). The stethoscope remains as a

**Table 1. Classification of Common Lung Sounds (American Thoracic Society)**

<table>
<thead>
<tr>
<th>Acoustic Characteristics</th>
<th>American Thoracic Society Nomenclature</th>
<th>Common Synonyms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Discontinuous, interrupted explosive sounds; loud, low in pitch</td>
<td>Coarse crackle</td>
<td>Coarse rale</td>
</tr>
<tr>
<td>Discontinuous, interrupted explosive sounds; less loud than above and of shorter duration; higher in pitch than coarse crackles or rales</td>
<td>Fine crackle</td>
<td>Fine rale, crepitation</td>
</tr>
<tr>
<td>Continuous sounds longer than 250 ms, high-pitched; dominant frequency of 400 Hz or more, hissing sound</td>
<td>Wheezes</td>
<td>Sibilant rhonchus</td>
</tr>
<tr>
<td>Continuous sounds longer than 250 ms, low-pitched; dominant frequency about 200 Hz or less, snoring sound</td>
<td>Rhonchus</td>
<td>Sonorous rhonchus</td>
</tr>
</tbody>
</table>

Lung sounds can be analyzed by the

1. airflow (upper portion of the figure): I (inspiration), E (expiration)
2. frequency of pressure waves per second in Hz (vertical axis)
3. time in seconds (horizontal axis) *amplitude of sound (through decibels); see vertical multi-colored bar on the right

**Time-expanded waveform** (27):

Time amplitude plots of lung sounds are generally made in two ways: expanded or unexpanded. The unexpanded method is similar to a phonocardiograph time amplitude display. This allows an overall view of the acoustic properties in real time. In the time expanded analysis the time or the x-axis is stretched out so that the details of the acoustic phenomena can be examined more carefully. In the following figures time domain plots are illustrated in both the time unexpanded and time expanded modes. It is clear that the pattern differences between the different types of lung sounds are seen more easily in the expanded mode. Figure 2 illustrates an time-expanded waveform of the lung sounds.

**Digital respirosonogram** (25, 26):

Digital respirosonogram provides the graphic representation of digitalized sound data or a tape-recorded sound. The waveform of the digitalized sound can now be analyzed by flow, frequency, amplitude, and time. Figure 1 illustrates a digital respirosonogram. The frequency of the pressure determines our perception of pitch. One hears low frequencies as low pitch and high frequencies as high pitch. The crest of the pressure wave has a given height or amplitude. The amplitude determines one’s perception of loudness. To accommodate the enormous range of sound amplitude they are usually measured in a logarithmic scale and expressed in **decibels (dB)**.

**Figure 1. Digital repirosonogram**

Lung sounds can be analyzed by the

**Multi-channel Stethograph (STG)** (28):

Stethographics automated lung sound analysis is a fast, effective means to diagnose and monitor disorders of the chest. Sixteen microphones embedded within the pads allow rapid capture of sounds. Some of its benefits are: (1) It provides documentation of both normal and abnormal lung sounds; and (2) it enables three-dimensional lung sound imaging; and (3) its waveforms can be interpreted just like an ECG.

**Multichannel lung sound analyzer**. This device collects data from 16 channels simultaneously. Following the recording the computer automatically calculates crackles and wheezes and displays their location on the chest as well as their timing in the respiratory cycle (28). (Figure 3)
Lung Sounds


Breath Sounds

Tracheal Breath sounds: Characteristics of the tracheal breath sounds are shown in Table 2.

Tracheal breath sounds, heard at the suprasternal notch or at the lateral neck serve special interest today. Clinicians are interested in tracheal sounds as indicators of upper airway flow obstruction as well for apnea monitoring in patients with sleep problems.

Normal breath sounds: The breathing-associated sound heard on the chest of a healthy person is called normal lung sound. The normal lung sound is devoid of discrete peaks and is not musical. It appears well established that its inspiratory component is generated primarily within the lobar and segmental airways. On the other hand, the expiratory component comes from more proximal locations (Table 2).

