Simplified Prediction Rule for Prognosis of Patients with Severe Community-Acquired Pneumonia in Intensive Care Units

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Pneumonia is be a major cause of morbidity and mortality. A means of predicting prognosis particularly in severe pneumonia where mortality is highest is important so that more aggressive treatment may be initiated and/or patients' families may be prepared for negative outcomes. This study was therefore undertaken to validate the specified prognostic prediction rule for VMMC patients with severe community-acquired pneumonia in the ICU's. All patients admitted at the Veterans Memorial Medical Center-Intensive Care Units (Pulmonary and Medical) with a diagnosis of severe community-acquired pneumonia from April, 2000 to April, 2001 were included in the study. To take account of the fact that the final prognosis of severe CAP depends on the initial severity of pneumonia as well as on the occurrence of complications during the ICU stay, a prediction rule based on a two-step analysis model was developed. Patient characteristics on admission (step 1) and status during ICU confinement (step 2) were analyzed and risk factors were identified using bivariate and multivariate analysis as predictors of outcome. Age, anticipated death within five years, chronic respiratory insufficiency, immunosuppression, aspiration, initial septic shock, acute respiratory failure needing mechanical ventilation and chest radiograph involvement were all identified as risk factors.

For patients in low or high risk classes, the initial prediction of final outcome showed that the higher the risk classes, the greater chance of a detrimental effect or vice versa. For patients with an imprecise initial prognosis, three factors collected during the ICU stay were essential to accurately predict outcome, namely HA-LRT, CAP-related complication and septic shock. Although further validation is needed in larger studies, the results show that as an aid to clinicians in stratifying the prognosis of patients exhibiting severe CAP, this simplified prediction rule could be useful for therapeutic decisions and appropriate care. *Phil Journal Chest Diseases. Vol. 12 No. 2 pp: 65 - 71*

Keywords: Severe pneumonia, mortality, prediction rule

Introduction

Is pneumonia the "old man's friend"- a terminal event for patients who will otherwise die soon of underlying chronic disease? If so, chronological age might influence treatment policy.[1] This is just one predictors of mortality initially stated by the pioneers before embarking on a task of establishing prognostic parameters for patients suffering from this malady.

Community-acquired pneumonia is presently one of the leading cause of mortality in the United States accounting for approximately 2.8% of all hospital admissions.[2] In the Philippines, pneumonia is the fourth leading cause of morbidity and the third leading cause of mortality in Filipinos based on the 1994 Philippine Health Statistics.[3] In the United States alone, it had an annual incidence of 11.6 per 1,000 persons among age group of more than 75 years old requiring hospitalization.[4] Despite continuous upgrading of the quality of antimicrobials and its supportive measures, the relative mortality rate remains high ranging from 22 to 53%.[5] Thus, development of prognostic parameters or criteria capable of aiding the physician in determining the risk involve in each patient would be the main concern of this study.

Community-acquired pneumonia is one of the most common infectious diseases treated in the ambulatory and hospital setting. Prognosis in this illness spans a broad range, from rapid full recovery of all physiologic and functional derangement to virtual certainty of death despite the use of a wide spectrum of intensive care measures. A well-validated index of prognosis for community- acquired pneumonia would help physicians decide which patient would benefit from more intensive forms of medical care.[2,6] Although a large number of patients can safely be treated on an outpatient basis, this infection is still a common cause of hospital admission.[7,8]

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However, despite all the improvement in both the antibiotic chemotherapy and a better knowledge of the etiologies that can cause community-acquired pneumonia, the mortality rate still averages between 10 and 20%.[7,9]

Different studies have shown that mortality is higher in those patients who develop severe acute respiratory failure and require mechanical ventilatory support because of their critical condition. Although recent reports have partially addressed this issue, the incidence, etiology, prognostic factors, and outcome of patients with severe community-acquired pneumonia requiring intensive care are still insufficiently known.

In the early 1990's, a study done by Fine and colleagues[6] developed and validated a prognostic index based on six predictors of mortality wherein they classified the patient into risk classes to aid the physician in identifying patients who could be safely managed in an ambulatory setting. A second index more complex than the first was developed and validated in order to improve decision about hospitalization and treatment wherein they were able to identify patient with low risk of death.

He validated this pneumonia prognostic index using the Medis Groups Comparative Hospital Database and obtained a hospital mortality rate of 13% in the derivation cohort and 11.1% in the validation cohort.[10] Further study done by the same author through meta-analysis showed overall mortality at 13.7% using eleven prognostic factors.[11]

Leroy, George's et al[5] used a canonical discriminant analysis to retrospectively develop a pneumonia-specific prognostic score for patient admitted to an Intensive Care Unit. This was based on 16 predictors of mortality which were subsequently validated in a prospective population and performed well in classifying patients as having low or high risk of death. Overall, 8.2% was associated with mortality.

Multivariate analysis have shown some baseline characteristics of patient but questions still remain if these prognostic indexes are capable of determining the outcome of their condition in an ICU setting. The following are some of the criteria that were used: anticipated death within five years, the initial severity of pneumonia (simplified acute physiology score, septic shock, and bacteremia) and the evolution during ICU stay (ineffective initial antimicrobial therapy, radiographic spread of pneumonia and occurrence of non-pneumonia related complications).

Knowledge about the prognosis of a disease allows physicians to inform their patient about the expected natural history of an illness, the likelihood of potential complications and the probability of successful treatment. Therefore, understanding the prognosis of this entity is of particular clinical relevance, since it ranges from rapid recovery of symptoms and functional impairment to serious morbid complications and death. The ability to accurately predict medical outcomes in community acquired pneumonia (CAP) influences patient management decisions made by physicians, including, whether to hospitalize the patient and duration of inpatient care if the patient is hospitalized. During the past three decades, the prognosis of patients with CAP has been evaluated in a large number of studies that have reported a wide range in mortality and varying predictors of mortality. However, relatively few studies have evaluated other clinically relevant patient outcomes such as morbid complications, symptoms resolution, functional status, and return to work or usual activities.

This study was therefore undertaken to validate the specified prognostic prediction rule for VMMC patients with severe community-acquired pneumonia in the ICU's. We also wanted to determine the association of risk stratification with hospital mortality rate for prognosis of patients admitted in the ICU based on the predictors of mortality which can aid the clinicians in their therapeutic decision and appropriate care.

Methodology

All patients admitted at the VETERAN'S MEMORIAL MEDICAL CENTER-Intensive Care Units (Pulmonary and Medical) with a diagnosis of severe community-acquired pneumonia from April, 2000 to April, 2001 were included in the study. All patients evaluated by Fellow on duty/Senior Medical Resident on duty. Criteria used for patient selection was based on the definition of Community Acquired Pneumonia (CAP) by Fine's et al namely: 1. age - 65 years; 2. RR-30/min.; 3. PR - 125/min.; 4. Temperature - 40^{o}C or 35^{o}C; 5. CXR: Progression of lesion to 50% on initial finding within 24 hrs.; 6. suspected aspiration; and 7. extra-pulmonary evidence of sepsis

Any of the following was also used to exclude patients: 1. Shock or signs of hypoperfusion, such as hypotension, altered mental status, urine output less than 30 ml/hr. OR 2. PAO_2 less than 60 mmHg. Or acute hypercapnea ($PaCO_2$ greater than 50 mmHg) at room air

Patients initially hospitalized either from home or admitted to the general ward for pneumonia then subsequently transferred to our ICU within two days were also included. Those that require mechanical ventilation or were judged to be unstable requiring

Table I. Point scoring system used to assess risk of death (step 1)

Prognostic Factors	Coefficient	Points
age >40 years old	0.4482	+1
anticipated death within 5 yrs	0.4718	+1
chronic respiratory insufficiency	0.4350	+1
immunosuppresion	0.4420	+1
aspiration	0.6056	+1
septic shock	1.6252	+3
ARF requiring MV	0.6386	+1
chest radiograph >1 lobe	0.5940	+1

Table II Point scoring system used to assess risk of death (Step 2)

Prognostic Factors	Coefficient	Points
initial antimicrobial combination therapy	0.4322	+1
ineffective initial antimicrobial therapy	0.4221	+1
inadequate initial antimicrobial therapy	0.4366	+1
ARF leading to secondary mechanical ventilator	0.6386	+ 1
use of inotropic support	0.2456	+1
use of hemodialysis	0.4262	+1
occurrence of CAP-related complications	2.1699	+4
occurrence of non-specific CAP-related complications	1.0923	+2

comprehensive medical care such as ventilatory support, septic shock or neurologic disturbance were included.

Those who were excluded are patients hospitalized for less than 30 days prior to developing pneumonia, with radiographic abnormalities attributed solely to a disease other than a pneumonic process, AIDS or HIV positive patients.

On admission (first 24 hours), all patients underwent clinical and radiologic evaluation. We recorded the following factors: age, sex, origin (home, other hospital etc.), underlying clinical illnesses and therapies, initial vital signs, mechanisms of lung contamination (aspiration or not), number of lobes involved and unilateral vs bilateral infiltrates on chest radiograph. Chronic respiratory insufficiency was diagnosed by combining the usual clinical and radiologic parameters.

Whatever the definite lung diseases (obstructive, restrictive or mixed) diagnosed, we considered all the patients to exhibit chronic respiratory insufficiency. Shock was defined as a sustained decrease greater than one hour in the systolic BP of at least 40 mmHg from baseline or a resultant systolic BP less than 90 mmHg after adequate volume replacement and in the absence of any antihypertensive drug. Neurologic status and changes in mental status was stratified according to the Glasgow- Coma scale.

The need for mechanical ventilation on admission or within 12 hours following admission defined initial acute respiratory failure. Aspiration pneumonia was diagnosed in patients with either witnessed aspiration or risk factors for aspiration (altered mental status, abnormal gag reflex or swallowing mechanism, intestinal obstruction) and suggestive chest radiograph infiltrates. Immunosuppression was defined as a leukocyte count of less than 1,000/mm^3, recent use of systemic corticosteroids, cytotoxic drugs, radiation treatment or asplenia. Follow-up of patient was until ICU discharge or death. During the patients' stay in the ICU, we recorded and considered as possible complications all events occurring after the first 24 hours of admission. We distinguished complications directly related to pneumonia, such as sepsis-related complications (secondary septic shock, ARDS, development of multiple organ failure or diffusion of pulmonary infection) or hospital acquired lower respiratory tract (HA-LRT) super-infections, from indirectly related or nonspecific complications such as ICU-related complications (eg., upper GI bleeding, catheter-related infection, suspected deep vein thrombosis and pulmonary embolism). Hospital acquired pneumonia was considered to be present when a new or progressive radiographic infiltrate that was not present on ICU admission developed after the third day following ICU admission. Evaluation of patient mortality was at the time of ICU discharge.

A two-step analysis model was established for the prediction rule. To take account of the fact that the final prognosis of severe CAP depends on the initial severity of pneumonia as well as on the occurrence of complications during the ICU stay, a prediction rule based on a two-step analysis model was developed.

STEP 1: was designed to quantify the risk of death solely on the basis of patients' medical history and initial examination on admission to ICU and to identify three subgroups of patient with various risks of death: a low risk, a high risk and an intermediate or undefined-risk group (*Table I*). Candidate predictor variables analyzed in step 1 were demographic variables etc. Each independent predictor of mortality was assigned a coefficient proportional to its prognostic magnitude in the credit scoring technique. An initial risk score was computed by adding each patient's total points. These are the point scoring system identified by the multivariate analysis done by Fine and colleagues[7] with their coefficient derived from the credit scoring technique:

STEP 2: The final prognosis of patients of each group was adjusted according to prognostic variables assessed during the ICU stay. The following candidate predictor variables were assessed during the ICU stay. As previously mentioned, a bivariate and multivariate approach based on credit scoring technique was carried out. An adjustment score risk was computed by adding each patient's total points. The final prognosis was adjusted for each initial risk score class according to the value of this adjustment risk score and to prognostic variable assess during the ICU stay. Table II shows the point system used for step 2:

Results

There were a total of 76 patients initially identified with severe community- acquired pneumonia. A total of five patients failed to satisfy the inclusion criteria. Those who died with no relation to pneumonia totaled three cases with cardiac failure = l; CVA = 1; others = 1. The efficacy of initial antimicrobial therapy was not assessed in three patients and the remaining two candidate prediction variables were missing. Therefore, a total of 7l patients were included for the prognosis study.

The study group consisted of 42 males and 29 females with a mean age of 7l yrs. A total of 67 patients were admitted directly from their own home while transferred cases from other hospitals numbered four patients. The variables which are considered to be the main underlying diseases with initial clinical and radiologic data were summarized in Table III.

Symptoms suggestive of aspiration were found in 4% (three patients.) of patients. At the time of ICU admission, 16% (12 pts.) had received prior antibiotic treatment for their pneumonia.

The initial antimicrobial therapy, empirically given in 96% (68 pts.), was monotherapy 50 %(36pts) and combination in 65% (46 pts.). The rest of the patients, 9% (6 pts.) was dependent on the availability of medication provided by the pharmacy. A total of 16% (12 patients) received prior antibiotic treatment (seven from other hospitals and five from the OPD in our institution). Based on the sensitivity patterns of antibiotics requested with sputum and/or tracheal aspirate as specimen, this antibiotic treatment was judged adequate in 80% (57 pts.) of patients while 25% (18 pts.) showed resistance to all the antimicrobials disk noted . Post-evaluation after 72 hrs of antibiotic treatment, initial therapy was considered effective due to improved clinical features in 25% (18 pts.) and 74.6% (53 pts) showed ineffective treatment. Failure of treatment was attributed to resistant strain 24% (17 pts.).

Table III Characteristics of Patients at Presentation

Variables	No. of Patients	(%)
Co-morbid illnesses		
Chronic Respiratory Illness	41	57.7%
Immunosuppression	4	5.6%
Non-fatal	31	43.6%
Ultimately fatal	30	42.2%
Rapidly fatal	2	2.8%
Severity of CAP		
Initial shock	11	15.4%
Immediate (less than 12 hours) mechanical ventilation	42	59%
Chest radiograph		
involvement	11	15.4%
greater than 2 lobes	21	29.5%
bilateral		

Table IV Prognostic Factors Related to Mortality (Step 1): Bivariate Analysis

Record of variables on admission	Mortality			p value
	No. of patients	No	%	
1. Age				
more than 40	70	40	57.1%	0.001
less than 40	1	0	0	
2. Anticipated death within 5 years				
No	8	2	25%	0.001
Yes	63	53	84.1%	
3. Chronic Respiratory Insufficiency				
No	9	3	33.3%	0.01
Yes	62	55	88.7%	
4. Immunosuppression				
No	62	10	16.1%	0.056
Yes	10	4	40%	
5. Aspiration				
No	68	20	29.4%	0.001
Yes	3	2	66.6%	
6. Initial Septic Shock				
No	63	11	17.4%	0.001
Yes	8	6	75%	
7. Acute Respiratory Failure leading to immediate mechanical ventilation (less than 12 hrs.)				
No	15	2	13.33%	0.001
Yes	56	17	30.3%	
8.Chest radiograph involvement				
1 lobe	51	8	15.6%	0.001
> 1 lobe	20	7	33.5%	
Unilateral	53	11	10.6%	
Bilateral	18	5	30.3%	0.004

Other factors that contributed to failure of treatment of patient include delayed mechanical ventilation 8% (6 pts.), inotropic support 10% (7 pts.) and undecided

relatives 7% (five patients.). During the ICU stay, CAP-related complications are sepsis-related situations; which include multiple organ failure 30% (21 pts.) and deterioration of initial pulmonary infection while 15% (11 pts.) had non-specific CAP-related complication. Finally, 56% (40 pts) died while in the ICU, with 28% (11 pts.) during the first 72 hours.

Prognosis Analysis

In step I, bivariate analysis identified eight prognostic factors (*Table IV*). Sex, origin of CAP and prior antimicrobial therapy for the current CAP were not associated with ICU outcome. Six independent prognostic factors were identified by multivariate analysis showing a high degree of association with mortality (age, aspiration, anticipated death, chest radiograph, use of ventilator and septic shock). All parameters were significantly associated with mortality except immunosuppression. An initial risk score was obtained by adding the points for each parameter present in the patient.

Based on its value, three risk classes were determined. The initial risk score was 0 to 2 in class I, 3 to 5 in class II, and 6 to 8 (the maximum score) in class III.

In step 2, all candidate predictor factors but two (use of inotropic support and non-specific CAP-related complication) appeared to be significantly associated with prognosis in bivariate analysis (*Table V*) however, this figure could be controversial since complication involved have a variety of causation. The three factors independently associated with the final outcome, their coefficients derived from the credit scoring technique and the point scoring system was as follows: HA-LRT super-infections (1 point); non-specific CAP-related complications and sepsis related complications (4 points) and the rest of the parameters have 1 point. In adding these points we obtained an adjustment risk score. *Figure 1* shows the initial classification of patients in three risk classes on ICU admission, as well as the ultimate adjustment in each initial risk class. In initial risk class I, two patients had complications leading to a final outcome adjustment (> 2 points); all of the complications occurred during the first week of the ICU stay. In initial risk class III, two patients had complications leading to a final prognosis adjustment (>2 points); all but one occurred during the first week of the ICU stay. In initial risk class II, seven patients had an adjustment risk score equal to 1 or 2 points. *Figure 1* shows the significant progression in mortality rate from class I to class III ($p<0.026$).

Table V Prognostic Factors Related to Mortality (Step 2): Bivariate Mortality

	Mortality			
Variables Recorded during ICU stay	No of pts.	No	%	p value
1. Initial antimicrobial combination therapy				
No	36	27	75%	0.000
Yes	46	15	32.6%	
2. Ineffective initial antimicrobial therapy				
No	18	2	11.1%	0.000
Yes	53	37	70%	
3. Inadequate initial antimicrobial therapy				
No	54	8	4.32%	0.000
Yes	17	11	64.7%	
4.ARF leading to secondary (> 12 hrs./admission) mechanical ventilation				
No	65	13	20%	0.026
Yes	6	4	66.6%	
5.Use of inotropic support				
No	66	16	24.2%	0.595
Yes	5	2	40%	
6.Use of hemodialysis				
No	66	13	19.6%	0.010
Yes	5	4	80%	
7 .Occurrence of CAP-related complications				
No	50	6	12%	0.000
Yes	21	18	85.7%	
8.Occurrence of non-specific CAP-related complications				
No	60	13	22%	0.057
Yes	11	6	54.5%	

Discussion

The mortality attributable to severe CAP requiring ICU admission was 53.5%. This rate was noticeably higher compared with overall mortality rate previously reported by Fine and colleagues in recent meta-analysis. Such could be explained by the fact that majority of our patients belong to the older age group bracket and worse co-morbid factors with concomitant exclusion of patient

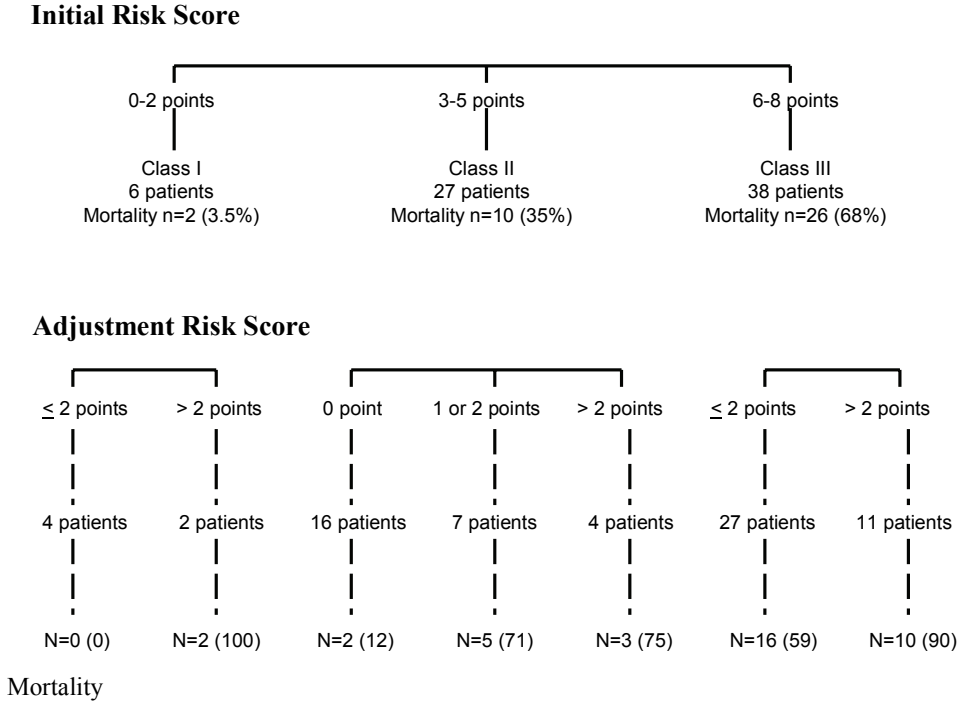

Figure 1. Initial risk classification and impact of the Adjustment risk score

whose deaths were unrelated to their pneumonia eg,. patients with CVA or renal failure, etc.

Previous studies have demonstrated that the prognosis of severe CAP depends on the initial severity of the infection, the underlying diseases and the occurrence of complications during ICU stay. To build a simplified prognostic prediction rule taking such results into account, we developed our prognosis study in two successive steps. The aim of the first step was to identify candidate prognostic factors among all variables easily available on ICU admission. Consequently, biological and bacteriologic data were disregarded and only clinical and radiologic variables were studied. Multivariate analysis identified six prognostic factors independently associated with final outcome. Four of them-anticipated death within five years, chest radiograph involvement of > l lobe, ARF requiring mechanical ventilation, and septic shock had already been reported and were not surprising. Chronic respiratory insufficiency and aspiration produced inconsistent findings with the previous studies compared.

The impact of age on CAP prognosis appears quite controversial. In some studies, age was an independent predictor of mortality. In others, age affected neither in hospital mortality nor the outcome during the 24 months after discharge. However, our study clearly established this relationship. According to the credit scoring technique, each of the six identified predictors was assigned a value. Five predictors had a point value of 1, for septic shock, the point value was 3, emphasizing the major prognostic impact of the presence of septic shock at ICU admission When these point values were added, an initial risk score was obtained and three risk classes of increasing mortality were identified. In class I (0 to 2 points), the mortality rate was low (3.5%). In class III (6 to 8 points), the mortality rate was very high (68%). In class II (3 to 5 points), the mortality rate was 35%, a value quite near the overall mortality rate (22.5%) compared with the other results.