Bronchial breath sounds: Bronchial breath sounds are similarly described just like tracheal breath sounds (thus some books described them also as tracheobronchial). They have a tubular quality. They are relatively louder in expiration than inspiration. When they are heard in locations at a distance from the central airways, they signify consolidation. This is believed to be due to better transmission of the centrally generated lung sound through the consolidated lung.

Bronchovesicular breath sounds: A third category of normal breath sounds is called bronchovesicular since they share some characteristics of both tracheal/bronchial and vesicular sounds. One can distinguish expiration more clearly than vesicular breath sounds. One can normally hear bronchovesicular sounds over regions of the chest that are close to the large airways- over the right upper lobe anteriorly and at the interscapular space posteriorly.

Vesicular breath sounds: These are the most common sounds heard over the chest. They are present in the sites when the stethoscope is over the lung parenchyma distant from the large airways. It is a soft sound that has been compared to a wind blowing through trees. It is louder in inspiration than expiration.

Adventitious Sounds

As previously emphasized, the American Thoracic Society in 1971 has developed a rational and clinically useful classification of adventitious sounds based on the acoustic analysis of tape recordings and nomenclature introduced by Forgacs (table 1) (20). With this approach, lung sounds are categorized as continuous (wheeze, rhonchus) or discontinuous (crackles). Presently, computer analysis of the sounds has paved the way for the newer understanding of these sounds (table 3) (29).
Wheezes: Wheezes are probably the most widely used acoustic term in respiratory medicine. Laennec has vividly described a wheeze and has classified them as sibilant or sonorous (table 3). Wheezes are continuous adventitious lung sounds. The American Thoracic Society defined wheezes as high-pitched continuous sounds with a domain frequency of 400 Hz or more (20).

The pathophysiologic mechanisms that generate wheezing are still unclear. Movement of airway secretions may produce wheezing but the more significant mechanism is the flutter of the airway walls. Studies by Grothberg and Davis have presented a theoretical model that predicted oscillating wall motion in collapsible tubes at critical airway diameters and at gas velocities greater than those of flow limitation (33). Their model clearly infers that flow is always limited when wheezing is present.

Hundreds of studies have referred to wheeze as a parameter to gauge the severity of obstructive airways diseases especially in asthma. A close relationship of the wheeze with the results of objective parameters of airflow obstruction such as FEV₁ (35, 36), PEFR (37), and results from bronchoprovocation tests (38) have been cited in the medical literature. However, many circumstances are suitable for the production of continuous adventitious sounds. They include all mechanisms narrowing airway caliber, mucosal edema, intraluminal tumor, and external compression. Thus wheezes can be heard in several diseases not only in asthma. In an epidemiological study, wheezes have been perceived at some time more than 25% of a population sample, whereas the prevalence of asthma in the population was 7% (39).

It is important to mention that lung sound analysis has confirmed the well-recognized finding that wheezing is absent in many patients with significant obstruction (40). The other clinical features of the patient may be more helpful in such cases as cited in the GINA guideline evaluation on the severity of asthma exacerbation (41).

Rhonchi: These are described as continuous sounds and are lower in pitch than wheeze (Table 3). They have a snoring quality and are mostly due to airway secretions. Other conditions causing airway narrowing may also produce rhonchi.

Crackles: Of the adventitious lung sounds, crackles are perhaps the most useful for clinical diagnosis (29). The origin of crackles may be from fluid bubbling of copious secretions in some patients. However, recent investigations (42, 43) have proven that crackles resulted from the explosive opening of airways as Forgacs had proposed (44). The acoustic wave produced resulted from either equalization of the downstream and upward pressures or by sudden alteration in the tension of the airway walls.