In order to adjust the prognosis to the evolution during ICU stay, for patients in class II particularly, we developed the second step of our prognostic analysis. In step 2, multivariate analysis demonstrated that only three factors were associated with final outcome occurrence of hospital acquired lower respiratory tract super-infections, non-specific CAP-related complications, and sepsis-related complications. Because the prognostic impact of these three complications varied widely from one another, each independent factor was assigned a different value to build an adjustment score. As a result of adjustment, mortality rates varied from 0 to 100% in initial risk class I; from 12 to 71% to 75% in class II and from 59% to 90% in class III. Attention is drawn to the

apparently wide differences between initial estimated mortality risk and final outcome. After evaluation with initial predictors of mortality and establishment of the initial risk score, six patients were in the low risk class 1. The overall estimated mortality rate in this class was 3.5%. Among these patients, four (66.6%) exhibited an adjustment score < 2 and no one died. Such data suggest that classification into a low risk class, after initial evaluation on ICU admission remains correct. Only two patients exhibited a more sever adjustment score and had a higher mortality rate (100%). Thirty-eight patients were initially categorized into a high risk class III.

Overall estimated mortality rate was 68%. Twenty seven patients (71%) exhibited an adjustment score < 2 and a final mortality rate of 59%. Eleven patients developed a more severe complication and had a higher mortality rate of 90%. Once again, the initial classification in the high risk class was correct for all of these patients since the mortality rate in this class was never < 49%. For the 27 patients in class II (38%), the estimated prognosis after the initial evaluation was nearest to the prognosis of the overall study population 35% vs.53% in this risk class, the prognostic impact of complications occurring during ICU stay appears dramatic. When no complications occurred, the mortality rate was 12 %. When patient exhibited HA-LRT or non-specific CAP related complications, the mortality rate reached 71°/o. Finally, when the previous complications occurred (adjustment risk score > 2), the mortality rate was 75%. To accurately predict the outcome for such patients, it was necessary to use the adjustment risk score to take into account complications occurring during ICU stay. Our simplified prediction rule was able to immediately and accurately determine the outcome for all patients based on information available as early as ICU admission.

Conclusion

In summary, the most important advantage of this method is that as early as ICU admission we can already identify parameters which can guide us in the management of our patient. For patients in low or high risk classes, the initial prediction of final outcome appeared correct that is, the higher the risk classes, the greater chance of a detrimental effect or vice versa. For patients with an imprecise initial prognosis, three factors collected during the ICU stay were essential to accurately predict outcome, namely HA-LRT, CAP-related complication and septic shock. These parameters were consistent and highly associated with hospital mortality in ICU. Therefore, our results clearly validate the simplified prognostic parameters in the prediction rule for determining hospital morality rate. Risk stratification in the initial or in the adjustment phase is an important process needed to distinguished variables seen on admission in ICU and during evolution of the disease. This produced a highly accurate information regarding mortality in the hospital wherein the higher the risk stratification, the higher would be the chances of these patient expiring based on the predictors of mortality we have presented. As an aid to clinicians in stratifying the prognosis of patients exhibiting severe CAP, this simplified prediction rule could be useful for therapeutic decisions and appropriate care. After validation in a large scale study, the implications for future therapeutic research or development of new preventive strategies should become evident.

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Arterial Blood Gas Interpretation: Validity of the University of Santo Tomas Hospital (USTH) Algorithm vs. Traditional Calculation Method

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OBJECTIVE: To determine the accuracy and reliability of the USTH algorithm compared to the traditional calculation method in the interpretation of arterial blood gas (ABG) of patients' blood samples submitted to the Pulmonary and Critical Care Laboratory for analysis.
DESIGN: Prospective case series
METHOD: All consecutive blood samples of patients, both outpatient and admitted, which were submitted to the Pulmonary and Critical Care Laboratory for ABG interpretation from March to August 2004 were analyzed. Demographic data such as age, sex, and admitting diagnosis were recorded together with ABG data such as pH, partial pressure of carbon dioxide (pCO_2), partial pressure of oxygen (pO_2), calculated bicarbonate (HCO_3), oxygen saturation (O_2sat) and inspired oxygen concentration (FIO_2).
STATISTICAL ANALYSIS: Analysis and comparison of the two different methods of acid-base interpretation was facilitated by a coding system based on five (5) categories namely; 1) normal/abnormal status, 2) pH abnormality (acidemia vs. alkalemia), 3) primary acid-base disturbance, 4) adequacy of compensation to primary acid-base disturbance, and 5) simple vs. mixed acid-base disorder. Degree of agreement between the two different methods was measured using kappa (κ) statistics aided by Byrt's guidelines. All statistical tests were performed using the Statistical Package for the Social Sciences (SPSS version 9.0).
RESULTS: Three hundred four patients underwent a total of 1,023 ABG analyses using both techniques of interpretation (USTH algorithm vs. traditional calculation method) with an average of 3.4 ABGs per patient. There were 150 males and 154 females with a mean age of 60.28 years (±18.3) and an age range of 10-97 years. Categories 1) normal/abnormal status, 2) pH abnormality (acidemia vs. alkalemia), and 3) primary acid-base disturbance showed measured kappa values of 1.000, 1.000, 1.000 respectively, which indicated an excellent agreement between the 2 methods. Categories 4) adequacy of compensation to primary acid-base disturbance, and 5) simple vs. mixed acid-base disorder, had kappa values of 0.447 and 0.215 respectively, which suggested a fair to slight agreement between the 2 methods.
CONCLUSION: The USTH algorithm is a valid and reliable method of ABG interpretation as it is easy, rapid, and simple to apply. The USTH algorithm has excellent agreement with the traditional calculation method in identifying ABG abnormality namely, the pH abnormality and the primary acid-base disturbance. However, in the evaluation of adequacy of compensation and whether there is a mixed acid-base disorder, the USTH algorithm falls short of the traditional way of interpreting acid-base disorder. Although the USTH algorithm was formulated to hasten a supposed long and arduous method of interpretation, it does not attempt to totally replace the calculation method because the algorithm can not define the expected limits of compensation thus it can not predict the degree of compensation that ought to occur in a primary disturbance and therefore, can not accurately and reliably identify multiple acid-base abnormalities. It seems reasonable to use the calculation method when expected compensation to primary acid-base disturbance is needed and when multiple acid-base disorders are suspected. *Phil Journal Chest Diseases. Vol 12 No. 2 pp: 72 - 80*

Keywords: Arterial blood gas, Interpretation, Acid base balance

Introduction

Arterial blood gas (ABG) analysis has become an integral part of the management of critically-ill patients. It is not only an essential tool in the emergency room for yielding valuable information in a variety of disease processes but it is also an important means of monitoring progress of patients in the intensive care unit. A major challenge in critical care medicine is the need to manage precipitous changes in a patient's ABG status thus its rapid interpretation is of paramount importance so that

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results are quickly obtained for immediate therapeutic intervention. However, interpretation by the traditional method is tedious, time-consuming and cumbersome because it involves lengthy and complicated calculations.

This has led to the creation of the University of Santo Tomas Hospital (USTH) algorithm[1] (unpublished manuscript, 1998, Appendix A) which provides an easy and rapid method of ABG interpretation that is based on simple concepts that needs no calculations. This simple algorithm has been adopted and implemented in the Pulmonary and Critical Care section since 1998, however, despite its usefulness, it has never been validated.

This study was conducted to determine the accuracy and reliability of the USTH algorithm compared to the traditional calculation method in the interpretation of ABG of patients whose blood samples were submitted to the Pulmonary and Critical Care Laboratory for analysis.

Materials and Methods

Study Design. Prospective case series

Setting: Tertiary private hospital

Selection of Subjects. All patients, both outpatient and admitted, whose blood samples were submitted to the Pulmonary and Critical Care section for ABG analysis from March to August 2004 were eligible for the study. Demographic data such as age, sex, and admitting diagnosis were recorded together with ABG data such as pH, partial pressure of carbon dioxide (pCO_2), partial pressure of oxygen (pO_2), calculated bicarbonate (HCO_3), oxygen saturation (O_2sat) and inspired oxygen concentration (FIO_2).

The method of interpreting oxygenation status is based on standard recommendation for evaluating hypoxemia using normal paO_2 values between 80 – 100 mmHg[1, 2, 3]. This interpretation was used for both USTH algorithm and traditional calculation methods. The USTH method of acid-base interpretation is based on an algorithm which was developed by one of the authors[1], and was approved for adoption in our institution in 1998[1]. The traditional method of acid-base interpretation is based on the popular technique described by various authors[4-7] and is based on several steps. Step 1 – does the patient have acid-base disturbance or not? Step 2 – if there is an acid-base disturbance, is there acidemia or alkalemia? Step 3 – determines whether the primary acid base disorder is respiratory or metabolic. Step 4 –evaluates whether the compensation to the primary disorder is adequate or not. Here we used the values as described by Mahnensmith.[4]

In order to eliminate subjective error in the interpretation, two (2) computer programs using a model based on the USTH algorithm method and another using the traditional method of ABG interpretation was made using Visual Basic. Net. All ABG data were then entered into the computer program for analysis. The USTH algorithm is shown in Appendix A while the values for compensation to the primary disorder used in the traditional calculation method is shown in Appendix B.

Data Analysis: In order to facilitate data analysis and comparison of the two different methods of acid-base interpretation, a coding system (Appendix C) was devised based on five (5) categories: 1) normal/abnormal status, 2) pH abnormality (acidemia vs. alkalemia), 3) primary acid-base disturbance, 4) adequacy of compensation to primary acid-base disturbance, and 5) simple vs. mixed acid-base disorder.

All data were analyzed using kappa (κ) statistics to measure the degree of agreement between the two different methods. The guideline by Byrt[8] for interpreting kappa was used (Appendix D).

All statistical tests were performed using the Statistical Package for the Social Sciences (SPSS version 9.0).

Sample Size: A minimum of 24 ABG analysis results were needed in order to estimate the kappa as a measure of agreement between any two raters or methods with 95% confidence level, kappa expected value of 0.2, and variance of kappa set at 0.25.

Results

Three hundred four patients underwent a total of 1,023 ABG analyses using both techniques of interpretation (USTH algorithm vs. traditional calculation method) with an average of 3.4 ABGs per patient. The mean age of patients is 60.28 years (±18.3)

Table I Demographic Characteristics of the Patient Population

Total number of patients	304
Total number of ABGs	1023
Average number of ABGs per patient	3.4
Mean age in years(± SD)	60.28 (± 18.3)
Age range, years	10-97
Sex	
Males	150 (49.3%)
Females	154 (50.7%)

Table II Various Indications for Arterial Blood Gas Analysis (N = 1023)

Admitting Diagnosis/Impression	N (%)
Acute Respiratory Failure	535 (52.3%)
CAP/HAP/aspiration pneumonia	218 (21.3%)
Trauma/flail chest	9 (0.88%)
COPD in exacerbation	76 (7.43%)
Bronchial asthma in exacerbation	53 (5.18%)
Sepsis syndrome/shock	9 (0.88%)
CHF/pulmonary edema/ARDS	65 (6.35%)
Central cause (CVA infarct, ICH, ruptured aneurysm, spinal cord compression/injury/ tuberculous meningitis, hydrocephalus, etc.)	68 (6.65%)
Others (pneumothorax, malignant hyperthermia, myasthenia gravis, GBS, etc.)	27 (2.64%)
Post-operative cases (craniotomy, cholecystectomy, rib resection, aneurysmal repair, etc.)	30 (2.93%)
CAP/HAP/aspiration pneumonia (not in respiratory failure)	83 (8.11%)
CAD/myocarditis/unstable angina	55 (5.37%)
Bronchial asthma in exacerbation (not in respiratory failure)	30 (2.93%)
COPD in exacerbation (not in respiratory failure)	24 (2.35%)
Carcinoma (various causes)	10 (0.98%)
Pleural effusion (parapneumonic, malignant, tuberculous, hemothorax, CHF, amoebic abscess, etc.)	26 (2.54%)
PTB/bronchiectasis/atelectasis, etc.)	13 (1.27%)
OSA/OHS	37 (3.62%)
Miscellaneous (encephalopathy, URTI, hypertension, DVT, CKD, etc.)	30 (2.93%)
Unknown (outpatient, emergency room, other hospitals,etc.)	160 (15.6%)

Legend: CAP = community-acquired pneumonia, HAP = hospital-acquired pneumonia, CAD = coronary artery disease, CHF = congestive heart failure, CVA = cerebrovascular accident, ICH = intracerebral hemorrhage, PTB = pulmonary tuberculosis, OSA = obstructive sleep apnea, OHS = obesity-hypoventilation syndrome, URTI = upper respiratory tract infection, DVT = deep venous thrombosis, CKD = chronic kidney disease, COPD = chronic obstructive pulmonary disease

Table III Category 1: Normal /Abnormal Status

Algorithm	1	2	Total
1	101	0	101
2	0	922	922
Total	101	922	1023

Kappa (measure of agreement) = 1.000
Kappa standard of error = 0.000
Kappa t value = 31.984

Table IV Category 2: pH Abnormality (acidemia vs. alkalemia)

Algorithm	Calculation			Total
	0	1	2	
0	101	0	0	101
1	0	304	0	304
2	1	0	618	618
Total	101	304	618	1023

Kappa (measure of agreement) = 1.000
Kappa standard of error = 0.000
Kappa t value = 40.257

Table V Category 3: Primary Acid-base Disturbance

Algorithm	Calculation					Total
	0	1	2	3	4	
0	101	0	0	0	0	101
1	0	165	0	0	0	165
2	0	0	139	0	0	139
3	0	0	0	223	0	223
4	0	0	0	0	395	395
Total	101	165	139	223	395	1023

Kappa (measure of agreement) = 1.00
Kappa standard of error = 0.000
Kappa t value = 59.430

with an age range of 10-97 years. There were 150 males and 154 females. *Table I* shows the demographic characteristics of the patient population.

Of the 1023 ABG analysis results, 535 (52.3%) were from patients with acute respiratory failure. Of these, 218 (21.3%) were secondary to pneumonia (community-acquired/hospital-acquired/aspiration), 76 (7.43%) from exacerbation of chronic obstructive pulmonary disease (COPD), 68 (6.65%) from central causes (cerebral infarct/intra-cerebral hemorrhage/etc.), 65 (6.35%) from pulmonary edema, 53 (5.18%) from exacerbation of bronchial asthma, and the remaining < 5% were from less common causes (neuromuscular diseases, sepsis and trauma). Other significant findings include: 83 (8.11%) of ABG samples from patients with pneumonia (not in respiratory failure), followed by 55 (5.37%) from coronary artery disease and 37 (3.62%) from obstructive sleep apnea/obesity-hypoventilation syndrome (OSA/OHS). A substantial percentage of samples were from patients with unknown diagnosis which may be from the emergency or outpatient sections or from other hospitals with 160 (15.6%). Table II shows the various indications for ABG analysis.

Table III shows that in category 1 (normal/abnormal status), the measured Kappa value was 1.000, with Kappa standard of error of 0.000 and Kappa t value of 31.984.

Table IV shows that in category 2 (pH abnormality – acidemia vs alkalemia), the measured Kappa value was 1.000, with Kappa standard of error of 0.000 and Kappa t value of 40.257.

Table V shows that in category 3 (primary acid-base disturbance), the measured Kappa value was 1.000, with

a Kappa standard of error of 0.000 and Kappa t value of 59.430.

Table VI shows that in category 4 (adequacy of compensation to primary disturbance), the measured Kappa value was 0.447 with a Kappa standard of error of 0.033 and Kappa t value of 19.017.

Table VII shows that in category 5 (simple vs. mixed acid-base disturbance), the measured Kappa value was 0.215 with a Kappa standard of error of 0.016 and Kappa t value of 19.246.

Table VI Category 4: Adequacy of Compensation to Primary Disturbance

Algorithm	Calculation			Total
	0	1	2	
0	101	0	0	101
1	0	11	125	136
2	0	73	713	786
Total	101	84	838	1023

Kappa (measure of agreement) = 0.447
Kappa standard of error = 0.033
Kappa t value = 19.017

Table VII Category 5: Simple vs Mixed Acid-Base Disturbance

Algorithm	Calculation			Total
	0	1	2	
0	101	0	0	101
1	0	322	559	881
2	0	0	41	41
Total	101	322	600	1023

Kappa (measure of agreement) = 0.215
Kappa standard of error = 0.016
Kappa t value = 19.246

Discussion

The USTH algorithm (unpublished manuscript, 1998) has been in use in our institution since 1998. The simplicity and ease by which ABG interpretation is made i.e., without the need for a calculator has facilitated its adoption and widespread use in our locality. Because USTH is an academic institution, this method has been taught and handed down through generations of medical students for the past eight years. It is therefore not surprising that graduates from our medical school had carried this knowledge beyond our academic boundaries. Yet, despite its widespread use, the USTH algorithm has never been validated and compared to more "standard" methods of ABG analysis that uses a calculation of compensation for the primary acid-base disorder[4]. This study was therefore undertaken with the goal of comparing the degree of agreement between the USTH algorithm and the calculation method.

According to Gallagher[9], to allow one to decide whether a new method can be substituted for an established method, the two methods should be in sufficient agreement. In this study, Kappa (κ) statistics was used to measure the degree of agreement between these two methods assisted by the guidelines set by Byrt[8] for interpreting Kappa. A coding system was devised to facilitate analysis and comparison of kappa. The coding system subcategorized acid-base interpretation into 5 categories: 1) normal/abnormal status, 2) pH abnormality (acidemia vs. alkalemia), 3) primary acid-base disturbance, 4) adequacy of compensation to primary disturbance, and 5) simple vs mixed acid-base disorder.

For the first category (Appendix C, Category 1), the USTH algorithm was compared with the traditional calculation method on whether the ABG sample was normal or abnormal (i.e. presence or absence of an acid-base disturbance). As shown in *Table II*, the kappa value of 1.000 indicates a perfect agreement[8] (Appendix D) between the two methods of interpretation. This indicates that the USTH algorithm can accurately determine the presence of abnormality in acid-base disturbance as well as the traditional method of interpretation. This is not surprising because both methods used the same reference values for normality (i.e. pH = 7.35 – 7.45, pCO_2 = 35 – 45 mmHg, HCO_3 = 22 – 26 mEq/L). However, the sequence of determining normality is different. In the traditional calculation method, the determination of normality is done first (step 1), while in the USTH algorithm (as shown in Appendix A) when the pH is between 7.35 and 7.45 the ABG sample is first evaluated whether there is an underlying acid-base disturbance that is completely compensated before saying that the ABG sample is normal.

With category 2 (Appendix C, Category 2), interpretation of abnormal acid-base disorder was determined whether the two methods of interpretation agreed on the primary pH abnormality i.e. acidemia or alkalemia. The kappa value of 1.000 again means a perfect agreement[8] (Appendix D). Therefore, the USTH algorithm is as useful as the traditional calculation method in identifying whether the primary disturbance in the ABG sample is an acidemia or an alkalemia. This again is not surprising because both methods used the same normal reference values for pH abnormality. Both methods followed the same sequence of steps at this point in the acid-base interpretation i.e. after knowing the pH is out of the normal range of 7.35 to 7.45, the ABG sample is said to be acidotic if the pH is less than 7.35 and alkalemic if the pH is greater than 7.45.

Whether the two methods of interpretation agreed that the primary disorder is a metabolic or respiratory was determined next. In this category (Appendix C, Category 3) there are four possible primary abnormalities – metabolic acidosis, metabolic alkalosis, respiratory acidosis or respiratory alkalosis. The kappa value as shown in *Table IV* was 1.000 demonstrating a perfect agreement[8] between the two methods of interpretation. This also reflects the same normal reference values used for both algorithm and calculation methods. When the pH is acidemic (pH < 7.35), a pCO_2 value greater than 45 mmHg reflects a primary respiratory acidosis otherwise (when pCO_2 less than or equal to 45 mmHg) the primary defect is a metabolic acidosis. Likewise, when the pH is alkalemic (pH > 7.45), a pCO_2 less than 35 mmHg reflects a primary respiratory alkalosis while a pCO_2 greater than or equal to 35 mmHg indicates a primary metabolic alkalosis.

The next two categories (Appendix C, Categories 4 and 5): compensation to disturbance (Category 4), and whether there is mixed acid-base disturbance (Category 5), had kappa values of 0.447 (Table 5) and 0.215 (Table 6), respectively. These suggest a fair to slight agreement (Appendix D) between the two methods based on Byrt's guidelines. These results reflect the limitation of the USTH algorithm. As can be expected, the only way to determine accurately the adequacy of compensation to a primary acid-base disorder and thus also to determine whether there is a secondary acid-base disturbance (i.e. mixed acid-base disorder) is to calculate the numeric value for the compensation (Appendix B). When the calculated value for the compensation is not the same as the actual value, then we can say that there is another acid-base disturbance that is affecting the pH abnormality. According to Narins[7], it is unusual to have a complete compensation to a primary acid-base disorder, except for respiratory alkalosis. Compensation to a primary acid-base disturbance therefore is not expected to return the pH to normal. In this respect the use of the term "completely compensated" in the USTH algorithm should be interpreted not in terms of adequacy of compensation but rather to the clinical value of knowing that the pH is in the normal range. One should therefore suspect a mixed acid-base disorder rather than a single acid-base disorder whenever the algorithm labels an interpretation "completely compensated". For a completely compensated metabolic alkalosis interpretation (with the USTH algorithm), a pCO_2 greater than or equal to 55 mmHg should be suspected as a metabolic alkalosis with an underlying respiratory acidosis for it is unusual for a respiratory compensation to a metabolic alkalosis to go above a value of 55 mmHg[7]. With our ABG samples, the pCO_2 ranges from 44 – 90 mmHg. Based on this information, a pCO_2 equal to or above 44 mmHg should be suspected as having a mixed metabolic alkalosis with a respiratory acidosis when interpreted in the USTH algorithm as a completely compensated metabolic alkalosis.

From our ABG samples, an interpretation of completely compensated metabolic alkalosis could also be a mixed metabolic alkalosis and respiratory alkalosis. The pCO_2 values for this sample range from 36 to 43 mmHg. Hence, to possibly extend the acid-base evaluation using the USTH algorithm, whenever an interpretation of completely compensated metabolic alkalosis is made one should suspect a metabolic alkalosis with an underlying respiratory acidosis if the pCO_2 is equal to or above 44 mmHg and underlying respiratory alkalosis when the pCO_2 is less than 44 mmHg.

With an interpretation of completely compensated metabolic acidosis on the USTH algorithm, the interpretation possibilities based on the calculation method are compensated metabolic acidosis, metabolic acidosis with respiratory acidosis, and metabolic acidosis with respiratory alkalosis. On further scrutiny, a pCO_2 value of 38 mmHg or above is noted in metabolic acidosis with respiratory acidosis, pCO_2 values below 34 mmHg are noted on metabolic acidosis with respiratory alkalosis and pCO_2 values between 34 – 38 mmHg approximates the values noted in ABG samples labeled as compensated metabolic acidosis also on the calculation method.

Majority of ABG samples (84%) were interpreted as completely compensated respiratory acidosis in the USTH algorithm and read as respiratory acidosis with a metabolic alkalosis on the calculation method. In this situation the pCO_2 ranges from 47-76 mmHg. High values of pCO_2 greater than 80 mmHg are noted on ABG samples interpreted on calculation method as acute respiratory acidosis with a metabolic acidosis. Here a HCO_3 value of 22 mEq/L or less further substantiates this type of mixed acid-base disorder.

A completely compensated respiratory alkalosis on USTH algorithm maybe a chronic respiratory alkalosis, acute on chronic respiratory alkalosis, acute respiratory alkalosis with metabolic alkalosis or a chronic respiratory alkalosis with metabolic acidosis on the calculation method. Values for pCO_2 and HCO_3 are very much overlapping that no particular value can be used to further scrutinize a mixed disorder.

The only time that a mixed acid-base disorder is recognized in the USTH algorithm method is when a combined acid-based disturbance is seen. This happens when pH is acidotic (pH < 7.35) or alkalotic (pH > 7.45) and the value of the supposed compensation is opposite

from what is expected (see Appendix A). Evaluation of the ABG samples revealed that an interpretation in the USTH algorithm of either combined respiratory and metabolic acidosis or combined respiratory and metabolic alkalosis highly reflects the calculation method of interpretation of acute respiratory acidosis with metabolic alkalosis and acute respiratory alkalosis with metabolic alkalosis respectively.

The designation of partly compensated and uncompensated acid-base disorders on the USTH algorithm are highly unreliable in determining adequacy of compensation and on whether there is a mixed acid-base disorder. No trend in the pCO_2 and HCO_3 values can help to further strengthen the relationship between the USTH algorithm and the calculation method.

Although the USTH algorithm was developed to hasten a supposed long and arduous method of interpretation, it does not attempt to totally replace the calculation method because the algorithm can not define the expected limits of compensation[2] thus it can not predict the degree of compensation that ought to occur in a primary disturbance and therefore, can not accurately and reliably identify multiple acid-base abnormalities. It seems reasonable to use the calculation method when expected compensation to primary acid-base disturbance is needed and when multiple acid-base disorders are suspected.

Conclusion

The USTH algorithm is a valid and reliable method of ABG interpretation as it is easy, rapid, and simple to apply. The USTH algorithm has excellent agreement with the traditional calculation method in identifying ABG abnormality; namely, the pH abnormality and the primary acid-base disturbance. However, in the evaluation of adequacy of compensation and whether there is a mixed acid-base disorder, the USTH algorithm comes short of the traditional way of interpreting acid-base disorder. From the analysis of 1023 consecutive ABG samples, insights into acid-base evaluation can be extended in the USTH algorithm by noting the following: 1) an interpretation of combined respiratory and metabolic acidosis or alkalosis is highly reflective of the traditional method of interpretation, 2) a completely compensated acid-base disorder is suggestive of a mixed acid-base disturbance. With a compensated metabolic acidosis a pCO2 of > 44 mmHg suggest an underlying respiratory acidosis. When pCO2 < 44 mmHg then an underlying respiratory alkalosis should be suspected. With a compensated metabolic acidosis, a pCO2 > 38 mmHg is suspicious of a concomitant respiratory acidosis, a pCO2 of < 34 mmHg is suspicious of an underlying respiratory alkalosis and pCO2 values between 34 and 38 mmHg are most likely simple metabolic acidosis. With an interpretation of a completely compensated respiratory acidosis, a pCO2 of > 80 mmHg plus a HCO3 of < 22 mEq/L is highly suggestive of an underlying metabolic acidosis.

Beyond this observations, especially with an interpretation of partly compensated, uncompensated acid-base disorder in the USTH algorithm, calculation for compensation should be performed to determine adequacy of compensation and possibly to reveal a secondary acid-base disorder.

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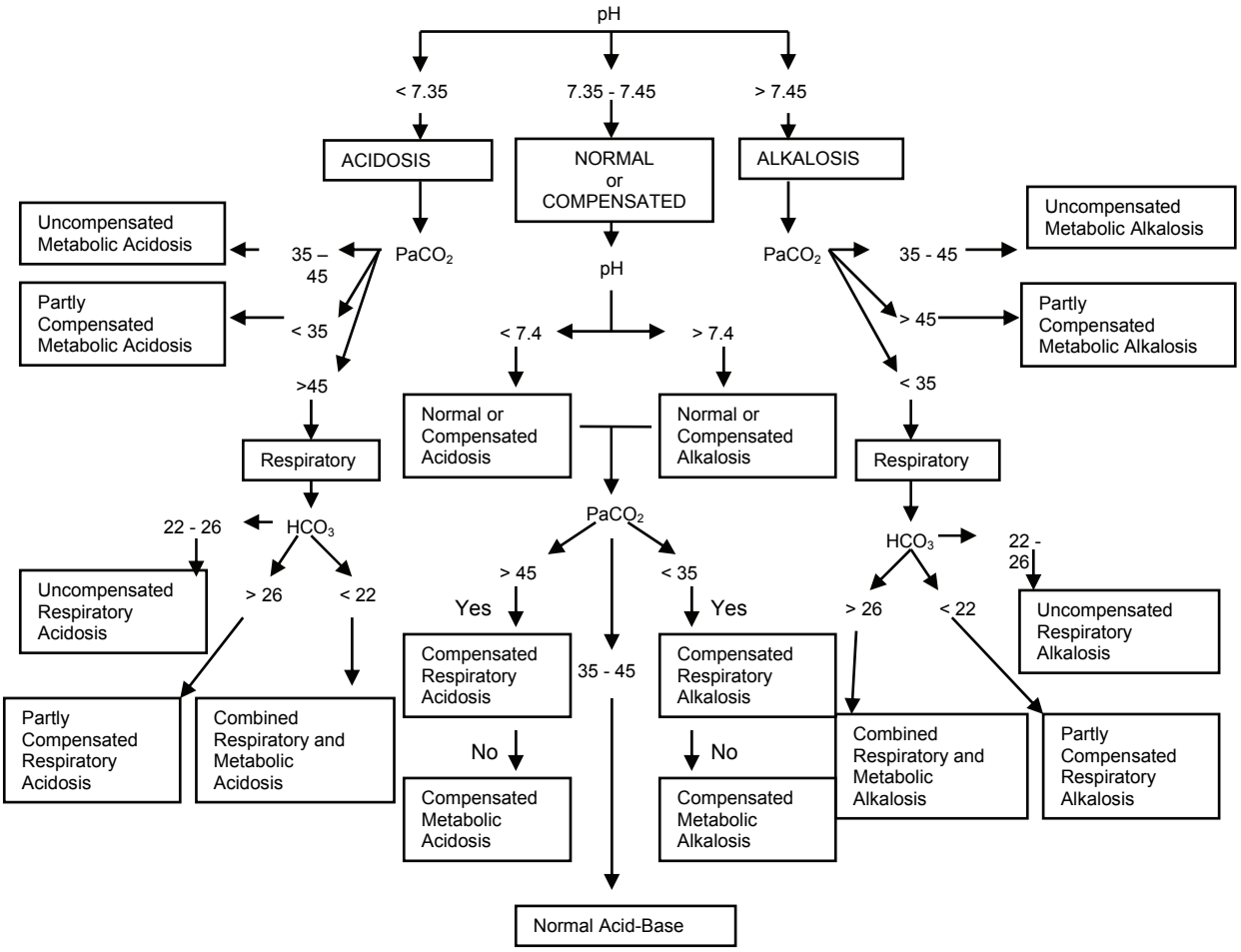
APPENDIX A: University of Santo Tomas Hospital Algorithm[1]



APPENDIX B: Calculation Method[7]

Summary of Expected Compensation for Simple Acid-base Disorders

Primary Disorder	Initial Chemical Change	Compensatory Response	Expected Range of Compensation
Metabolic Acidosis	HCO3 decrease	pCO2 decrease	pCO2=1.5(HCO3)+8±2 pCO2=last 2 digits of pH ΔpCO2=1-1.3(ΔHCO3)
Metabolic Alkalosis	HCO3 increase	pCO2 increase	pCO2: variable increase pCO2=0.9(HCO3)+9 pCO2=increases 0.6 mm Hg for each mEq/L increase in HCO3
Respiratory Acidosis	pCO2 increase	HCO3 increase	Acute: $\Delta(H^+)$=0.8 (ΔpCO2) HCO3 increases 1 mEq/L for every 10 mm Hg increase in pCO2 Chronic: Δ(H+)=0.3 (ΔpCO2) HCO3 increases 3.5 mEq/L for every 10 mm Hg increase in pCO2
Respiratory Alkalosis	pCO2 decrease	HCO3 decrease	Acute: Δ(H+)=0.8 (ΔpCO2) HCO3 falls 2 mEq/L for each 10 mmHg fall in pCO2 Chronic: Δ(H+)=0.17 (ΔpCO2) HCO3 falls 5 mEq/L for each 10 mmHg fall in pCO2

APPENDIX C: CODING SYSTEM

Category 1: Normal/Abnormal Status

Algorithm	Calculation
Normal – 1 Normal Acid Base Status	Normal – 1 Normal Acid Base
Abnormal – 2 All other interpretations	Abnormal – 2 All other interpretations

Category 2: pH Abnormality (Acidemia vs Alkalemia)

Algorithm	Calculation
Normal – unrated – 0	Normal - unrated - 0
Acidosis – 1	Acidosis - 1
Alkalosis – 2	Alkalosis – 2

Category 3: Primary Acid base Disturbance

Algorithm	Calculation
Normal – unrated - 0	Normal – unrated - 0
Metabolic Acidosis –1	Metabolic Acidosis -1
Respiratory Acidosis – 2	Respiratory Acidosis - 2
Metabolic Alkalosis – 3	Metabolic Alkalosis - 3
Respiratory Alkalosis – 4	Respiratory Alkalosis – 4

Category 4: Compensation to Primary Disturbance

Algorithm	Calculation
Normal – unrated – 0	Normal – unrated - - 0
Completely compensated -1 Completely Compensated Metabolic Alkalosis Completely Compensated Metabolic Acidosis Completely Compensated Respiratory Acidosis Completely Compensated Respiratory Alkalosis	Compensated/Chronic – 1 Compensated Metabolic Acidosis Compensated Metabolic Alkalosis Chronic Respiratory Acidosis Chronic Respiratory Alkalosis
Partly compensated / Uncompensated – 2 Partly Compensated Respiratory Acidosis Partly Compensated Metabolic Acidosis Partly Compensated Metabolic Alkalosis Partly Compensated Respiratory Alkalosis Uncompensated Respiratory Acidosis Uncompensated Metabolic Acidosis Uncompensated Metabolic Alkalosis Uncompensated Respiratory Alkalosis	Acute - 2 Acute on Chronic – 2 Chronic - 2 Acute Respiratory Acidosis with Metabolic Acidosis Acute Respiratory Acidosis Acute Respiratory Alkalosis with Metabolic Acidosis Acute Respiratory Alkalosis Acute on Chronic Respiratory Acidosis Acute on Chronic Respiratory Alkalosis Chronic Respiratory Acidosis with Metabolic Alkalosis Chronic Respiratory Alkalosis with Metabolic Alkalosis
Combined – unrated - 0 Combined Respiratory and Metabolic Acidosis Combined Respiratory and Metabolic Alkalosis	Combined – unrated - 0 Combined Metabolic and Respiratory Acidosis Metabolic Acidosis with Respiratory Alkalosis Combined Metabolic and Respiratory Alkalosis Metabolic Alkalosis with Respiratory Acidosis

Category 5: No. of Disturbance

Algorithm	Calculation
Normal – unrated – 0 Normal Acid Base	Normal – unrated – 0 Normal Acid Base
Single disorder- 1 Completely Compensated Respiratory Alkalosis Completely Compensated Metabolic Alkalosis Completely Compensated Metabolic Acidosis Completely Compensated Respiratory Acidosis Uncompensated Respiratory Acidosis Partly Compensated Respiratory Acidosis Uncompensated Metabolic Acidosis Partly Compensated Metabolic Acidosis Uncompensated Respiratory Alkalosis Partly Compensated Respiratory Alkalosis Uncompensated Metabolic Alkalosis Partly Compensated Metabolic Alkalosis	Single disorder- 1 Acute Respiratory Acidosis Chronic Respiratory Acidosis Acute on Chronic Respiratory Acidosis Compensated Metabolic Acidosis Acute Respiratory Alkalosis Chronic Respiratory Alkalosis Acute on Chronic Respiratory Alkalosis Compensated Metabolic Alkalosis

Multiple disorder - combined – 2 Combined Respiratory and Metabolic Acidosis Combined Respiratory and Metabolic Alkalosis	Multiple disorder - (with/and) – 2 Acute Respiratory Acidosis with Metabolic Acidosis Acute Respiratory Acidosis with Metabolic Alkalosis Chronic Respiratory Acidosis with Metabolic Acidosis Chronic Respiratory Acidosis with Metabolic Alkalosis Acute on Chronic Respiratory Acidosis with Metabolic Alkalosis Acute on Chronic Respiratory Acidosis with Metabolic Acidosis Combined Metabolic and Respiratory Acidosis Metabolic Acidosis with Respiratory Alkalosis Acute Respiratory Alkalosis with Metabolic Alkalosis Acute Respiratory Alkalosis with Metabolic Acidosis Chronic Respiratory Alkalosis with Metabolic Alkalosis Chronic Respiratory Alkalosis with Metabolic Acidosis Acute on Chronic Respiratory Alkalosis with Metabolic Alkalosis Acute on Chronic Respiratory Alkalosis with Metabolic Acidosis Combined Metabolic and Respiratory Alkalosis Metabolic Alkalosis with Respiratory Acidosis

APPENDIX D: Guidelines by Byrt[8] for Interpreting Kappa

0.93-1.00	Excellent agreement
0.81-0.92	Very good agreement
0.61-0.80	Good agreement
0.41-0.60	Fair agreement
0.21-0.40	Slight agreement
0.01-0.20	Poor agreement
$\leq$ 0.00	No agreement

Re-evaluation of Pneumonia Requiring Admission to an ICU: A Prospective Study

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Community acquired pneumonia is the most common cause of death from infectious diseases both in western and developing countries. The choice of antibiotic is probably the most important decision in ensuring survival. This study was therefore undertaken to discover the factors which are associated with severe pneumonia in patients admitted to the Intensive Care Unit of the Chinese General Hospital. Of the 45 patients included in this study, 91% are > 65 yo, with a mean age of 80 ± 10 years. Majority of the co-morbid illness associated with pneumonia are the following: diabetes mellitus, neoplastic diseases, neurologic diseases, cardiac diseases (the most common), renal diseases, pulmonary diseases, chronic liver disease and chronic alcohol abuse. Most of the patients presented with the three cardinal signs and symptoms: fever (30 patients or 69%), cough (39 or 87%) and dyspnea (35 or 78%).

Parameters measured to be associated with mortality were age > 60, septic shock, requirement for mechanical ventilation, bilateral pulmonary involvement, and *Pseudomonas aeruginosa* as the most isolated etiologic agent. Gram-negative bacilli ranked the second most common etiologic agent also with high mortality then *Candida albicans* or *spp* followed by *Staphylococcus aureus*. And on follow-up, the following were the outcome or causes of death: hospital-acquired pneumonia, acute respiratory failure or acute lung injury, Acute Respiratory Distress Syndrome and multi-organ failure with sepsis. The study showed a great mortality of 53%. Early diagnosis, appropriate antibiotic, and prompt ICU transfer may influence the outcome of the disease. Around half of the patients improved, with those in moderate risk not progressing to high risk CAP. Some high risk patients improved (24%). *Phil Journal Chest Diseases. Vol. 12 No.2 pp: 81 - 89*

Keywords: Severe pneumonia, treatment guidelines, mortality

Introduction

Community acquired pneumonia is the most common cause of death from infectious diseases both in western and developing countries. Despite the introduction of newer antibiotics, vaccinations, and better supportive care, CAP still remains a common, frequently fatal disease. Pneumonia is a lower respiratory tract infection presenting with an acute onset of within 24 hours to less than two weeks which when acquired in the community is referred to as Community Acquired Pneumonia (CAP). It is fourth leading cause of morbidity and the third leading cause of mortality in Filipinos (1994 Phil. Health Statistics).

CAP is likely to be severe in the very elderly and clinically significant in those with hepatic or renal insufficiency, cardio pulmonary disease or impaired host defense. Age and co-existing illness influence which infectious agents are most likely to cause infections. Severity of illness and clinical features are influenced by various host factors and by the virulence of the infectious agents. These pathogens determine prognosis, complications and duration of therapy. Mortality and Morbidity are reduced by the rapid institution of appropriate antimicrobial therapy. Because of the limitation of presently available diagnostic tests, many patients are started on empiric regimens, and in up to half of these individuals, a cause is not identified.

Empiric antimicrobial therapy should be based on likely pathogen, not severity of illness which affects the potency but not spectrum of antibiotics selected. Although, there are a number of potential pathogens, it is possible to identify likely pathogens based on easily identifiable clinical factors such as age, presence of co-morbid illness, severity of illness at presentation and the need for hospitalization.

[1] Chinese General Hospital and Medical Center

Table I Potential Pathogens and Empiric Antimicrobial Therapy In CAP

	Minimal Risk CAP (1)	Low Risk CAP (II)	Moderate Risk CAP (III)	High Risk CAP (IV)
Potential Pathogens	*S. pneumoniae* *H. influenzae* *C. pneumoniae* *M. pneumoniae*	*S. pneumoniae* *H. influenzae* *C. pneumoniae* *M. pneumoniae* *M. catarrhalis* Gram-negative bacilli (enteric)	*S. pneumoniae* *H. influenzae* *Legionella* *C. pneumoniae* *M. pneumoniae* Gram-negative bacilli Anaerobes	*S. pneumoniae* *H. influenzae* *Legionella* *C. pneumoniae* *M. pneumoniae* Gram-negative bacilli Anaerobes *P. aeruginosa*
Empiric therapy	Amoxycillin Or Extended macrolides Or Co-trimoxazole	Co-trimoxazole Or Co- Amoxyclav Or Sultamicillin Or 2nd gen. oral cephalosporins or extended macrolide	IV Beta Lactams w/ or w/o anaerobic coverage +/- erythromycin IV* or levofloxacin alone	Anti-pseudomonal beta-lactams +/- aminoglycoside or ciprofloxacin** + Erythromycin IV*

* Use only if *Legionella* is strongly suspected

** Combined therapy with beta-lactam for *P. aeruginosa* and *Enterobacter*.

Using this approach, CAP in immunocompetent adults may be divided into 4 categories. In this study, the clinical practice guidelines on CAP by the consensus of PSMID & other various societies such as PCCP, ACEP-FC, etc. It is specific only for empiric therapy of immuno competent adults which has been drafted to provide the clinician with practical approaches in the resolution of the important issues on the diagnosis, management and prevention of CAP. (*Table I*)

Methods

A prospective cohort study was done on patients with Community Acquired Pneumonia admitted at the Chinese General Hospital and Medical Center from January 2000 to October 2000. The study limits itself to patients admitted to the Intensive Care Unit/Coronary Care Unit (ICU-CCU) either as a direct admission or transfer from a private room after a few days from initial admission secondary to pneumonia. Patients are either in the moderate or high risk category which both warranted hospital admission; the difference lies in the place where you put the patient - the ward or the ICU. Patients who have exhibited symptoms suggestive of lower respiratory tract infection, a new infiltrate on the chest radiograph at the time of hospital admission are included in this study as well as patients re-admitted secondary to pneumonia. Those patients that were discharged, 10 days before the onset of symptoms of pneumonia are excluded in this study.

Data Collection. The PSMID Clinical Practice Guidelines on Community Acquired Pneumonia is used as the parameter for selecting and follow-up patients. The following parameters are recorded such as age, sex, clinical symptoms, co-morbidity/type of morbidity; in addition, vital signs such as respiratory rate, heart rate, and the blood pressure both systolic and diastolic are measured and diagnostic work-up such as chest xray and arterial blood gas are done. In following up the patient, microbial etiology, empiric antibiotic treatment regimen used, and outcome of the pneumonia and its complication such as respiratory failure and sepsis are also observed and recorded.

Results

A prospective cohort study of 45 patients diagnosed to have community acquired pneumonia with moderate to high risk category admitted directly or subsequently to ICU-CCU in accordance to the clinical guidelines in the management of CAP by the consensus of the PSMID was undertaken. As shown in *Table II*, 91% (41 patients) admitted at the ICU-CCU are > 65 yo, predominantly male (68%) and only 22% are female. The rest of the four patients are < 65 yo (8%). The mean age of the cohort group is 80 $\pm$ 10 (70-90 yo) which corresponds to 80% of the study population.