Crackles are intermittent explosive sounds lasting less than 20 ms. Time expanded-waveform techniques have shown them to consist of an initial deflection followed by a few rapidly decaying oscillation.

The waveform, timing, number and regional distribution of crackles are associated with the severity and character of the underlying pulmonary disorder (45 and 46). This is illustrated in Figure 5.

OTHER ADVENTITIOUS SOUNDS

Pleural friction rub: They arise from friction between pleural surfaces when inflammation or neoplasms involve the pleural space. Friction rubs have been compared to the noise of old creaking leather. They may appear as repetitive series of coarse crackling sounds during inspiration often with a reverse sequence during expiration (26).

Squawk: Squawk are short musical sounds that have been described in patients with fibrotic pulmonary disorders. They are very short wheezes (53). Forgacs explained that these sounds are generated when a closed airway suddenly opens in inspiration but for a brief moment the airway walls remain in light contact to each other; thus, the inflowing inspiratory air can cause the walls to oscillate producing a wheezing sound (54).
The use of the stethoscope best symbolizes the practice of medicine up to this time (55). It is not an unreliable instrument that some studies have concluded (56). Technology has advanced in recent years stimulating a resurgence of interest in auscultation. Computer technology is making auscultation a more useful and diagnostic clinical instrument as presented in this article. Studies of the correlation of lung sounds with disease states have reaffirmed that the sounds contain objective information of clinical value (57). The accuracy of lung sounds are described in terms of likelihood ratio (LR) where a LR > 2 increases the probability of a diagnosis and > 10 affirms it (58). Expressed in terms of likelihood ratio:

- fine end-inspiratory crackles are associated with pulmonary fibrosis (LR +5.9)
- wheezing during quiet breathing predicts asthma (LR +6)
- wheezing in chronic bronchitis (LR +6)
- fine or coarse early inspiratory crackles in chronic bronchitis (LR +14 to +20)
- decreased breath sounds with emphysema (LR +10.2)
- fine and coarse crackles in congestive heart failure (LR +3.4)
- accentuated bronchial breath sounds associated with fever and cough predict pneumonia (LR +3.3).

These findings may caution us regarding the dangers that may arise with the misinterpretation of the auscultatory findings. Patients with interstitial fibrosis are given diuretics inappropriately as the crackles may be mistaken for congestive heart failure. This reaffirms the importance of proper education in physical diagnosis. Indeed advances in digital respiratory sounds are inevitable. But one should not expect computer-based sound analyzers to replace the stethoscope-bearing clinician anytime. The physician’s voice and the physical bond he creates with the use of the stethoscope will remain as standards of compassionate care and should never be substituted by advances in computer technology.

## SUMMARY AND RECOMMENDATIONS

### Table 5 Categories of Respiratory Sounds (ATS Classification)

<table>
<thead>
<tr>
<th>Adventitious sounds</th>
<th>Acoustics/ Waveform</th>
<th>Mechanisms</th>
<th>Origin</th>
<th>Relevance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coarse crackle</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Discontinuous, interrupted, explosive sounds</td>
<td>Rapidly damped wave deflection (duration typically &lt; 20 ms)</td>
<td>Airway wall stress-relaxation</td>
<td>Central and lower airways</td>
<td>Airway closure, secretions</td>
</tr>
<tr>
<td>Loud, low in pitch</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fine crackle</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Discontinuous, interrupted, explosive sounds</td>
<td>Rapidly damped wave deflection (duration typically &lt; 20 ms)</td>
<td>Airway wall stress-relaxation</td>
<td>Central and lower airways</td>
<td>Airway closure, secretions</td>
</tr>
<tr>
<td>Less loud than above and of shorter duration; higher in pitch than coarse rates or crackles</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

References


42. (Nath AR and Capel LH. Inspiratory crackles and mechanical events of breathing. Thorax 1974; 29: 695-698.


46. “Lecture on Lung auscultation” American College of Chest Physician Convention. USA. Lecture Notes


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