As shown in *Table III*, majority of the co-morbid illness associated with pneumonia are the following: diabetes mellitus, neoplastic diseases, neurologic diseases, cardiac diseases, renal diseases, pulmonary diseases, chronic liver disease and chronic alcohol abuse. The most common co-morbid illness concomitant with pneumonia is cardiac in origin. The heart diseases include hypertensive heart disease (23), congestive heart

Table II Age and Sex distribution of moderate to high risk patients with community acquired pneumonia admitted at CGH-ICU-CCU on January to October 2000

Age	f	Sex	
		Male	Female
<60	1	1	---
60 - 65	3	2	1
66 -70	1	1	---
71 -75	7	5	2
76 - 80	8	5	3
81 - 85	13	11	2
86 - 90	8	5	3
91 - 100	4	4	---
Total	45		

Table III The different co-morbid Illnesses commonly seen associated with Pneumonia

Co-morbid Illness	Single Entity	Plus CNS	or Cardiac	or Renal	or Pulmo	Or Misc
DM	2	1	5	5	2	1
Cancer	2	1	5	2	1	---
CNS	1	--	10	3	--	---
Cardiac	6	--	---	2	5	---
Renal	--	--	---	--	--	---
Pulmo	3	--	---	--	--	---

Table IV Signs and symptoms presented in patients with community acquired pneumonia in moderate to high risk category

Signs and Symptoms	Present	Absent
Fever	30	15
Cough	39	6
Dyspnea	35	10
Chest pain	4	41
Easy fatigability	7	38
Orthopnea/PND	8	37
Anorexia	14	31
Body weakness	5	40
Dec level of Sensorium:	---	25
Disoriented	5	---
Stuporous	10	---
Unconscious	5	---
Vital Signs		
SBP<90/DBP<60 or BP= 0	24*	21
CR > 125 or < 60/min or 0	14*	31
RR > 30/min or 0	30*	15
ABG		
pCO_2 >50mmHg	14	28
pO_2 < 60 mmHg	13	29
PaO_2/ FiO_2 <200	24	18

* 6 patients came in dead on arrival
**3 patients had no ABG

failure (16), ischemic heart disease/coronary heart disease, and cardiac arrhythmia.

Almost half of the study group (64%) had at least one or two co-morbid illness including again cardiac followed by CNS problems such as cerebrovascular diseases which could be thromboembolic or hemorrhagic (12) and Parkinson's disease (2). Next in line are the pulmonary and renal diseases (11 each). Majority of the renal patients are chronic renal insufficiency or chronic renal failure secondary to hypertension or diabetes mellitus, a little of glomerulonephritis while pulmonary patients are all with chronic obstructive pulmonary disease of emphysematous type related to smoking. In this study, 33% were not able to fill up the smoking and alcohol history but still a large number of patients (42-46%) had a strong history of chronic smoking and chronic alcohol abuse. Next are diabetes mellitus (10) and neoplastic disease (6) such as bladder, lung, prostatic, colonic cancers and dysgammaglobulinemia.

Actually, 95% of the patients (43) had the above co-morbidities which can exist simultaneously with pneumonia be it a single or multiple co-morbidity. There are 13 patients who had one co-morbidity, 16 patients with two co-morbidities, eight patients with three co-morbidities and six patients with four co-morbidities.

As shown in *Tables IV* and *V*, the different signs and

Table V Comparison with PE findings of the lungs to radiologic findings of pneumonia in moderate to high risk patients.

PE findings location	Chest xray Result							
	CXR Not done	Pneumonia						ARDS
		Right	Left	Bases	Both lung fields	w/ congestion	w/ effusion	
Crackles w/ or w/o rhonchi; wheeze	1	2	-	1	-		-	-
Basal	-	1	-	-	1	7	2	-
Bilateral	1	1	-	2	4	5	9	2
Right	2	2	-	-	-	-	-	-
Left	-	-	1	-	-	-	1	-

symptoms, vital signs, initial ABG results and clinical lung findings in correlation to the chest xray findings are tabulated. Reviewing the tabulated results, majority of the patients presented with the three cardinal signs and symptoms: fever (30 patients or 69%), cough (39 or 87%) and dyspnea (35 or 78%). Other nonspecific signs and symptoms such as chest pain, easy fatigability, orthopnea, paroxysmal nocturnal dyspnea, anorexiea and body weakness are also experienced which could be the signs and symptoms of the concomitant cardiac, pulmonary or renal diseases.

On follow-up of the 45 patients, the different classification of CAP and its corresponding outcome with regards to the use of inotropics, ventilatory support and the endpoint of the disease are shown in *Table VI*. Through the help of the PSMID Clinical guidelines in the management of CAP, there are 35 patients (78%) under the high risk category while 10 patients (22%) under the moderate risk category

Majority of the CAP patients in this cohort study are high risk and one of the criteria in differentiating patients in moderate to high risk are the signs of hypoperfusion such as changes in the level of sensorium and hypotension, plus hypoxemia which is best gauged by the use of the arterial blood gas.

There are 56% of the patients in the study who came in coherent but were classified as high risk because of hypotension while 44% came in with depressed level of sensorium either in an unconscious or arrested stage (11%), stuporous (11%) and disoriented (22%). With regards to the vital signs upon admission, around 40-50% of the patients came in hypotensive with Systolic BP < 90mmHg and Diastolic BP < 60mmHg (18) plus tachypneic with respiratory rate > 30/min (24) and only nine patients (20%) exhibited tachycardia or bradycardia. Six patients came in arrested (13%) with suspected aspiration as cause of death.

Clinical lung findings of crackles could be grouped as occasional (4) up to bibasal (11) unilateral (5) and bilateral lung field (25). In correlation to the chest xray findings, majority of the patients presented with bilateral crackles on both lung fields or bibasal crackles with or without rhonchi or wheeze. Some showed pneumonia with effusion (9) and some with congestion (15) and some purely pneumonia (10), with two cases of Adult Respiratory Distress Syndrome. Other findings of occasional or unilateral crackles showed pneumonia on one side more on the right (6) than the left (1).

With regards to the arterial blood gas, more than 60% of the patients did not exhibit hypercarbia or hypoxemia taken as isolated pO_2 and pCO_2. About 30-40% (13-14) presented only with hypercarbia or hypoxemia. But when the pO_2/FiO_2 ratio was computed, majority of the patients (24 out of the 45 or 54%)) showed pO_2/FiO_2 < 200 which is more specific for signifying hypoxemia than simple pCO_2 or pO_2 alone.

In high risk CAP, there are 32 patients (71%) who needed inotropics; 18 patients came in initially

Table VI Classification of CAP based on PSMID in patients admitted at the CGH-ICU/CCU due to pneumonia with corresponding management and outcome.

Management & Outcome of the disease	Category of Pneumonia	
	Moderate Risk CAP	High Risk CAP
Inotropics		
+	1	32
-	9	3
Ventilatory support		
Mechanical ventilation	-	29
BiPAP/CPAP	1	3
MV + BiPAP/CPAP	-	3
None	9	-
Outcome		
Expired	-	24
Improved	10	11

Table VII Indications for Using Ventilatory Support based on Arterial Blood Gas

Type of Ventilatory Support	ABG Result			
	PaO_2/FiO_2 < 200	PCO_2 > 50 mmHg	PO_2 < 60 mmHg	No ABG
Mechanical ventilation	22	1 (7)	3	2
Non-invasive ventilation (BiPAP/CPAP)	2	- (2)	-	-
Both (MV + BiPAP/CPAP)	2	- (1)	-	-

Table VIII The different organisms isolated thru Sputum Gram Stain & Culture in patients with moderate and high risk CAP.

Organism	Moderate Risk CAP	High Risk CAP
Acinetobacter spp.	2	1
Branhanmella catarrhalis	4	-
Candida albicans	-	2
Candida spp.	3	6
Coagulase (-)staphylococcus	1	1
Escherichia coli	-	4
Enterobacter spp.	-	2
Klebsiella oxytoca	-	3
Klebsiella ozanae	2	4
Klebsiella spp.	2	1
Pseudomonas aeruginosa	-	12
Pseudomonas spp.	2	5
Staphylococcus aureus	-	2

Table IX Antibiotics used in Patients with Moderate to High risk CAP.

ANTIBIOTICS USED	Moderate Risk CAP	High Risk CAP
Cephalosporin		
2nd generation - cefuroxime	3	3
3rd generation –		
ceftriaxone	1	-
ceftazidime	1	18
cefdinir	-	1
4th generation-		
cefpirome	4	5
cefipime	-	17
Beta-lactams		
Carbapenems - Imipenems	-	6
Meropenem	-	7
Piperacillin-tazobactam	3	12
Aminoglycoside - amikacin	1	12
Macrolide- dirithromycin	7	12
Clavulinic acid *w/* amoxicillin	2	2
Sulbactam *w/* ampicillin	2	-
Fluconazole	-	16
Amphoteriin B	-	2
Anti-TB	-	5
Clindamycin	1	11
Metronidazole	-	2
Cotrimoxazole	1	5

Table X The different causes of death in patients with high risk CAP Admitted at the ICU-CCU from January to October 2000

Cause of Death	N
Multi-organ Failure plus sepsis	9
Sepsis	3
Hospital Acquired pneumonia	2
Ventricular Fibrillation	2
Dead on arrival *	4
Acute Respiratory Distress Syndrome	2
Discharge against medical advice	2

* all DOA are suspected cases of aspiration

hypotensive while six patients came in arrested and the rest (eight) subsequently developed low blood pressure. In moderate risk CAP, only one patient was placed on inotropics; not because of the hypotension but for cardiac support secondary to the cardiac problem. The number of inotropics used varied depending on the severity of the illness and its effect on the patient's blood pressure. Inotropics used were dopamine, dobutamine, norepinephrine and rarely vasopressin. Majority of the patients were hooked to two inotropics (17) with the rest on one inotropic (10) or with three inotropics (5) and four inotropics (1). Only nine patients improved with the use of inotropics (20%) consisting of one patient in moderate risk CAP and eight patients in high risk.

In high risk CAP, there were 29 patients (64%) who needed mechanical ventilation, six patients were hooked to non-invasive ventilation such as BIPAP/CPAP and out of the six, three (11%) were subsequently hooked to a mechanical ventilator because of severe hypoxemia. All high risk CAP (35) were placed on ventilatory support be it non-invasive or invasive. Majority of the patients intubated are because of impending acute respiratory failure type 1 secondary to hypoxemia ($pO_2/FiO_2 < 200$) in severe CAP. In moderate risk CAP, only one patient was hooked to a BIPAP/CPAP because of hypercapnea (+ COPD, not in hypoxemia).

The over-all endpoint of the disease or the mortality rate of high risk CAP is 53% (24 patients with 22 patients on mechanical ventilation and two on BIPAP) and only 24% (11) improved. While in moderate risk CAP, there was zero mortality (all 10 improved). In this study, the algorithm has helped in classifying CAP patient who needed better monitoring in the ICU-CCU or not at all.

The average days admitted at the hospital with respect to the endpoint of death or mortality (l - 5days: 7 patients; 6 – 10 days: 3 patients; 11 - l5days: 5 patients) on the average was at the first week of admission. Improved patients (l – 5 days: 3 patients 6 - 10 days: 6 patients; 11 - l5 days: 5 patients) on the average also of first to second week of admission . Indeed, the different parameters used help predict the outcome of the disease regardless of the days admitted at the hospital.

In this study, the different organisms isolated thru sputum Gram stain and culture is shown in *Table VIII*. In moderate risk CAP, the most common organism is *Branhanmella catarrhalis*; others are *Acinetobacter* and *Pseudomonas spp*. In high risk CAP, *Pseudomonas aeruginosa* and *Pseudomonas spp.* are the commonly isolated organisms followed by gram negative bacilli, then *Staphylococcus aureus*, *Candida albicans* and *Candida spp*., and *Acinetobacter spp*. The contaminant isolated is coagulase negative *Staphylococcus*. In general, organisms found in moderate risk ranges more on Gram negative than Gram positive and in high risk, a wide range of pathogens should be considered from Gram positive and Gram negative as well as fungal organisms.

Blood culture and sensitivity were done only on 41 patients with only four being positive while the rest were negative (37). All positive cultures plus 14 patients with negative culture succumbed to death; two went home against medical advice. Four patients had no blood cultures.

In *Table IX* are the different antibiotics used in the group of patients in this study. These are the

combinations of antibiotics used initially as empiric treatment and as sequential therapy based on the sputum gram stain and culture-sensitivity tests. Majority of all the antibiotics used are included in the treatment guidelines for the CAP for moderate to high risk.

In both high and moderate risk categories, macrolides, both oral and IV, are widely used. And the most common antibiotics used in high risk group are the different generation of cephalosporins especially the third and fourth generation and quinolones followed by the carbapenems, aminoglycosides and piperacillin + tazobactam. Anaerobic coverage is also used especially in suspected cases of aspiration which in this study amounts to 10 cases – clindamycin, metronidazole and oxacillin are used. Likewise, antifungal agents such as Diflucan and amphotericin B are used in cases with pneumonia of fungal origin and candidemia

In *Table X* are the different causes of mortality seen in this study. Majority of the mortality in high risk CAP is still multi-organ failure plus sepsis (12). Out of the six arrested patient on admission, four eventually died, suspected cause was aspiration while only two improved. Other causes are hospital-acquired pneumonia (2), Adult Respiratory Distress Syndrome (2), ventricular fibrillation (2) and discharged against medical advise (2).

Discussion

Both age and co-morbidity are independent predictors of mortality. There is a direct association with old age > 65 yo. Likewise, diabetes melllitus, neurological, neoplastic and renal disease with congestive heart failure are also predictors of a complicated course of CAP. Due to the anatomic interrelatedness of the heart and the lungs functioning as one, cardiac diseases are very prone to have pulmonary complications such as congestion especially in patients with cardiac dysfunction which could be precipitated by an infection such as pneumonia. That's why in this study we could see a lot of pneumonia cases with concomitant pulmonary congestion and/or effusion especially in the elderly patients.

We presented no data on chronic liver disease or chronic alcohol abuse as predictors of mortality but it is an important predisposing factor in the development of pneumonia. A study done by Fernandez, et.al in 1995, showed that an increase in alcohol intake is the main risk factor for developing CAP. In this situation, it also confers a worse prognosis, which should be treated with a broad spectrum antibiotic for a longer period. The causative agents usually are gram-negative bacilli, *Candida albicans* and *Staphylococcus aureus*. They usually present with severe clinical symptoms, require longer intravenous antibiotic treatment, longer hospital stay and slow resolution of infiltrates on chest xray compared to non-alcoholics.

A patient with cough who has abnormal vital signs of tachypnea > 20/min; tachycardia > 100/min and fever T >37^{o}C with at least one abnormal chest finding of diminished breath sounds, rhonchi, crackles, or wheeze, probably has pneumonia. However, these clinical findings are not sufficiently accurate in diagnosing pneumonia. The typical signs and symptoms of pneumonia such as cough, sputum productivity, dyspnea and pleuritic chest pain can present with significant inter-observer variability in eliciting these clinical signs and symptoms of respiratory illnesses, which may reflect inadequate clinical skills of the health care providers. Hence, chest radiologic findings of a new parenchymal infiltrate that has no alternative cause such as lung carcinoma is the reference diagnostic standard for pneumonia to confirm the diagnosis. Still, radiologic lag should be considered in patient with clinical findings of crackles but normal chest xray.

In addition to confirming the diagnosis of pneumonia, an initial chest xray is essential in assessing the severity of the disease, presence of complications, for prognostication, identification of bilateral or multi-lobar involvement, rapid progression of the infiltrates in severe disease, and indication for hospital admission. Chest xray may also suggest possible etiologies and help in differentiating pneumonia from other conditions that may mimic it.

Based on the PSMID algorithm for CAP, fever, cough and dyspnea are considered one of the clinical signs and symptoms to look for in suspected cases of CAP. Physical and laboratory findings are predictive of increased morbidity and mortality. The presence of the following: RR > 30/min, or DBP < 60 mmHg were associated with a 20% mortality compared with 2% mortality when only one or none of these features were present.

Patients with respiratory failure manifested as PaO_2 < 60 mmHg or acute hypercapnea of $PaCO_2$ > 50 mmHg at room air or PaO_2/FiO_2 ratio < 250 mmHg have a grave prognosis with a mortality rate of 25%.

The establishment of an etiologic agent is ideal as a diagnostic standard. However, despite adequate studies using good microbiologic techniques, an identifiable organism is found in only 40-50% of cases of CAP. Sputum gram stain and culture is therefore not recommended for routine use particularly in patients who do not require hospitalization where etiology is predictable. However, for hospitalized patients with

severe disease just like in this cohort study where more pathogens need to be considered. In these patients, blood cultures at least on two separate sites are highly recommended. Although of low sensitivity, a positive blood culture is specific and is considered as the gold standard in the etiologic diagnosis of pneumonia. Gram stain and cultures of appropriate pulmonary secretions in addition to a blood culture should be part of the initial work-up of patients hospitalized for severe pneumonia.

The etiologic diagnosis is considered definite when the pathogen is isolated from the blood, pleural fluid, secretions obtained from transtracheal aspiration or lung aspiration. A pathogen such as *M tuberculosis*, *Legionella spp*., viruses and fungi that are not normal colonizers of the upper airways, when isolated from respiratory secretions, are also considered definite etiology of pneumonia.

It is considered probable etiology if the pathogens are demonstrated by smear or culture isolated in moderate and heavy quantity from respiratory secretions including expectorated sputum, or brush catheter specimen or BAL (bronchoalveolar lavage). Although with limitations, when Gram stain and culture and sensitivity are done on appropriate sputum of good quality (PMN > 25/lpf and squamous epithelial cells < 10/lpf) reflect cultures of transtracheal aspirate and may provide useful information in patients hospitalized with severe CAP. It also aid physicians in selecting appropriate monotherapy in approximately 94% of the time by the predominant morphology from the gram-stained sputum.

Routine cultures of expectorated sputum are more difficult to interpret. Because of the contamination from the resident flora of the upper airways that may include potential pathogens, cultures are not specific, and may yield false positive results.

Appropriate treatment of severe CAP requiring admission to a medical ICU depends on the knowledge of the likely etiological agents in any community. This is aided by doing sputum culture and sensitivity, blood culture and sensitivity and serologic studies. A study by Dalmasch in 1994 regarding pneumonia requiring ICU, it showed that gram negative rods were the predominant pathogens in CAP and that *Mycobacterium tuberculosis* also as a cause of tuberculous pneumonia. *M. tuberculosis* should be considered as cause depending on the geographical region especially in our country where pulmonary tuberculosis still accounts for a great number of patients when choosing initial empirical antimicrobial therapy.

In many studies, (Hirani, et. al., Rello, et. al.), *Streptococcus pneumoniae, Legionella pneumophilia* and *Staphylococcus aureus* or Gram-negative bacilli were the most frequent cause of severe CAP. Others such as *Mycobacterium tuberculosis* and *Pneumocystis carinii* should also be considered. Usually *Legionella* and *Pneumocystis* were diagnosed thru serologic tests.

In 1995 by Almirall, et. al., a study regarding the prognostic factors of pneumonia requiring ICU admission was done and the following were associated with fatal outcome: age > 70, septic shock, bilateral pulmonary involvement, *P. aeruginosa* as the etiologic agent. Another study by Tower, et. al. also showed the same prognostic factors, in addition, bacteremia, progressive spread in the pulmonary infiltrates, ARDS, FiO_2 requirement > 60%, use of PEEP and inadequate antibiotics were also identified. In summary, the two factors significantly related to prognosis are the (fast) radiologic spread of pneumonia during ICU admission and the presence of septic shock.

A study by the Leroy group last 1995 showed the following parameters to be associated with mortality (univariate analysis): age > 60, immunosuppression, septic shock, requirement for mechanical ventilation, bilateral pulmonary involvement, bacteremia, WBC < 3,500mm^3, Total protein of < 45g/l, Creatinine > 15mg/l, non-aspiration pneumonia, initial ineffective therapy and complications. There are five factors associated with prognosis (multivariate analysis): anticipated death within 5 years, shock, bacteremia, non-pneumonia complication and ineffective antimicrobial therapy. The effectiveness of the initial therapy appears to be the most significant prognosis factor and as the one and only related to the initial medical intervention, which suggest a need for sustained optimization of our antimicrobial strategies and the importance of prevention of hospital acquired super-infections.

In Leroy, et. al., 1999, a follow-up study showed the six independent predictors of mortality are age $\geq$ 40 yo, anticipated death within 5 years, non-aspiration pneumonia, chest xray findings in more than one lobe, acute respiratory failure requiring mechanical ventilation, and septic shock. During follow-up in the ICU, there are three independent predictors of mortality: hospital-acquired lower respiratory tract super-infections, non-specific CAP-related complications and sepsis-related complications. As an aid to clinicians in stratifying the prognosis of patients with severe CAP, the simplified prediction rule used in the study could be useful for therapeutic decisions and appropriate care.

Another study (Moine, et. al.) also has the same association with mortality as stated above, in addition, impairment of alertness and *Streptococcus pneumoniae* or *Enterobacteriaciae* as the cause of pneumonia.

In the study of the Impact of the Management Guidelines on the Outcome of Severe CAP in 1997 by Hirani, et. al. used the casual pathogens, clinical, laboratory features of severity, antibiotic therapy and mortality as parameters. As concluded, the management guidelines for severe CAP have been widely adopted without a decrease in the mortality. Factors other than early diagnosis, appropriate antibiotics or prompt ICU transfer may influence the outcome in severe CAP.

On the study of severe CAP with emphasis on outcome done by Rello, J., Quintana, et. al in 1993, showed > 50% mortality on the first five days because of septic shock, hemoptysis (TB) and hypoxia. However it is still the main fatal complication and all late occurring deaths more than five days were due to hypoxia. Such data is important in planning strategies and protocol to improve prognosis.

A study by Pachon, et. al. in 1990 regarding severe CAP concluded that the diagnosis of the causative agent did not aid in increasing the survival rate, but it did allow for better patient management. Gram-negative bacillary pneumonia was a frequent finding among the patients who did not recover, making empirical treatment with erythromycin plus third generation cephalosporins most advisable for severe cases of CAP.

Once empiric therapy has been initiated, therapy should be continued for at least 72 hours unless clinical deterioration is noted. Within four days, fever and leucocytosis should return to baseline but abnormal PE (i.e. crackles) require longer to resolve, especially with co-existing illness. Chest xrays are the last to return to baseline and are especially delayed if the patient is bacteremic or has structural lung disease. Not all patients respond to initial empiric therapy. Reasons for this include antimicrobial resistance, the presence of non-bacterial pathogens (such as respiratory viruses), unusual bacterial pathogen, non-infectious cause that may mimic CAP, infectious complications (empyema) and pneumonia occurring in patients with unrecognized severe immunosuppression. Failure to improve after 72 hours and development of deterioration are indications for repeat diagnostic work-up and consideration of alternative diagnosis. More invasive diagnostic tests are appropriate in severely ill patients and in those conditions where there is rapid deterioration.

Severe CAP causes a high mortality despite ICU management. Bacterial diagnostic rate was decreased but made no difference to over-all mortality. Knowing that mortality is increased in patient with CAP who require mechanical ventilation, in the study of Pascual, et. al., it was hypothesized that the severity of acute lung injury could be used along with non-pulmonary factors to identify patients with the highest risk of death. The five independent predictors are: 1) extent of lung injury assessed by the hypoxemia index; 2) number of non-pulmonary organs that failed; 3) immunosuppresion; 4) > 80 yo; 5) co-morbidity with a prognosis for survival less than five years.

Conclusion

This study in our local setting of a tertiary hospital compared with the previous studies from foreign countries likewise showed the same parameters as measured to be associated with mortality such as the age > 60, septic shock, requirement for mechanical ventilation, bilateral pulmonary involvement, and *Pseudomonas aeruginosa* as the most isolated etiologic agent which were majority seen in our high risk patients. Gram-negative bacilli ranked the second most common etiologic agent also with high mortality then *Candida albicans* or *spp* followed by *Staphylococcus aureus* which were also organisms included in the guidelines. Because of the limitation of serologic studies in our hospital, *Legionella* and *Pneumocystis* were not done. And on follow-up, the following were the outcome or causes of death such as hospital-acquired pneumonia, acute respiratory failure or acute lung injury, Acute Respiratory Distress Syndrome and multi-organ failure with sepsis as observed in the study which are also predictors of mortality, in addition to co-morbid illnesses and altered sensorium. In general, the mortality rate goes higher and higher as one approach from minimal risk CAP to the other end of the category, the high risk CAP. And the guidelines used did help in the management of patient by categorizing them correctly, giving them the right empirical antibiotics but showed no decrease in the survival rate. The study did show a great mortality of 53%. Early diagnosis, appropriate antibiotic, and prompt ICU transfer may influence the outcome of the disease. Still, around half of the patients improved, the moderate risk did not progress to high risk CAP (22%) and some high risk patients did improve (24%) with some requiring tracheostomy (6).

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Assessment of Severe Community-acquired Pneumonia ATS Severity Criteria

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Community-acquired pneumonia (CAP) is a common reason for confinement in a hospital. This is more so for the severe types of CAP where current guidelines recommend confinement to the ICU. The American Thoracic Society (ATS) lists down several criteria which a clinician may use to help in this determination. However, these criteria have not yet been validated, especially in the local setting, thus the reason for this study.

Patients 16 years old and above admitted at Chinese General Hospital with pneumonia between May 1999 and October 1999 were prospectively studied. They were assessed according to the ATS severity criteria and their outcomes determined. In the end, a total of 90 patients were admitted with community-acquired pneumonia, with 58 patients as non-severe pneumonia (64%) and 32 patients as severe pneumonia (36%) based on ATS criteria. All severity criteria, except the radiographic criteria and RR > 30/min., were significantly associated with death. The sensitivity, specificity, positive predictive value and negative predictive value measures were further reported and discussed. Although there are a limited number of subjects, the ATS guidelines for severe community-acquired pneumonia showed that they are highly specific but poorly sensitive and the application of these parameters must be exactly defined. *Phil Journal of Chest Diseases. Vol. 12 No. 2 pp: 90 - 93*

Keywords: Community-acquired pneumonia, mortality, severity criteria

Introduction

Community-Acquired Pneumonia (CAP) remains a common and serious illness. In the Philippines it is the 4th leading cause of morbidity and the 3rd leading cause of mortality based on the 1994 Philippine Health Statistics.

Pneumonia is increasingly common among older patients and those with co-morbidities. In the outpatient setting the mortality rate remains low (1-5%), but among patients with community-acquired pneumonia who require hospitalization, the mortality rate approaches 25%, particularly if the patient requires admission into the Intensive Care Unit.

About 10% of all hospitalized patients with community-acquired pneumonia require admission to the intensive care unit and the mortality of these patients reach 20-50%. The American Thoracic Society (ATS) published (1993) guidelines for the initial management of adults with CAP and included criteria in order to provide a tentative definition of severe illness and the presence of any one of this criteria was used to determine a pneumonia case as severe and require an admission to the ICU (*Table I*), which have been shown to be associated with death. However, there has been only one preliminary communication about validation of these severity criteria. Also, the predictive potential of

Table I ATS criteria for severe community-acquired pneumonia

Presence of at least one of the following conditions justifies defining the pneumonia as severe:
-Respiratory frequency >30 breaths min. at admission
-Severe respiratory failure defined by PaO2/FiO2 ratio <250 mmHg
-Requirement for mechanical ventilation
-Chest radiograph showing bilateral involvement or involvement of multiple lobes. In addition, an increase in the size of the opacity by 50% or greater within 48 h of admission
-Shock (SBP < 90mmHg or DBP < 60mmHg)
-Requirement for vasopressors for more than 4 h
-Urine output lower than 20 ml/hr, or total urine output lower than 80 ml in 4 h, unless another explanation is available, or acute renal failure requiring dialysis

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Table II Clinical Characteristics of Patients

Parameter	Non-Severe	Severe
Sex (male/female)	30/28	21/11
Co-morbidity present	36/58(62)	23/32(71.88)
Type of co-morbidity		
DM	9(20)	4(11.43)
Neoplastic	5(11.11)	3(8.57)
Neurologic	1(2.22)	5(14.28)
CHF	7(15.55)	5(14.28)
Immunosuppressive		2(5.71)
Renal insufficiency	1(2.22))	2(5.71)
COPD	8(17.78)	10(28.57)
HPN or HCVD	9(20)	3(8.57)
Asthma	5(11.11)	1(2.86)
RR > 30/min	4/58(6.90)	16/32(50)
PCO_2 > 44mmHg		6/32(18.75)
Systolic blood pressure < 90mmHg	2/58(3.45)	7/32(21.88)
Diastolic blood pressure < 60mmHg	1/58(1.72)	7/32(21.88)
Heart rate > 130 beats/min	1/58(1.72)	7/32(21.88)
Bilateral involvement	1/57(1.75)	14/32(43.75)
Multi-lobar involvement	9/58(15.51)	12/32(37.5)
PaO_2/FiO_2 < 250mmHg		19/32(59.38)
Pleural Effusion	10/58(17.24)	2/32(6.25)
Renal Failure	5/58(8.62)	9/32(28.12)
Requirement for mechanical Ventilation	1/58(1.72)	12/32(37.5)
Alcoholic	11/57(19.30)	1/31(3.22)
Smoker	27/57(46.55)	18/31(58.06)
Confusion		10/32(31.25)
Signs and Symptoms		
Fever	41(27.52)	23(25.84)
Cough	55(36.91)	31(34.83)
Dyspnea	25(16.78)	21(23.60)
Chest pain	13(8.72)	5(5.62)
Headache	5(3.36)	1(1.12)
Chills	2(1.34)	2(2.25)
Anorexia	8(5.37)	6(6.74)

Table III Operative indices of Severity criteria for Severe CAP

Criteria	Sensitivity	Specificity	PPV	NPV
RR > 30/min	16/32 (50)	54/58 (93.10)	16/20 (80)	54/70 (77.14)
PaO_2/FiO_2 < 250	19/32 (50.38)	56/58 (96.55)	19/21 (90.48)	56/69 (81.16)
Bilateral involvement	14/32 (43.75)	49/58 (84.48)	14/23 (60.87)	49/67 (73.13)
Multilobar involvement	12/32 (37.5)	48.58 (82.76)	12/22 (54.54)	48/68 (70.59)
SBP < 90 mmHg	7/32 (21.88)	57/58 (98.27)	7/8 (87.5)	57/82 (69.51)
DBP < 60 mmHg	7/32 (21.88)	57/58 (98.27)	7/8 (87.5)	57/82 (69.51)
Requirement for mechanical ventilation	12/32 (37.5)	57/58 (98.27)	12/13 (92.30)	57/77 (74.02)
Renal Failure	9/32 (28.12)	58/58 (100)	9/9 (100)	58/81 (72)

Table IV Prognostic implication of severity criteria for CAP as defined by ATS

Criteria	RR	95% CI	p value	PPV (%)
RR > 30/min	1.67	0.382-10.81	0.414	31
PaO_2/FiO_2 < 250	4.79	0.748-66.0	0.061	37
Bilateral involvement	1.29	0.28-7.0	0.681	29
Multilobar involvement	1.00	0.191-5.22	1.000	25
SBP < 90 mmHg	10.71	5.31-897-85	0.000	86
DBP < 60 mmHg	10.71	5.31-897.85	0.000	86
Requirement for mechanical ventilation	Too large		0.000	67
Renal Failure	Too large		0.000	80

any of the single criteria, as well as of the definition of severe pneumonia provided by the guidelines, have not been validated in an individual hospital setting.

This study tried to assess the patients with severe CAP admitted at ICU based on ATS criteria, also, the predictive potential of each criteria.

Methods

Patients 16 years old and above admitted at Chinese General Hospital with pneumonia between May 1999 and October 1999 were prospectively studied. All patients who had symptoms suggestive of lower respiratory tract infection, or a new infiltrate on chest radiograph at the time of hospital admission were included in the study, while patients that were discharged less than 10 days before the onset of symptoms of pneumonia, or obstructive pneumonia were excluded in the study. Patients were classified as non-severe and severe community- acquired pneumonia based on the ATS criteria.

Data collection On admission the following parameters were recorded: age, sex, clinical symptoms, co-morbidity/type of co-morbidity, respiratory rate, heart rate, arterial systolic and diastolic blood pressure, PaO_2/FiO_2, chest radiograph findings, smoking and alcohol habits.

Microbial etiology was also retrieved during hospitalization.

Table V Performance of additional severity criteria significantly related to mortality but not included in the ATS criteria

Parameter	Sensitivity	Specificity	PPV	NPV
Dyspnea	5/8 (63)	8/24 (33)	5/21 (24)	8/11 (73)
Confusion	4/8 (50)	18/24 (75)	4/10 (40)	18/22 (82)
PCO_2 > 44	0/8	18/24 (75)	0/6	18/26 (69)
Pleural effusion	0/8	22/24 (92)	0/2	22/30 (73)
HR > 130/min	4/8	21/24 (88)	4/7 (57)	21/25 (84)

Assessment of ATS criteria The ATS classified CAP into non-severe and severe CAP. Any patients with one or more of the following findings should be considered to have severe disease: Three parameters reflecting respiratory failure (RR > 30/min at admission, PaO_2/FiO_2 < 250 mmHg, requirement of mechanical ventilation); Radiographic parameters (bilateral involvement or multi-lobar involvement, increase in size of infiltrates by > 50% at 48h); and four criteria reflecting circulatory compromise (SBP < 90 mmHg, DBP < 60 mmHg, requirement of vasopressors for > 4h, and total urine output < 80ml in 4h or acute renal failure requiring hemodialysis). In the presence of at least one of the criterion, admission to the ICU was strongly recommended.

Some of the criteria were not exactly defined with regards to the time during clinical course at which they should be applied (eg., PaO_2/FiO_2 < 250 mmHg, chest radiograph showing bilateral or multi-lobar involvement, SBP < 90 mmHg, DBP < 60 mmHg).

The severity criteria were tested for their ability to correctly classify severe pneumonia. The following operative indices of each criterion were assessed: (1) Sensitivity (ratio of predicted severe to truly non-severe cases); (2) Specificity (ratio of predicted non-severe to truly non-severe cases); (3) Positive Predictive Value (ratio of predicted severe cases to number of cases meeting the criterion); (4) Negative Predicted Value (ratio of predicted non-severe cases to number of cases not meeting the criterion). The prognostic implications of each severity criterion were assessed by *chi-square test*.

Results

Patient Characteristics. A total of 90 patients were admitted with community-acquired pneumonia, with 58 patients as non-severe pneumonia (64%) and 32 patients as severe pneumonia (36%) based on ATS criteria. The main baseline clinical characteristics are compared in *Table II*.

Twenty-three of 32 patients with severe pneumonia admitted at the ICU within the first 24h on admission, while four patients within 48h, two patients within 32h, two patients within fourth hospital day and two patients within the sixth hospital day.

Mortality was seven out of 80 (8%) patients admitted with CAP, and these patients all have severe CAP (22%).

Microbial etiology The microbial etiology could be determined in 22 of the 90 patients (27%). Overall, 34 pathogens were isolated by sputum examination. *Streptococcus pneumoniae* constituted 13 of the 34 pathogens (38%), and was the most frequent pathogen. Other pathogens detected were: *Pseudomonas aeruginosa* in seven (20%); *Klebsiella spp*. in four (11%); *Moraxella catarrhalis* in two (6%); *Acinetobacter* in two (6%); *E. coli* in two (6%); *Staphylococcus aureus* in two (6%); and *Candida albicans* in one (3%).

The most frequent pathogen isolated from patients with severe CAP was *P. aeruginosa* being seen in five patients (45%).

Assessment of ATS guideline severity criteria for CAP Parameters reflecting arterial hypoxemia (respiratory rate > 30/min and PaO_2/FiO_2 at admission) had a specificity of 93% and 96% respectively, but a low sensitivity 50% and 59%, respectively. The requirement of mechanical ventilation was 98% specific but only 37% sensitive. The radiographic criteria had a high specificity with 84% and 82% respectively, but the positive predictive values are low (60% and 54%, respectively). The systolic blood pressure < 90mmHg and diastolic blood pressure < 60mmHg were highly specific (98%) but at the cost of a very low sensitivity (21%). Renal failure had a specificity of 100% and a sensitivity of 28%. (*Table III*)

All severity criteria, except the radiographic criteria and RR > 30/min., were significantly associated with death. The prognostic implications of each criterion are listed in *Table IV*.

Discussion

The prospective assessment of the criteria for severe CAP proposed by the ATS revealed that both criteria reflecting arterial hypoxemia, namely, RR and PaO_2/FiO_2 have a high specificity but are weakly associated with mortality from severe pneumonia and are

insensitive. This may be due to the high incidence of pulmonary co-morbid illnesses, as well as those of cardiac nature. The initial blood pressure was highly correlated with the severity at the given cutoffs but had a low incidence which accounts for its very low sensitivity. The criteria of requirement for mechanical ventilation and renal failure closely reflected severity of pneumonia and also had high predictive values for severity. However because of its limited incidence the sensitivity remained low. The radiographic criteria had a high specificity but still remained insensitive and had a low positive predictive value; also, both are weakly associated with death. This is due to fact that the correlation of severe pneumonia with the extension of infiltrates visible on chest radiograph was only moderate.

Some parameters in the ATS guidelines for severe CAP were not properly defined like multi-lobar involvement, also with regards to the time during clinical course at which they should be applied. In addition, urine output is usually not exactly assessed in patients with non-severe pneumonia. This may have been brought about by the low incidence of some of the criteria giving the low sensitivity values.

Although there are a limited number of subjects, the ATS guidelines for severe community-acquired pneumonia showed that they are highly specific but poorly sensitive and the application of these parameters must be exactly defined.

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The Use of Antibiotic Prophylaxis in the Prevention of Ventilator Associated Pneumonia

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BACKGROUND: Ventilator associated pneumonia is a serious and often fatal infection that appears preventable, at least in some patients. Prevention of Ventilator associated pneumonia is based on eliminating the underlying pathogenic mechanism which may involve contamination of the respiratory/gastrointestinal tract by pathogens and aspiration of infected secretions into the terminal areas of the respiratory tract.

OBJECTIVE: To determine the role of using antibiotic prophylaxis in the prevention of ventilator associated pneumonia by comparing the rate of infection among patients given with and without antibiotic prophylaxis.

MATERIALS AND METHODS: All newly intubated patients were enrolled in the study except those with a) signs and symptoms of pneumonia b) history of antibiotic intake for the last 3 days c) who developed pneumonia less than 48 hours trom the day of admission d) on Sucralfate or Antacid medications e) who died without developing pneumonia in less than 5 days post intubation period. Patients were selected randomly and half of the populations received antibiotic prophylaxis consisting of single doses of Ceftazidime and Netilmycin. Repeat parameters for the diagnosis of pneumonia were requested among patients who developed fever within the 5 days post-intubation period.

RESULTS: Of the 64 patients enrolled, 57 had clinical data evaluated. 8 patients developed nosocomial pneumonia among those who did not receive antibiotic prophylaxis while 7 patients developed nosocomial pneumonia among those who received the antibiotic prophylaxis.

CONCLUSION: Upon comparing the two groups of patients who received and who did not receive antibiotic prophylaxis, the study showed that the use of antibiotic prophylaxis has no added benefit in the prevention of ventilator associated pneumonia. *Phil. Journal of Chest Diseases. Vol.12 No. 2 pp: 94 - 96*

Keywords: pneumonia, mechanical ventilator, antibiotics

Introduction

Nosocomial infections are acquired during or as a result of hospitalization. Fever after 48 hours in the hospital or within 72 hours after discharge is considered hospital acquired infection. Direct contact with contaminated hands of health care workers is the most frequent mode of acquisition. Other modes include inhalation, either thru droplet nuclei from other patients or fungal spores from environmental sources, parenteral means, or device or instrumentation-related.

The second most common nosocomial infection ranking after urinary tract infections is nosocomial pneumonia which strikes as many as 40% of all critically ill or immunocompromised patients. It is by far the most deadly with fatality rates ranging from 13%-55%.

Pneumonia is also much more costly to fight than urinary tract infection. It prolongs the average hospital stay by 4-9 days and results in additional hospital charges of about $1.3 billion annually in America.

Patients who are in mechanical ventilation are especially at risk. In fact, intubated patients are 20 times more likely to get pneumonia than non-intubated patients. That's largely because an artificial airway impairs the gag and cough reflexes that help keep organisms out of the lower respiratory tract. It also prevents the upper respiratory system from heating and humidifying inspired air, which is necessary to enhance mucociliary clearance.

Early onset ventilator associated pneumonia occurs within 72 hours of initiation of intubation, is usually due to aspiration during that procedure, and is most often produced by antibiotic-sensitive organisms such as *Streptococcus pneumoniae* and *Haemophilus influenzae*. Late onset ventilator associated pneumonia is seen 72

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hours post intubation, and is frequently due to antibiotic-resistant organisms, such as oxacillin resistant *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Acinetobacter* and *Enterobacter* species.

Prevention of ventilator associated pneumonia is based on eliminating or reducing the underlying pathogenic mechanisms, which may involve: 1) contamination of the respiratory/gastrointestinal tract by pathogens and 2) aspiration of infected secretions into the terminal areas of the respiratory tract. Measures directed at reducing bacterial colonization in these locations and or diminishing aspiration of organisms are the mainstay of prophylaxis.

The following should be considered in the choice for antimicrobial prophylaxis: The prophylactic program should be directed against the specific likely pathogen. The regimen should be simple to improve compliance such as single dose in lieu of multiple doses whenever possible. The recommended drug should be cost effective. Antibiotics intended for therapy should not be used for prophylaxis

This study was therefore undertaken to determine the role of using antibiotic prophylaxis in ventilator associated pneumonia. It will also compare the rate of infection in those with and those without antibiotic prophylaxis among ventilator assisted patients.

Materials and Methods

The study was conducted among all newly intubated patients at the Veterans Memorial Medical Center, from December 12, 2000 -December 31, 2001.

Exclusion Criteria: The following were not included in the study: all patients with signs and symptoms of pneumonia at the time of intubation; all patients with a history of intake of any antibiotic for the last 3 days up to the time of intubation; all patients who developed pneumonia less than 48 hours from the day of admission; all patients on sucralfate or antacids; all patients who died without developing pneumonia in less than 5 days post intubation period.

Chest x-ray and CBC were requested on the day of intubation.

Patients were selected randomly and given ceftazidime 2 grams via continuous infusion for the first 24 hours and netilmicin 350 mg IV push on the day of intubation only. (In anuric patients or patients with creatinine clearance of < 10 ml/minute, ceftazidime was adjusted to 500 mg via continuous infusion while no dose adjustment done on netilmicin).

Daily follow-up of patients was done until the 5th post intubation period.

Repeat chest x-ray and CBC were requested among patients who developed fever (temperature > 38°C) within 5 days of post intubation period.

Gram stain, culture and sensitivity testing of endotracheal aspirate of patients who developed pneumonia were also done.

The following data were recorded and tabulated: Number of patients who received antibiotic prophylaxis and did not develop pneumonia within the first 5 days of post intubation; Number of patients who received antibiotic prophylaxis but developed pneumonia within the first 5 days of post intubation; Number of patients who did not receive antibiotic prophylaxis and did not develop pneumonia within the first 5 days of post intubation; Number of patients who did not receive antibiotic prophylaxis but developed pneumonia within the first 5 days of post intubation.

The demographic data of our study population was described as to the patient's age and sex.

Study Design: Prospective

Statistical Analysis: Chi Square Test Analysis was used to evaluate the significance of using antibiotic prophylaxis in the prevention of ventilator associated pneumonia. Level of confidence used was $p < 0.05$.

Results

There were 64 newly intubated patients enrolled in the study. However, 7 out of these 60 patients were excluded due to presence of signs and symptoms of pneumonia on the time of intubation (4 patients) and death within the 5 days post intubation period (3 patients).

Among the 57 patients who were included in the study, there were 33 males (58%) and 24 females (42%) with a mean age of 71 years old. Of these 57 patients, 30 (53%) did not receive prophylactic antibiotics while 27 (47%) received prophylactic antibiotics.

Of these 30 patients who did not receive antibiotic prophylaxis, 8 patients developed nosocomial pneumonia which showed the following isolates on endotracheal aspirate: 5 *Enterobacter aerogenes*, 1 *Pseudomonas aeruginosa*, 1 *Streptococcus pneumoniae* and 1 no growth while among the 27 patients who received antibiotic prophylaxis, 7 patients developed nosocomial pneumonia within the 5 days post

intubation period. Isolates were as follows: 4 *Enterobacter aerogenes*, 2 *Pseudomonas aeruginosa* and 1 no growth.

Discussion

It is well known that nosocomial pneumonia is an important cause of morbidity, mortality and health care related cost among hospitalized patients. It is identified 4 to 7 times per 1000 hospitalizations and ventilator associated pneumonia occurs at a rate of 15 cases per 1000 ventilator days. Ventilator associated pneumonia is a serious and often fatal infection that appears preventable, at least in some patients. However, the exact role of infection versus the impact of debilitating underlying disease in contributing to the high mortality of ventilator associated pneumonia remains unanswered, because thus far, studies have shown conflicting results.

In this study, we investigated the role of antibiotic prophylaxis as other option modality in the prevention of ventilator associated pneumonia. There were 57 patients included in the study. Of the 30 patients who did not receive antibiotic prophylaxis, 8 of them developed nosocomial pneumonia, while 7 of the remaining 27 patients who received antibiotic prophylaxis developed nosocomial pneumonia. Chi- Square Test Analysis was used to compare the two groups of patients with regards to the development of pneumonia and showed a *p-value* of 0.812 which is not statistically significant. Though not statistically significant, you would notice that isolated organisms among patients who received antibiotic prophylaxis showed no growth of early onset ventilator associated pneumonia organisms as compared to those who did not receive antibiotic prophylaxis which has one isolated *Streptococcus pneumoniae* organism.

Conclusion

Upon comparing the two groups of patients who received and who did not receive antibiotic prophylaxis, the study showed that the use of antibiotic prophylaxis has no added benefit in the prevention of ventilator associated pneumonia.

Table I. Sex Distribution of Patients

Sex	Frequency	Percent	Cumulative %
Male	33	57.9%	57.9%
Female	24	42.1%	100.0%
Total	57	100.0%	

Table II. Age Distribution

Age Range	Frequency	Percent	Cumulative Percentage
41-50	3	5.4	5.6
51-60	3	5.4	10.8
61-70	20	36.4	47.2
71-80	28	50.9	98.1
81-90	1	1.8	100
Total	55		

Table III. Single Table Analysis

Prophylactic Antibiotics	Nosocomial Pneumonia		Total
	Positive	Negative	
With	8	22	30
Without	7	20	27
Total	15	43	57

p = 0.812

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Clinical Practice Guidelines on Community-Acquired Pneumonia: Effects on Clinical Outcome

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Background: Clinical practice guidelines (CPG's) are recommendations based on evidence derived from a critical review of the literature and opinion of a group of experts designed to minimize practice variations and irrationality of management decisions. Its value was clinically tested to evaluate its effect on clinical outcomes in the management of community-acquired pneumonia among immunocompetent adults admitted at Metropolitan Hospital.
Study Design: Chart-based Retrospective Study
Setting: Metropolitan Hospital, a tertiary hospital in Manila, Philippines
Methods: All adult patients admitted with a diagnosis of community¬ acquired pneumonia from January to December 2000 were reviewed. Demographic, clinical and laboratory variables, management schemes and length of hospital stay were recorded. Statistical analysis was performed using SPSS version 10 and Statistica version 5.0. The significance of the difference between 2 groups was tested using the test of 2 proportions.
Results: 343 patients were included in the review, 23 were excluded. There was a higher (88%) compliance to the guideline noted among Internists compared to non-Internists (52.4%). But the over-all compliance rate is 71.8%. The higher percentage (79.2%) of patients having a shorter hospital stay (<10 days), the lesser percentage (20.8%) of patients staying >10 days in the hospital and the lower mortality rate (6.9%) among those cases that conformed (compliant) to the CPG was not statistically significant when compared to those that did not conform to the CPG (non-compliant).
Conclusion: Compliance to CPG did not significantly affect clinical outcomes in the management of community-acquired pneumonia. *Phil Journal of Chest Diseases. Vol. 12 No. 2 pp: 97 - 100*

Keywords: community-acquired pneumonia, treatment guidelines

Introduction

The field of Medicine is constantly changing with proliferation of newer antibiotics, diagnostic technology, and therapeutic modalities that exert much pressure on the practicing physician to keep up with new knowledge. The demands of clinical practice leave the majority of health professionals little time to appraise these developments. Consequently, patients are exposed to wide variations in clinical care even for similar conditions with great potential for irrational management. The utilization of clinical practice guidelines (CPG's) is one way of addressing these problems.

The Philippine Society for Microbiology and Infectious Diseases (PSMID) in collaboration with various medical specialty societies concerned with care of patients with community-acquired pneumonia, such as the Philippine College of Chest Physicians, American College of Chest Physicians-Philippine Chapter, Philippine Academy of Family Physicians, Department of Health, Philippine College of Radiology and Philippine College of Emergency Medicine and Acute Care, came up with clinical practice guidelines through the Philippine Practice Guidelines Group on Infectious Diseases to provide the clinician with practical approaches in the resolution of important issues on the diagnosis, management and prevention of community-acquired pneumonia in adult patients.

This paper studied the utilization of the above guidelines and its effects on clinical outcome, for guidelines to be of value, they need to be seen to change practice and change outcomes.

We wanted to determine if compliance to CPG led to better treatment outcomes among patients diagnosed to have community-acquired pneumonia (CAP). We also wanted to describe the socio-demographic and clinical

[1] Metropolitan Hospital

Table I Compliance to guidelines according to specialization

Specialization	Compliance		TOTAL
	Compliant	Non-compliant	
Internists	154	21	175
Non-internists	76	69	145
Total	230	90	320

Table II Distribution of patients according to certain parameters

Parameter	N (%)
Admission	
ER	254 (79.4)
Direct to room	66 (20.6)
Sex	
Male	176 (55)
Female	144 (45)
Attending Physician	
Internist	175 (54.6)
Non-internist	145 (45.4)
Co-morbid Condition	
Diabetes mellitus	107 (33.4)
Hypertension	94 (29.4)
Cerebrovascular disease	30 (9.4)
Cancer	27 (8.4)
Coronary artery disease	22 (6.9)
Renal	8 (3.1)
Diagnosis	
CAP I	61 (19.1)
CAP II	47 (14.7)
CAP III	179 (55.9)
CAP IV	33 (10.3)
Laboratory Tests	
CBC	320 (100)
Chest xray	320 (100)
Blood culture	170 (53)
Sputum culture	166 (51.9)
ABG	144 (45)

profile of adult patients admitted to Metropolitan Hospital due to CAP from January to December 2000.

Materials and Methods

All adult patients admitted at Metropolitan Hospital with a diagnosis of community-acquired pneumonia from January to December 2000 were reviewed. The criteria for inclusion were that the clinical history, physical examination findings and chest radiograph were consistent with pneumonia and that the patient chart was available for review. Patients with DNR (Do Not Resuscitate) order and immunocompromised patients (leucopenia, with absolute neutrophil count < 500) were excluded.

Demographic, clinical and laboratory variables, management schemes and length of hospital stay were recorded.

The outcomes were measured in terms of death and discharged improved. Statistical analysis was performed using software *SPSS version 10* and *Statistica version 5.0* and the significance of the difference between two groups was tested using the test of two proportions. A p value of < 0.05 was considered significant.

Results

Three hundred forty three patients were included in the review and 23 patients were excluded. Of these 254 patients (79.4%) were admitted at the Emergency Department, 175 patients (54.6%) were attended by Internists while 145 patients (45.4%) were attended by other specialty physicians/general practitioners (non-Internists). Two hundred thirty admissions (71.8%) conformed to the guidelines. Among the Internists group, 154 (88%) conformed to the guidelines while 76 (52.4%) conformed to the guidelines among the non-Internists group (*Table I*).

The mean age was 63.4 $\pm$ 19.6 yrs. One hundred seventy six patients (55%) were male (*Table II*).

The co-morbidities included diabetes mellitus in 107 patients (33.4%), hypertension in 94 patients (29.4%), CVA in 30 patients (9.4%), cancer in 27 patients (8.4%), CAD in 22 patients (6.9%) and renal disease in eight patients (3.13%) (*Table II*).

One hundred seventy nine patients (55.9%) were categorized under community-acquired pneumonia moderate risk (CAP III). The rest, 61 patients (19.1 %) under minimal risk (CAP I); 47 patients (14.7%) under low risk (CAP II); and 33 patients (10.3%) under high risk (CAP IV).

Complete Blood Count and Chest Radiography were obtained at the time of admission in all 320 patients. Blood culture (53%), Sputum culture (51.9%) and arterial blood gases (ABG) (45%) were done but mostly among moderate and high risk pneumonia.

Table III Outcomes according to compliance

Outcomes	Compliant	Non compliant	p Value
Hospital Stay			
< 10 days	182 (79.2)	63 (70)	0.1467
> 10 days	48 (20.8)	27 (30)	0.3742
Mortality			
Death	16 (6.9)	11 (12)	0.6527
Home, improved	214 (93.1)	79 (88)	0.1708

The choice of antibiotics was second-generation (42.5%) and third-generation (28.1%) cephalosporins for moderate and high-risk pneumonia and first-generation cephalosporins (23.8%) for low and minimal risk pneumonia.

The length of hospital stay was subdivided into less than 10 days and more than 10 days. (*Table III*) This cut-off number was based on the guideline treatment recommendation of 7-10 days for typical pneumonia. For those that conformed to guideline, 182 patients (79.2%) stayed in the hospital for less than 10 days and 48 patients (20.8%) stayed more than 10 days. For those that did not conform to the guideline, 63 patients (70%) stayed less than 10 days while 27 patients (30%) stayed more than 10 days. The mean length of hospital stay was 6.5 $\pm$ 3.6 days. Among the compliant group 214 patients (93.1%) were successfully discharged improved and 79 patients (88%) in the non-compliant group.

There were 27 deaths (11.7%) in the study, 16 (59.25%) from the compliant group and 11 (40.75%) from the non-compliant group.

Discussion

Community-acquired pneumonia is a common disease with a large economic burden. In this institution alone, it accounts for 5% of admissions and ranks first among the top 10 diseases with most number of admissions for the year 2000.[1] It is also the fourth leading cause of morbidity and the third leading cause of mortality in Filipinos based on the 1994 Philippine Health Statistics.[2]

The constant advancements in the field of medicine exert pressure on the practicing physician to keep up with new knowledge but leave little time to critically appraise such developments. Consequently, patients are exposed to wide variations in clinical care even for similar conditions and with great potential for irrational management that can have a substantial impact both in health and economic terms.

One way to address these problems is through the utilization of clinical practice guidelines (CPG). However, for guidelines to be of value, they need to be seen to change practice and change outcomes.[3] It has been argued that CPGs must be tested clinically to evaluate their effect on outcomes if they have been designed to improve patient care.[4]

In this study, 71.8% of cases conformed to the recommendation of the CPG on CAP showing a slightly lower compliance rate as compared to the retrospective/prospective study by Marras and Chan in Toronto, Canada that showed an adherence rate of 80% in the retrospective group.[5] The compliance rate between the Internists group, however, was higher than the non-Internist group (88% and 52.4%, respectively).

The guideline requires chest radiograph to confirm diagnosis of pneumonia. Although prediction rule may be utilized to identify patients with pneumonia in situations where a chest xray may not be available, all subjects (320) in the study had their chest xray taken.

The guideline highly recommends blood cultures among patients with severe disease. Although sensitivity is low, a positive culture is specific and is considered as the gold standard in the etiologic diagnosis of pneumonia. In this study, 51.9% had blood cultures done.

The guideline does not recommend routine use of sputum culture. In this study, 51.9% had sputum culture done but mostly among moderate and high risk group pneumonia as recommended by the guideline.

For the observed outcomes (length of hospital stay and mortality), there was higher percentage (79.2%) of shorter hospital stay (<10 days) among the compliant group compared with the non-compliant group (70%). However, this was not statistically significant. ($p=0.1467$). The lesser number of patients (20.8%) staying longer than 10 days in the hospital among the compliant group was not also statistically significant ($p=0.3742$) when compared to that of the non-compliant group (30%). Finally, comparing the mortality rate between the compliant and non-compliant group (6.9% and 12% respectively) was not statistically significant ($p=0.6527$) as well.

In this study, compliance to clinical practice guidelines did not significantly affect clinical outcomes of community-acquired pneumonia. However, even if adherence did not result in superior clinical outcomes, guidelines may still be valuable as guidelines present a summary of available evidence and the opinion of a group of experts thus provide pragmatic direction in the management of a specific condition. Guidelines may also serve to contain costs and decrease physician error and practice variability.

This study has several limitations. First, its retrospective design cannot eliminate the possibility of error of commission or omission in recording clinical variables Secondly, this study failed to calculate co-morbidity index and APACHE II (acute physiology and chronic health evaluation) severity of illness score, which are also important determinants of clinical outcomes. Therefore, a prospective, randomized controlled study is highly recommended.

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Management of Community-Acquired Pneumonia in a Tertiary Hospital: Impact of the 1999 Philippine Clinical Practice Guidelines

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BACKGROUND OF THE STUDY Studies have documented great geographic variability in physicians' management and hospital admission decision for adult Community-Acquired Pneumonia (CAP), suggesting that criteria physicians use for hospitalization are inconsistent. The 1999 Philippine Clinical Practice Guidelines was formulated to provide clinicians with rational and practical approaches for the diagnosis, empiric management, and prevention of CAP in immunocompetent adults.

OBJECTIVES To determine the impact of the Philippine Clinical Practice Guidelines on the management scheme of Community-Acquired Pneumonia at Manila Doctors Hospital. Specifically, to determine the percentage of admitted patients who satisfied the criteria for admission set by the Philippine Practice Guidelines Group in Infectious Diseases (PPGG-ID) guidelines and compare it with those who did not fulfill such conditions. It intended to determine also the percentage of patients admitted in the ward and with its subgroup of patients with indications for ICU admission. Finally, to compare the medical outcomes (in terms of improvement of clinical symptoms, length of hospital stay, and survival) for patients whose antimicrobial therapy was either consistent or inconsistent with the PPGG-ID guidelines.

METHODOLOGY This is a prospective cohort study of total 190 patients aged 18 yrs and above, admitted at MDH from April 2002 to Sept 15, 2002 with an admitting diagnosis of Community-Acquired Pneumonia (CAP) who were then followed up until discharge. Demographic and clinical data included were age, sex, diagnostic work-ups used, initial therapeutic interventions, presence of co-morbid illnesses, and patient outcomes in terms of improvement of clinical symptoms, duration of hospital stay, and survival. Patients were divided into two major groups based on compliance or non-compliance with the admission criteria set by PPGG-ID, then subdivided into four subgroups coinciding with the four risk categories of the guidelines, with their corresponding initial therapy given. Final outcome measures were determined and compared using chi-square test where p value < 0.05 was considered significant.

RESULTS Majority of patients admitted (75.3%) were found to be eligible for hospitalization. Out of this group, only eleven (7.7%) were initially admitted at ICU and the remainder (92.3%) were admitted at the wards. A subset of 27 patients (20.5%) who were admitted at the wards had the indications for ICU admission if the criteria set by the Guidelines were followed. Comparison of the two groups showed a significant correlation with positive outcome measures for patients who received therapy consistent with PPGG-ID guidelines. For each category, patients belonging to Moderate and High-risk groups who received therapy consistent with the local recommendation showed a significantly earlier clinical response.

CONCLUSION Conformity with the PPGG-ID guidelines in the initial management of community-acquired pneumonia was shown to be evident among physicians at the Manila Doctors Hospital. Subsequently, this adherence to the local recommendation was significantly correlated with overall positive outcome measures, in addition to lowering the rate of hospital admission and subsequently, lower costs of therapy.

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Introduction

Community-Acquired Pneumonia (CAP) is a serious illness with a significant impact on individual patients and society as a whole. It remains an important cause of morbidity and mortality for both ambulatory and hospitalized adults despite the appropriate use of more advanced and improved diagnostic techniques, newer antimicrobial agents, and the advent of effective vaccines in selected cases. It ranks as the country's fourth leading cause of morbidity and third leading cause of mortality, according to the 1994 Philippine Health Statistics.[1] In the United States, pneumonia is the sixth leading cause of death with the mortality rates generally reported at 20-40%.[2]

[1] Manila Doctors Hospital

Management decisions in patients with pneumonia entail a great deal of variation in terms of physician's clinical judgment. Despite the advent of numerous guidelines and recommendations, a lot of factors influence physicians' approach to management: foremost are economics, then patient's compliance to prescribed therapy; personal experiences, some pharmaceutical company influences, and other host/ social factors.[3]

The initial site-of-care is perhaps the single most important clinical decision made by physicians during the entire course of illness for patients with community-acquired pneumonia. It has a direct bearing on the intensity of laboratory testing, microbiologic evaluation, antibiotic therapy, costs of treatment,[8] and potential exposure to possible nosocomial complications.

Previous studies[4,5] have documented great geographic variability in hospital admission rates for adult community-acquired pneumonia, suggesting that physician's criteria used for hospitalization are inconsistent. Worse, it may reflect uncertainty among physicians in assessing the severity of the illness and the perceived benefits of care.[11]

Therapeutic decisions are greatly simplified if the infecting pathogen is known. Unfortunately, the medical history, physical examination, chest radiograph patterns and even the initial Gram stain may not be reliable guides in predicting the causative pathogen. Recognition of these limitations resulted in a review of epidemiologic data, which, together with stratification by the presence of risk factors, became the basis for current recommendations for empiric antibiotic therapy.[7] The most publicized CAP guidelines were established by the American Thoracic Society (ATS) in 1993,[8] and more recently in 2001, which divided CAP into four risk categories according to illness severity and common pathogens involved. The Canadian guidelines followed similar categories, but used 65 as the cut-off age for higher risk CAP. In Europe, France published its guidelines for CAP in 1991, followed by Spain, the United Kingdom and Italy in 1992, 1993 and 1995, respectively.[7]

In 1998, the Infectious Disease Society of America (IDSA) published its guidelines for CAP,[15] classifying patients according to different risk categories based on age, the presence of co-morbid illnesses and abnormal or deranged physiologic parameters. Following this, the Philippine Practice Guidelines Group in Infectious Diseases (PPGG-ID) developed its own CAP guidelines[9] which is essentially a modification of the ATS and IDSA guidelines. The therapeutic recommendations of the PPGG-ID guidelines are based on local prevalence and bacterial resistance patterns. The algorithm for risk stratification and the empiric antibiotic therapy for each risk category proposed are designed to simplify the management of CAP. Thus, this local guideline has been followed by Manila Doctors Hospital for almost two years now.

To date, few researches have been made regarding the impact of the ATS guidelines in the management of CAP. Gleason et al[3] studied the cost-effectiveness using the ATS recommendation for treating adult outpatients with CAP. Guglielmo BJ, et al[10] reported that majority of institutions in the United States follow the ATS guidelines in terms of empiric antimicrobial therapy for CAP and further mentioned that regimens not consistent with the guidelines were associated with prolonged hospital stay. Locally, Panaligan, MM et. al[11] studied the impact of ATS guidelines among in-patients at University of the East Ramon Magsaysay Memorial Medical Center (UERMMMC) and showed that majority of physicians did not adhere to the recommendations given by the Society, but showed significant correlation with positive outcome measures for patients who received therapy consistent with the ATS guidelines.

This study was conceived in order to determine the impact of the Philippine Clinical Practice Guidelines on the management scheme of Community-acquired Pneumonia at Manila Doctors Hospital. Specifically, this study aimed to determine the percentage of admitted patients who satisfied the criteria for admission set by the PPGG-ID guidelines and compare it with the percentage of admitted patients who did not fulfill such conditions. It also intended to determine the percentage of patients admitted in the ward and with its subgroup of patients with indications for lCU admission. Finally, this paper aimed to compare the medical outcomes (in terms of improvement of clinical symptoms, length of hospital stay, and survival) for patients whose antimicrobial therapy was either consistent or inconsistent with the PPGG-ID guidelines.

Materials and Methods

A total of 190 patients aged 18 years and above, admitted at the Manila Doctors Hospital from April 2002 to Sept. 15, 2002 with an admitting diagnosis of Community-Acquired Pneumonia (CAP) were enrolled in the study. Each patient was followed up until discharge. On enrollment, clinical and laboratory data were collected.

Demographic and Clinical Data Demographic data included age, gender, and marital status. Clinical data gathered were diagnostic work-ups used, initial therapeutic interventions, presence of co-morbid illnesses, and patient outcomes - in terms of

Table I Clinical characteristics of patients whose admissions are inconsistent with PPGG-ID Guidelines

Parameter		No. (%)
Age	≤ 65 yo	47 (100)
	> 65 yo	0
Sex	Male	14 (29.8)
	Female	33 (70.2)
Co-morbid Illness		20 (42.6)
DM		7 (14.9)
COPD		4 (8.5)
CRF		3 (6.4)
CHF		3 (6.4)
CVD		2 (4.3)
Chronic liver disease		1 (2.1)
NONE		27 (57.4)

Table II. Clinical characteristics of patients whose admissions are consistent with the PPGG-ID guidelines

Parameters		No. (%)
Age	≤ 65 yo	44 (30.8)
	> 65 yo	99 (69.2)
Sex	Male	77 (53.8)
	Female	66 (46.1)
Co-morbid Illness		104 (72.7)
Single		78 (55.2)
Multiple		25 (17.5)
NONE		39 (27.3)
Presence of Signs/Symptoms specified as Risk Factors		
RR > 30		57 (39.9)
HR > 125		12 (8.4)
Hypotension		14 (10)
Altered sensorium		15 (10.5)
Multiple risk factors		39 (27.3)
Laboratory Predictors		
Unfavorable x-ray		30 (21)
PaO2 < 60; PaCO2 > 50		30 (21)
Oliguria		10 (7)
Need for mechanical ventilation		15 (10.5)

improvement of clinical symptoms, duration of hospital stay, and survival.

Exclusion Criteria 1. patients who were admitted primarily because of medical conditions other than pneumonia. 2. patients who later on developed Hospital-Acquired Pneumonia. 3. patients with concomitant active infections (urinary tract infections, active PTB, acute tonsillopharyngitis, sinusitis, etc.) 4. patients who had cardiopulmonary arrest on admission. 5. patients who were allergic to antimicrobials specified as initial therapy by the PPGG-ID guidelines (e.g. beta-lactams, sulfonamides). 6. Immunocompromised patients

Study Design Prospective, Cohort study.

Table III. Bacteriologic studies requested during confinement for pneumonia

Pneumonia type	Sputum GS/CS	Blood CS
Minimal Risk (n=12)	8 (66.7)	0
Low Risk (n=35)	22 (63)	0
Moderate Risk (n=105)	94 (89.5)	0
High Risk (n=38)	38 (100)	38 (100)
Total (n=190)	162 (85.2)	38 (28)
Discharged prior to release of CS report	14 (7.4)	

Data Analysis Data collated were grouped into two major categories: a group of admitted patients not compliant with the PPGG-ID guidelines, and a group of admitted patients complying with the conditions set by the PPGG-ID for admission. Each group was subdivided into two categories such that four subcategories would eventually coincide with the four risk categories of the PPGG-ID guidelines. Furthermore, each of these subcategories were further divided into two small groups based on the initial therapy given - either based on the PPGG-ID recommendation or not. The proportion of patients admitted and treated consistently or inconsistently with the guideline were computed. Final outcome measures including improvement of clinical symptoms, duration of hospital stay and survival for each group were determined and compared using the chi-square test where a p value of <0.05 was considered significant.

Definition of Terms The PPGG-ID developed the Clinical Practice Guidelines to provide clinicians with practical approaches for the diagnosis, management and prevention of Community-Acquired Pneumonia (CAP) in immunocompetent adults.

Four major categories of CAP were defined: 1. MINIMAL RISK CAP (I) - Adult patients with CAP who are <65 years of age with stable vital signs (RR < 30 breaths/min, diastolic BP > 60 mmHg and systolic BP > 90 mmHg, pulse < 125 beats/min, and temperature < 40°C) and NO co-morbid condition. This is associated with low morbidity and mortality rate of < 1 % and is considered suitable for out-patient care. 2. LOW RISK CAP (II) - Patients with stable co-morbid conditions such as controlled DM, neoplastic disease in remission, stable neurologic disease, class I CHF, compensated COPD, chronic liver disease, and renal failure not on dialysis. This is associated with mortality rate of < 5% and may be treated as out-patients if there is a reasonable assurance for follow-up. However, they should be considered for hospitalization in the event that the co-morbid condition is aggravated by or aggravating the

Table IV. Comparison of outcome of patients who received treatment which was either consistent or inconsistent with the PPGG-ID recommendation.

	PPGG-ID	Not PPGG-ID	p value
MINIMAL RISK (N=12)			
Improvement of Symptoms			
≤ 72 hrs	3	6	NS
> 72 hrs	2	1	
Hospital Stay			
≤ 5 days	2	7	NS
> 5 days	2	1	
Adherence (%)	1 (8.3)	11 (91.7)	
LOW RISK (N=35)			
Improvement of Symptoms			
≤ 72 hrs	18	3	0.001
> 72 hrs	8	6	
Hospital Stay			
≤ 5 days	13	5	NS
> 5 days	6	6	
Adherence (%)	11 (31.4)	24 (68.6)	
MODERATE RISK (N=105)			
Improvement of Symptoms			
≤ 72 hrs	46	28	0.02
> 72 hrs	9	22	
Hospital Stay			
≤ 5 days	38	23	0.02
> 5 days	14	30	
Survival			
Yes	50	44	0.04
No	3	8	
Adherence (%)	83 (79)	22 (21)	
HIGH RISK (N=38)			
Improvement of Symptoms			
≤ 72 hrs	21	4	0.001
> 72 hrs	5	8	
Hospital Stay			
≤ 5 days	15	6	0.04
> 5 days	8	9	
Survival			
Yes	30	6	0.001
No	1	1	
Adherence (%)	30 (79)	8 (21)	
OVERALL (N=190)			
Improvement of Symptoms			
≤ 72 hrs	88	41	0.001
> 72 hrs	24	37	
Hospital Stay			
≤ 5 days	70	41	0.001
> 5 days	33	46	
Survival			
Yes	118	54	0.001
No	7	11	
Adherence (%)	125 (65.8)	65 (34.2)	

pneumonia. 3. MODERATE RISK CAP (III) – Patients > 65 years of age regardless of clinical condition OR patients, regardless of age, with anyone of the following physical findings: RR > 30 breaths/min, pulse > 125 beats/min, or temperature < 35°C or > 40°C; those with radiographic findings of bilateral or multi-lobar involvement, progression of lesion to 50% of initial finding within 24 hrs, pleural effusion, abscess; those with suspected aspiration; and those with extra-pulmonary evidence of sepsis. These are associated with complicated outcome and higher mortality rate of = 21%, thus patients need to be hospitalized for parenteral therapy. 4. HIGH RISK CAP (IV) - Patients with impending or frank respiratory failure (i.e., hypoxemia with PaO_2 < 60 mmHg or acute hypercapnea with $PaCO_2$ > 50 mmHg) or hemodynamic alterations and hypoperfusion (i.e., altered mental state, DBP < 60 mmHg or SBP < 90 mmHg, or urine output < 30 cc/hour). These are associated with mortality rate of > 36.5% and warrants admission in the intensive care unit.

Results

Out of the total 190 patients enrolled in the study, 47 (24.7%) did not satisfy the PPGG-ID criteria for admission (Group I) while 143 admitted patients (75.3%) were found to be eligible for hospitalization based on the PPGG-ID guidelines (Group II). Under this second group, only 11 of the 143 patients (7.7%) were admitted in the Intensive Care Unit (ICU). This subgroup fulfills the requirements for ICU admission. Twenty-seven out of the 132 patients (20.5%) who were admitted in the general ward had indications for ICU admission based on criteria set by the PPGG-ID. (*Figure 1*).

Table I shows the clinical characteristics of patients who did not fulfill the conditions for admission set in the PPGG-ID guidelines. All patients belonged to age group < 65 years old, with female to male preponderance ratio of 70% vs. 30%. Twenty-seven of the 47 patients (57.4%) had no co-morbid illnesses. Diabetes Mellitus was the most common co-morbid factor, which was present in almost 15% of cases. These patients were assessed to have only mild infections.

Table II shows the clinical characteristics of patients who satisfied the conditions set by PPGG-ID for admission. Majority of patients (69.2%) were more than 65 years old with the proportion of males being higher than that of females (53.8% vs. 46%). More than half of patients (55.2%) had at least one co-morbid illness. Multiple risk factors presented on admission were seen in 27.3% of cases, with tachypnea as the most common physical finding (39.9%) and hypxemia together with unbfavorable x-ray findings as the most common laboratory abnormalities encountered (21% each).

Table V. Initial antimicrobial choices for treatment of community-acquired pneumonia

Antibiotics	N (%)
Minimal Risk (n=12)	
Beta-lactamase inhibitor (BLI) + macrolide	5 (41.6)
Cefuroxime	3 (25)
Cefuroxime + macrolide	2 (16.6)
Macrolide	2 (16.6)
Low Risk (n=35)	
IV BLI + macrolide	12 (34.3)
IV cefuroxime + macrolide	10 (28.6)
Ciprofloxacin	4 (11.4)
Cefuroxime	3 (8.6)
BLI	2 (5.7)
Ceftazidime	2 (5.7)
Others	2 (5.7)
Moderate Risk (n=105)	
IV BLI + macrolide	40 (38.1)
IV cefuroxime + macrolide	33 (31.4)
Ceftazidime	7 (6.7)
IV Cefuroxime	7 (6.7)
Ceftazidime + macrolide	5 (4.8)
Meropenem	2 (2)
Tazobactam + piperacillin	3 (2.8)
Cefoxitin + macrolide	2 (2)
Others	6 (5.8)
High Risk (n=38)	
Ceftazidime + macrolide	27 (71)
Ceftazidime	2 (5.7)
Cefepime + macrolide	2 (5.7)
IV BLI + macrolide	2 (5.7)
Meropenem	1 (2.7)
Cefepime	1 (2.7)

Table III shows the percentage of bacteriologic studies requested during the study period. Overall, 162 (85.2%) of the total 190 patients had bacteriologic studies (sputum GS and CS). Seven percent of patients were discharged prior to the release of the culture report. Only those patients belonging to the high-risk group had blood cultures requested.

Table IV shows the outcome of patients who received treatment for community-acquired pneumonia that was either consistent or inconsistent with the PPGG-ID Guidelines. In each category (except the minimal risk group) there was statistically significant difference between the result of treatment following the recommendations of PPGG-ID guidelines and the treatment that was inconsistent with it. This table also shows the low percentage of treatment regimens adhering to the PPGG-ID guidelines in minimal (8.3%) and low risk (31.9%) groups, in contrast to high percentage of adherence among moderate (79%) and high risk (79%) groups – which eventually reflected shorter hospital stay and faster resolution of symptoms. Over-all, there was statistically significant difference between guidelines adherence among the two treatment groups which correlated with positive outcome measures.

Table VI. Clinical characteristics of patients who died secondary to pneumonia

Parameters		N (%)
Age	≤ 65 yo	6 (33.3)
	> 65 yo	12 (66.7)
Sex	Male	5 (27.7)
	Female	13 (72.2)
Co-morbid Illness		
Single		6 (33.3)
Multiple		11 (61.1)
NONE		2 (11.1)
Presence of Signs/Symptoms specified as Risk Factors		
RR > 30		10 (55.5)
HR > 125		3 (16.6)
Hypotension		8 (44.4)
Altered sensorium		11 (61.1)
Laboratory Predictors		
Unfavorable x-ray		9 (50)
PaO2 < 60; PaCO2 > 50		9 (50)
Oliguria		2 (11.1)
Need for mechanical ventilation		12 (66.6)
Admission to ICU		3 (16.6)

Table V shows the initial antimicrobial therapy given (by category). Parenteral beta-lactamase inhibitors (Co-Amoxiclav or Ampicillin-Sulbactam) with or without combination with Macrolide were the first choices in Minimal (41.6%), Low Risk (34.28%), and Moderate Risk (35.2%) groups. Ceftazidime in combination with Macrolide accounts for 65.8% of antimicrobial choice for High Risk groups.

Table VI shows the clinical characteristics of patients who died due to pneumonia. Majority of patients (67%) were more than 65 years old, with 61 % having single co-morbid illness each. Altered sensorium and tachypnea, were seen in 61% and 55.5% respectively, and more than half (67%) required mechanical ventilation. Only three patients (16.6%) were admitted at ICU on admission.

Discussion

Studies[8,12] have documented that there is considerable variability in management as well as rates of hospitalization for patients with community-acquired pneumonia, sadly in part, because of physicians' uncertainty in assessing the severity of illness at presentation. Some may rely on their subjective impressions of a patient's clinical appearance in making the initial decision about the site of care.[8] On the other hand, some physicians may tend to overestimate the risk of death in patients with pneumonia, and these

overestimates are associated with the decision to hospitalize patients even at low risk. Worse, patients themselves may request admission based on their own risk-assessment of their illness.

As shown in this study, although different attending physicians and residents at Manila Doctors Hospital have different approaches to this common but serious problem, majority of patients with community-acquired pneumonia were admitted in concordance with the PPGG-ID guidelines. Consequently, adherence to this local recommendation significantly correlated with shorter hospital stay, faster resolution of symptoms, and survival. In effect, this should also lower the rate of hospital admission, and subsequently lower the cost of therapy.

In terms of drugs used, the choice of parenteral beta-lactam/beta-lactamase inhibitors or second-generation cephalosporin as first line agents in our study proved the overestimation of risk by some physicians for patients that can be categorized as low risk (*Table V*), thereby compounding the problem of cost-effectiveness of the therapeutic intervention. Furthermore, although there are low resistance patterns of *Streptococcus pneumoniae* in the Philippines, the possible introduction and spread of resistant strains into the country remains a hazard. New mutant strains may emerge with continued indiscriminate antibiotic use.[7]

Non-adherence to the PPGG-ID guidelines may also impose danger to our admitted patients. In this study, 20.5% of the admitted patients in the general ward, who satisfied the criteria for admission, should have been admitted at ICU implying that these patients should be watched closely and managed aggressively since mortality rate for this category may go as high as 47-76%.[13,14]

However, in our country, it is recognized that this requirement cannot be imposed on all patients due to financial constraints.

Another issue uncovered by this study is the routine use of Sputum Gram's Stain (GS) and culture/sensitivity (CS) as part of bacteriologic studies requested even for Minimal and Low Risk categories (67% and 63% respectively), which is contrary to the PPGG-ID guideline. Since identifiable pathogens are seen in only 40% to 50% of CAP cases and the etiology of mild cases is predictable, sputum GS/CS studies are not routinely recommended for ambulatory patients with minimal to low risk CAP.[1,9] Although of low sensitivity, positive blood culture is specific and still remain as the gold standard in the etiologic diagnosis of pneumonia for moderate to high risk CAP cases. In this study, however, blood culture studies were requested only for patients under High-Risk group.

Over-all, although we have seen treatment success with the use of drugs not recommended by PPGG-ID,[9] we have clearly showed that compliance to the guidelines have significant correlation with positive outcome measures in addition to cost-effectiveness of treatment.

Taking things in stride, the Clinical Practice Guidelines advocate the best treatment options for all patients. However, there should always be some flexibility for certain patients who may have peculiar or special conditions that exclude them from certain guideline categories.[7] After all, under no circumstance will this article supervene the experienced clinical judgment of the treating physician.[9]

Conclusion and Recommendations

In summary, conformity with the guidelines set by the Philippine Practice Guidelines Group in Infectious Diseases in the initial management of community-acquired pneumonia was shown to be evident among physicians at the Manila Doctors Hospital.

Consequently, this adherence to the local recommendation was significantly correlated with overall positive outcome measures, in addition to lowering the rate of hospital admission and subsequently, lower costs of therapy.

A disseminated information campaign is hereby recommended to most, if not all, medical practitioners so that guidelines can be utilized in the cost-effective management of adult community-acquired pneumonia. The input of information from the medical community is, and will continue to be, essential in the further refinement of these guidelines.

A physician's survey could also be relevant to assess their reasons for treating in a hospital or ambulatory setting and how they make the hospitalization decision.

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Etiology of Community-Acquired Pneumonia at Chinese General Hospital and Medical Center

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Community-acquired pneumonia or CAP continues to be a common and serious illness, in spite of the availability of potent new antimicrobials and effective vaccines. Two major guidelines such as the one from Infectious Disease Society of America (IDSA) and the American Thoracic Society (ATS) differ from each other in terms of recommending the etiologies of CAP. This study therefore was conducted to determine the etiology of CAP and determine the adherence of physicians at the Chinese General Hospital to the ATS Guidelines in terms of recommended antibiotics.

One hundred two cases of pneumonia were thus enrolled in the study. Using the 2001 ATS guidelines, we were able to reclassify patients and noted that there were Group 1 patients admitted (9.8%), while, group IIIA and IIIB predominates, 37.25% and 34.31%, respectively. Of the 102 patients, only 74 samples yielded a specific pathogen. *Pseudomonas aeruginosa* (20.27 %) and alpha-hemolytic *Streptococcus* (16.21%) were the predominant pathogens isolated from sputum samples of these patients. In the end, this study demonstrated that not all physicians adhere to the ATS guidelines regarding antimicrobial therapy. *Phil Journal Chest Diseases. Vol. 12 No. 2 pp: 108 -112*

Keywords: community acquired pneumonia, treatment, guidelines

Introduction

Community- acquired pneumonia (CAP) remains a common and serious illness, in spite of the availability of potent new antimicrobials and effective vaccines. In the United States, pneumonia is the sixth leading cause of death, and the number one cause of death from infectious diseases.[1] Early treatment of this disease is associated with an improved outcome however, the responsible pathogen is not defined in as many as 50% of patients, even when extensive diagnostic testing is performed[2-4] and search for an etiologic agent takes time. Accordingly, many guidelines have been proposed to aid physicians in the initial empiric therapy of this infection. Included are those from the Infectious Diseases Society of America (IDSA), those from the local Philippine Society for Microbiology and Infectious Diseases, and those produced in various other countries, including Canada, and countries in Europe. One of the latest guidelines is that from the American Thoracic Society (ATS), released in the year 2001.

The latest ATS guidelines integrate those recommendations that were released in 1993, as well as those from the latest IDSA CAP guidelines and from the recently published Canadian CAP document.

Studies have identified a series of risk factors that increase either the likelihood of death or the risk of a complicated course for community-acquired pneumonia. One approach, developed by the British Thoracic Society (BTS) was aimed at identifying high-risk patients who require admission, as well as those needing ICU care,[5] whereas the Pneumonia Patient Outcomes Research Team (PORT) approach separated patients into those with a high or low risk of death.[6]

Based on the identified risk factors that indicate a complicated course or an increased chance of death, the ATS separate patients into four groups. The pathogens most commonly encountered in each group differ; moreover, there are factors that increase the risk of infection with specific pathogens. Consequently, the recommended medications are adjusted accordingly. These recommendations are not hard and fast rules, but rather serve to help physicians in choosing a rational mode of therapy to cover for the most probable microorganisms that may be encountered, in order to minimize morbidity and death.

The ATS guidelines differ from those of IDSA in that the latter emphasizes that a search for the etiologic

[1] Chinese General Hospital

Table I Patient characteristics

Parameter	N	%
Age (mean 68 yo)		
<65	32	31.37
>65	70	68.62
Sex		
Male	46	45
Female	56	55
Smoking Hx		
Smoker> 4 packs/year	39	38.2
Alcohol intake	6	5.88
Co-morbidities		
COPD/asthma	18	17.65
DM	25	25.49
HPN	39	38.24
Heart disease	13	12.75
Renal disease	5	4.9
Liver disease	3	2.94
CVD	3	2.94
Malignancy	3	2.94

Table II Presenting symptoms

Symptom	N	%
Cough ..	97	95
Expectoration	33	32.35
Fever	60	58.82
Pleuritic chest pain	10	9.8
Dyspnea	61	59.8
Altered mental status	6	5.88

Table III Classification of CAP according to ATS guidelines

	N	%
CAP I	10	9.8
CAP II	2	1.96
CAP IIIA	38	37.25
CAP IIIB	35	34.31
CAP IVA	12	11.7
CAP IVB	5	4.9

agent be made. Other studies have concluded that in non-severe CAP without co-morbidities, there is limited, or even, no value in using sputum gram stains and sputum and blood cultures in the search for an etiology. Nevertheless, IDSA recommends that, as much as possible, the etiology must be determined, in order that epidemiologic data may be gathered, and resistance patterns maybe known.[7]

This study thus aims to determine the common organisms isolated in patients hospitalized in our institution with community-acquired pneumonia, to reclassify the pneumonia according to the latest ATS guidelines and determine the compliance of physicians in our institution to the said guidelines. Although the diagnostic yield could be enhanced by the use of other procedures such as blood culture, serologic tests, bronchial washings, etc., this study is limited to the use of sputum gram-stain and culture only. Microorganisms that are not routinely detected by the latter means thus cannot be measured.

Table IV Pathogens isolated from 74 patients

	n	%
Branhamella catarhalis	10	13.51
Coag. Negative Staph.	6	8.1
Alpha- hemolytic Strep	12	16.21
Klebsiella sp.	4	5.4
Klebsiella pneumoniae	7	9.46
Pseudomonas sp.	4	5.4
P. aeruginosa	15	20.27
Candida	8	10.81
Staph. aureus	2	2.7
Acinetobacter	2	2.7
Brukholderia cepacia	1	1.35
Enterobacter cloacae	1	1.35
E. coli	1	1.35
E. aerogenes	1	1.35

Methodology

Between November 1, 2001 and May 31, 2002, we, prospectively studied all adults > 18 years of age who came to the hospital with a clinical diagnosis of community-acquired pneumonia. All patients fulfilling the criteria of CAP described by Fang et al[8] were eligible for the study. Criteria included (1) > 18 years of age with a putative diagnosis of pneumonia, (2) a new infiltrate observed on chest radiograph (CXR), and (3) acutely presenting clinical findings of either one major criteria (axillary temperature > 37.8^{o}C, cough, or expectoration) or at least two minor criteria (pleuritic chest pain, dyspnea, leukocytosis with WBC count > 12,000/ml, altered mental status or lung consolidation by clinical examination).

Exclusion criteria included patients transferred from another hospital or hospitalized within the last two weeks, lung cancer, post-obstructive pneumonia, or immunocompromise (> 40 mg/d of methylprednisolone or equivalent dose of other steroid; AIDS or HIV positive with a CD4+ count < 200, granulocytopenia < 500/mm^3.

Table V Antimicrobials used in the different groups of CAP

Antibiotic	CAP I	CAP II	CAP III	CAP IIIA	CAP IVA	CAP IVB
Amikacin			3	2	1	1
Ampicillin-sulbactam		1	2	1	1	
Azithromycin	4		11	11	2	
Cefipime			1	1	1	
Cefotaxime	1					
Cefpirome	2		14	9	2	1
Ceftazidime			1		1	3
Ceftriaxone	1		1	3		
Cefuroxime	7		7	7	1	
Clarithromycin				4		
Clindamycin				2	1	2
Ciprofloxacin			1	3	2	
Co-amoxiclav	1		2	2		
Erythromycin					1	
Gatifloxacin		1	2	5	2	
Imipenem			1		2	
Levofloxacin				1		
Meropenem			2		1	
Metronidazole					1	1
Pip- tazobactam			2	8	4	2
Roxithromycin	4	1	8	2	2	
Ticarcillin- clavulanic	1		3			
Vancomycin					1	

On entry into the study, a clinical research form was filled out. Other variables recorded were age, sex, symptoms, criteria for pneumonia, any antimicrobial therapy for any indication, past medical history, alcohol and smoking history. Presenting CXR pattern and physical examination (respiratory rate; heart rate; BP; axillary or rectal temperature; and respiratory signs such as consolidation, rales, reduced breath sounds, rhonchi or evidence of pleuritis or effusion) were recorded.

Table VI Pathogens isolated in the different groups of CAP

	I	II	IIIA	IIIB	IVA	IVB
B. catarrhalis	3	1	4	1	1	
Coag (-) Staph				4	2	
Alpha- hemolytic Strep	1		5	6		
Klebsiella sp.				2	2	
Klebsiella pneumoniae.			5		1	1
Pseudomonas sp.			2	1	1	
P. aeruginosa	1		5	5	2	2
Acinetobacter		1	1			
Candida			7	1		
Brukholderia cepacia				1		
Staph. Aureus				1	1	
Enterobacter cloacae				1		
E. aerogenes					1	
E. coli			1			

Routine test obtained initially included CXR and microbiological evaluation. All of the patients have CBC with differential count, electrolytes, creatinine and blood gas analysis (paO_2, $paCO_2$, pH and oxygen saturation) were requested in most of these patients.

At entry, cases were classified according to the ATS 2001 guidelines and ICU admission and therapy was decided by the residents, subspecialty fellows and attending physicians.

Results

Patient Characteristics. One hundred two cases of pneumonia were enrolled in the study. Two patients were enrolled on two occasions each because of recurrent pneumonia. Admitted patients have a mean age of 68 years and females predominate. Most patients experienced co-morbidities including bronchial asthma, COPD, diabetes mellitus, heart disease, liver disease and a significant number of them have hypertension (*Table I*).

Using the 2001 ATS guidelines, we were able to reclassify patients and noted that there were Group 1 patients admitted (9.8%), while, group IIIA and IIIB predominates, 37.25% and 34.31%, respectively (*Table III*).

Of the 102 patients, only 74 samples yielded a specific pathogen. *Pseudomonas aeruginosa* (20.27 %) and alpha-hemolytic *Streptococcus* (16.21%) were the predominant pathogens isolated from sputum samples of these patients (*Table IV*).

In Group I, predominantly used antimicrobials were the macrolide and first and 2nd generation cephalosporins, however, there are few patients who received 3rd generation and 4th generation cephalosporins, and extended penicillin on this category. As noted, there is a significant use of 4th generation cephalosporins on Group IIIA and IIIB.

As expected, gram positive organisms predominate in all the groups and the gram negative organisms followed in groups IIIA and onwards. Note that Candidial growth is noted in group IIIA and IIIB

Discussion

Pneumonia is increasingly being recognized among older patients and those with co-morbidity. We should remember that age was used as a major discriminating factor among patients to define bacterial etiology. As seen in our study that patients > 65 years old predominates the admission number. As discussed in previous studies, the elderly patient can have infection by atypical pathogens and enteric gram- negatives are common primarily in those with co-morbid illness (particularly underlying COPD), recent antibiotic therapy and in patients residing in nursing homes.[4,9]

One of the most controversial recommendations in the 1993 ATS guidelines for CAP was that a sputum Gram's stain and culture not be performed routinely in all admitted patients.[10] However, some experts, believe that a properly collected and examined Gram's stain of expectorated sputum is helpful for focusing initial empiric therapy in CAP. Studies of the sputum Gram's stain have shown limitations, which include the following: not all patients can produce a sample (either because of an inability to provide adequate sample or because the sample is of poor quality), interpretation is observer dependent, atypical pathogens cannot be seen, the definition of positive varies from study to study and a positive result for pneumococcus is poorly predictive of the ability to recover that organism from a sputum or blood culture.[11] Routine bacterial cultures of sputum often demonstrate pathogenic organisms, but sensitivity and specificity are poor, as seen in our study that significant samples grew fungi not supported by blood cultures, and findings should be correlated with the predominant organism identified on Gram's stain.[11] However, recovery from cultures of organisms that are not usually part of the normal respiratory flora may be meaningful.

Appropriate diagnostic tests for atypical pathogens are not readily available and the incidence of infection with these atypical organisms has been as high as 40-60% of all admitted patients, often as part of a mixed infection.[12-14] These may account for the negative growth in the sputum specimens in some of our patients. There is still controversy about the true incidence of gram-negative infection in patients with CAP, since diagnostic testing that involves sputum culture cannot always distinguish between colonization by these organisms and true infection.

Patients should initially be treated empirically, based on the likely pathogens for each of the four patient groups, although when culture results become available organism specific therapy may be possible for some patients. Adherence to the available guidelines may help us to start appropriate antimicrobials to our patient. It is desirable to give as narrow a spectrum of therapy as possible, avoiding excessively broad antibiotic therapy, if it is not needed. This goal is easily achieved if a specific etiologic diagnosis is made, but it is impossible in at least half of all patients and the results of many diagnostic studies are not immediately available, making relatively broad spectrum empiric therapy a necessity for most patients, initially[15]. For all patients, there is value in using initial empiric therapy based on guidelines. This type of approach not only assures timely therapy, but can also provide coverage for the possibility of mixed bacterial and atypical pathogen infection. Data in both outpatients and inpatients have shown that empiric therapy based on the initial ATS guidelines leads to a better outcome than if non guideline therapy is used.[16-18]

Conclusion

Patients > 65 yrs old dominated our admission for community-acquired pneumonia. *Pseudomonas aeruginosa*, alpha- hemolytic *Streptococcus* and *Branhanmella catarhalis* were the top three pathogen isolated by our institution. However, as noted, gram-positive bacteria were the predominant pathogen isolated in all groups of CAP. Not all physicians adhere to the ATS guidelines regarding antimicrobial therapy.

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Pattern of Resistance of Sputum Isolates among Patients with Nosocomial Pneumonia: MCM Experience

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Resistance to antibiotics in the treatment of infections, especially nosocomial pneumonia remains an important concern. It is therefore necessary that patterns of resistance be monitored in order to make the appropriate recommendations for choice of antibiotics in empiric therapy. This study was undertaken to define this pattern in nosocomial pneumonia at the Medical Center Manila. A total of 58 patients and 46 patients were included in a retrospective study of the years 1999 and 2000. Male patients accounted for 62.07% of admissions and 37.93% for female patients in the period of 1999. The mean age for patients was 62.8 and 63.7 among males and females, respectively. The same is true for the period of year 2000 wherein 71.74 % are males and 28.26% are females. The mean age for patients was 68.9 and 61.6 among males and females respectively. Most of the patients had stroke and congestive heart failure as co-morbidities for both male and female for 37.5% for the period of 1999 and congestive heart failure (30.26%) for males and stroke (28.95%) for females.

In the year 1999, there were 26 isolates of *Pseudomonas aeruginosa*, seven isolates (26.92%) were resistant to ceftazidime followed by ciprofloxacin, amikacin, clindamycin and imipenem (19.23%). *Klebsiella* resistance was also noted with highest resistance to ceftazidime (25.00%) followed by amikacin (16.67%). In the year 2000, there were 21 isolates of *Pseudomonas aeruginosa* which was resistant to ceftazidime (38%) followed by amikacin (19.05%) and ciprofloxacin and tazobactam (14.29% each). *Klebsiella* was isolated in 11 cultures which showed resistance to ciprofloxacin and ceftazidime (45.45%) followed by amikacin (27.27%). *Phil Journal Chest Diseases. Vol. 12 No. 2 pp: 113 - 116*

Keywords: Nosocomial pneumonia, resistance, sputum culture

Introduction

Antimicrobial resistance is one of the growing concerns in treating patients with infections especially in patients acquiring nosocomial pneumonia. Patients with tracheal intubation and/or requiring mechanical ventilation have a 6- to 20-fold increased risk for nosocomial pneumonia. There is a relatively constant 1 % to 3% risk per day for developing ventilator-associated pneumonia (VAP) in medical and surgical intensive-care units (ICUs). The rates are much lower in non-intubated patients. The estimated prevalence of nosocomial pneumonia within the intensive care setting ranges from 10% to 65%, with fatality rates greater than 25% reported in most studies.[6,7]

Several studies have demonstrated that mortality rates for hospital-acquired pneumonia (HAP) are higher if the initial antimicrobial therapy was inadequate as demonstrated by subsequent invasive culture results. In nosocomial pneumonia, both the diagnosis of the disease and the identification of the pathogen agent are crucial. The lack of standard diagnostic criteria can lead to the inappropriate use of broad-spectrum antibiotic therapy and the emergence of drug bacteria. There is also evidence to suggest that if the initial empiric choice of antibiotics is incorrect, subsequent shift to a more appropriate choice does not improve the mortality rate in patients with ventilator-associated pneumonia (VAP). It appears that in severely ill patients, the initial empiric therapy is the most important decision a physician can make.

Thus microbiologic techniques have been developed to permit recognition of the causative pathogen. It would be preferable to identify the pathogen since such identification makes optimal antimicrobial selection possible. This is particularly relevant in this era of increasing antimicrobial resistance. Knowledge of the pathogen also limits the consequences of antibiotic abuse, including: Higher costs, increased resistance adverse drug reactions. However, these bacteriologic isolates vary from centers and risk factors associated with the patients.

[1] Medical Center Manila

Table I Patient Demographics

Patient Characteristics	1999		2000	
	Male	Female	Male	Female
Age (mean)	62.8	63.7	68.9	61.6
Sex	36(62.07)	22(37.93)	33(71.4)	13(28.26)
Co-morbidities				
CHF	9(18.75)	5(15.63)	23(30.26)	10(26.32)
Stroke	18(37.50)	12(37.50)	22(28.95)	11(28.95)
COPD	3(6.25)	2(6.25)	6(7.89)	3(7.89)
Malignancy	5(10.42)	3(9.38)	5(6.58)	2(5.26)
DM	6(12.50)	8(25.00)	12(15.79)	7(18.42)
Surgery	4(8.33)	2(6.25)	4(5.26)	3(7.89)
Asthma	2(4.17)	0(0.00)	1(1.32)	0(0.00)
Renal	1(2.08)	0(0.00)	3(3.95)	2(5.26)

Table II Antibiotic regimen

	1999		2000	
Ceftazidime	18	31.03%	14	30.43%
Ceftazidime + Amikacin	9	15.52%	5	10.87%
Ceftazidime + Metronidazole	4	6.90%	1	2.17%
Ceftazidime + Clindamycin	3	5.17%	3	6.52%
Ceftazidime + Erythromycin	2	3.45%	2	4.35%
Cefepime	6	10.34%	4	8.70%
Imipenem	2	3.45%	2	4.35%
Meropenem	12	20.69%	10	21.74%
Tazobactam + Piperacillin	2	3.45%	5	10.87%

Table III Culture studies for 1999

Bacteria	N (%)
Pseudomonas aeruginosa	26 (44.83)
Acinetobacter	5 (8.62)
Enterobacter	5 (8.62)
Klebsiella spp.	12 (20.69)
Staphylococcus aureus	10 (17.24)

Table IV Culture studies for 2000

Bacteria	N (%)
Pseudomonas aeruginosa	21 (45.65)
Acinetobacter	2 (4.35)
Enterobacter	5 (10.8)
Klebsiella spp.	11 (23.91)
Staphylococcus aureus	5 (10.87)

The objective of this study is therefore to identify the antimicrobial resistance patterns of microbiological isolates based on sputum studies in patients with nosocomial pneumonia.

Materials and Methods

This is a two-year retrospective study that aims to review all the sputum cultures of newly admitted patients at MCM IMU from January 1999 to December 2000.

Definition of Terms. Hospital-acquired pneumonia (HAP) is defined as pneumonia occurring 48 hours after admission to the hospital and excluding those incubating at the time of admission. Early Onset HAP is pneumonia occurring within five days of admission. Late Onset HAP is pneumonia occurring after more than five days of admission

Inclusion Criteria: Newly admitted patients at the IMU with sputum cultures that were requested > 48 hours after admission at the IMU with the clinical suspicion of nosocomial pneumonia based on the ATS criteria for diagnosing nosocomial pneumonia: When a new or progressive radiographic infiltrate developed in conjunction with one of the following: 1) radiographic evidence of pulmonary abscess formation (i.e., cavitation within preexisting pulmonary infiltrates); 2) histologic evidence of pneumonia in lung tissue; a positive blood or pleural fluid culture; or two of the following: fever (temperature >38.3°C, leucocytosis (leukocyte count > 10 x 10^3/mm^3), and purulent tracheal aspirate

Exclusion Criteria: Sputum cultures that were done < 48 hours after admission, patients admitted due to community acquired pneumonia, and patients who were initially admitted in the ward then transferred to IMU.

Data Analysis: Data collected were analyzed using the statistical software SPSS.

Results

A total of 58 patients and 46 patients were included in the study from the year 1999 to 2000. Male patients accounted for 62.07% of admissions and 37.93% for female patients in the period of 1999. The mean age for patients was 62.8 and 63.7 among males and females, respectively. The same is true for the period of year 2000 wherein 71.74 % are males and 28.26% are females. The mean age for patients was 68.9 and 61.6 among males and females respectively. Most of the patients had stroke and congestive heart failure as co-morbidities for both male and female for 37.5% for the period of 1999 and congestive heart failure (30.26%) for males and stroke (28.95%) for females (*Table I*).

Most of the patients (31.03% and 30.43%) were treated empirically using a monotherapy of a third generation cephalosporin for the year 1999 and 2000 respectively. While a combination therapy of third generation cephalosporin and aminoglycoside accounted for 15.52% and 10.87% of the patients for the year 1999 and 2000 pending culture results. (*Table II*)

Pseudomonas aeruginosa accounted for 44.83% and 45.65% of culture yields from the period of 1999 to 2000. This was followed by *Klebsiella sp* accounting for 20.69% and 23.91% of the culture yields. (*Tables III* and *IV*)

Table V Antimicrobial resistance pattern for the year 1999

Antimicrobials	Pseudomonas n=26	Klebsiella n= 12	Enterobacter n=5	Staphylococcus n= 10	Acinetobacter n=5
Amikacin	3 (11.54%)	2 (16.67%)	2 (40.00%)	4 (40.00%)	0(0.00%)
Cefipime	2 (7.69%)	1 (8.33%)	1 (20.00%)	1 (10.00%)	2 (40.00%)
Ceftazidime	7 (26.92%)	3 (25.00%)	1 (20.00%)	1 (10.00%)	2 (40.00%)
Ciprofloxacin	3 (11.54%)	1 (8.33%)	1 (20.00%)	1 (10.00%)	1 (20.00%)
Clindamycin	3 (11.54%)	1 (8.33%)	0 (0.00%)	1 (10.00%)	0 (0.00%)
Imipenem	3 (11.54%)	1 (8.33%)	0 (0.00%)	0(0.00%)	0 (0.00%)
Meropenem	2 (7.69%)	1 (8.33%)	0 (0.00%)	1 (10.00%)	0(0.00%)
Ofloxacin	2 (7.69%)	1 (8.33%)	0 (0.00%)	1 (10.00%)	0(0.00%)
Tazocin	1 (3.85%)	1 (8.33%)	0 (0.00%)	0 (0.00%)	0(0.00%)

Table VI Antimicrobial resistance pattern for the year 2000

Antimicrobials	Pseudomonas n=21	Klebsiella n= 11	Enterobacter n=5	Staphylococcus n=5	Acinetobacter N=2	E. coli n=2
Amikacin	4(19.05%)	3(27.27%)	1(20.00%)	0(0.00%)	0(0.00%)	0(0.00%)
Cefepime	2(9.52%)	1(9.09%)	0(0.00%)	0(0.00%)	1(50.00%)	0(0.00%)
Ceftazidime	8(38.10%)	5(45.45%)	1(20.00%)	1(20.00%)	0(0.00%)	0(0.00%)
Ciprofloxacin	3(14.29%)	5(45.45%)	1(20.00%)	2(40.00%)	1(50.00%)	1(50.00%)
Clindamycin	1(4.76%)	0(0.00%)	0(0.00%)	1(20.00%)	0(0.00%)	1(50.00%)
Imipenem	0(0.00%)	0(0.00%)	0(0.00%)	0(0.00%)	0(0.00%)	0(0.00%)
Meropenem	1(4.76%)	0(0.00%)	1(20.00%)	0(0.00%)	0(0.00%)	0(0.00%)
Tazocin	1(4.76%)	2(18.18%)	0(0.00%)	0(0.00%)	0(0.00%)	0(0.00%)

In the year 1999, there were 26 isolates of *Pseudomonas aeruginosa*, seven isolates (26.92%) were resistant to ceftazidime followed by ciprofloxacin, amikacin, clindamycin and imipenem (19.23%). *Klebsiella* resistance was also noted with highest resistance to ceftazidime (25.00%) followed by amikacin (16.67%). (*Table V*)

In the year 2000, there were 21 isolates of *Pseudomonas aeruginosa* which was resistant to ceftazidime (38%) followed by amikacin (19.05%) and ciprofloxacin and tazobactam (14.29% each). *Klebsiella* was isolated in 11 cultures which showed resistance to ciprofloxacin and ceftazidime (45.45%) followed by amikacin (27.27%) (*Table VI*)

Discussion

Nosocomial pneumonia is one of the leading causes of mortality and morbidity among patients admitted in the ICU. It is recognized that ICU patients acquire nosocomial infections at a much higher rate than patients elsewhere in the hospital.[5] The growing prevalence of multi-resistant gram-negative rods in ICU patients, for example, makes it critical that physicians understand the risk factors contributing to that resistance and the optimal therapies for those organisms.

The result of antimicrobial surveillance pattern for the past two years have shown relatively high resistance rates nosocomial pneumonia particularly to cultures yielding *Pseudomonas aeruginosa* and *Klebsiella*. Most of these patients were empirically treated with a third generation cephalosporin (31 % and 30% respectively) for the past two years. The pattern of antimicrobial resistance varies from center to center but surveillance studies,[1,15] however, have shown that prescribing habits of physicians had been associated with rampant use of third generation cephalosporin and a rising trend in the resistance pattern of bacteria to these organism. Schiappa has identified use of ceftazidime or aztreonam as a risk factor for ceftazidime resistant *Klebsiella* bacteremia. This pattern of resistance is likely conferred with a plasmid mediated resistance among gram negative bacilli. Gram-negative bacilli are able to produce ESBL (extended spectrum beta lactamase) enzyme which is responsible for removing the protective side chain of third generation cephalosporins, especially the amino-thiazole-oxime agents: ceftazidime, ceftriaxone, and aztreonam.[8]

ESBL production is suspected if the isolate demonstrates in vitro ceftazidime resistance and sensitivity to cefotaxime, ceftriaxone, and the beta-lactamase inhibitors (for example, c1avulanic acid, sulbactam,. or tazobactam). This susceptibility pattern can be used as a guide for the presence of ESBL and to make important therapeutic decisions. ESBL can be overlooked if bacterial strains exhibit a low-level resistance or if the microbiology laboratory does not routinely perform ceftazidime susceptibility tests.[9]

Institutional prescribing practices place important selection pressures on the native microbial flora and their degree of sensitivity to commonly used antibiotics and as clinicians it is our duty to be always guided these culture studies. Finally, the key to control of antibiotic-resistant pathogens in the ICU is rigorous adherence to infection control guidelines and prevention of antibiotic misuse.

Recommendations

Aside from the duties and responsibilities of a physician in preventing nosocomial infection, several strategies are recommended to avoid the emergence of such resistance. It is recommended to the laboratory personnel to follow the guidelines set by the National Committee for Clinical and Laboratory Standards (NCCLS)

Screening test Disk diffusion (ceftazidime + c1avulanic acid and cefotaxime + c1avulanic acid): increase > 5 mm suggests the presence of an ESBL.

Confirmatory test MIC (ceftazidime + clavulanic acid and cefotaxime + c1avulanic acid) > 3-fold decrease in MIC suggests the presence of an ESBL. Breakpoints have been lowered from 8 mcg/mL to 2 mcg/mL.

Scheduled changes of antibiotic classes for the empirical treatment of Gram-negative bacterial infections can also be adopted to can reduce the occurrence of inadequate antibiotic treatment for nosocomial infections. For example, in a study by Koellef, ceftazidime is the recommended empiric agent in the first six-month interval; in the second period, ciprofloxacin; and in the third interval, cefepime. This rotational schedule led to a decrease in administration of inadequate antibiotic treatment for nosocomial gram-negative bacterial infections, with rate of inadequate treatment falling to 1.6% by the end of the 18-month study. Overall ICU mortality was not affected, although the mortality of patients with APACHE II scores $\geq$ 15 was statistically less in the third time period compared to the first time period (21% vs 8%; $p < 0.001$).

Lastly, it is recommended to the infection control committee of the hospital to do surveillance studies in order for clinicians to be guided with the present antimicrobial flora and resistance patterns of the present microbial flora in the ICU setting.

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Knowledge of Physicians in Chinese General Hospital about Community-Acquired Pneumonia Clinical Practice Guidelines

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Bacterial pneumonia is a common condition that is seen both in the outpatient clinics as well as in the admitting sections of local hospitals. There are several guidelines published, notably that of the American Thoracic Society and Infectious Diseases Society of America, as well as a local one as a result of collaboration between the Philippine College of Chest Physicians and the Philippine Society of Microbiology and Infectious Diseases. This study was therefore undertaken to discover the knowledge of physicians at the Chinese General Hospital with regards to these guidelines.

Sixty eight physicians practicing Internal Medicine answered a questionnaire prepared for this purpose. Most of the respondents (69%) were aware of the treatment guidelines, while some (19%) were not fully conversant with these guidelines, and the rest were completely unaware of any guidelines. Of those knowledgeable of the guidelines, most (50%) utilized the ATS guidelines; 21% utilized the PCCP guidelines, 1% utilized the IDSA guidelines, while the rest did not utilize any guideline at all. Although majority of the respondents were aware of these guidelines, most 79% did not apply these to all patients. Statistical analysis using *chi-square test* showed that there was no significant difference as to whether the respondent were in-training, consultants in other subspecialties of Internal Medicine or Pulmonologists.

Of those who applied the guidelines to all their patients, the primary reason given was that these guidelines led to a high treatment success rate. On the other hand, those who did not use these guidelines on all their patients gave as their primary reason their perception that the medications being recommended are expensive. Again, using the *chi-square test*, there were no significant differences in the perceptions of the respondents in-training versus the consultants in other subspecialties and the pulmonologists.

Based on these findings, it is recommended that further dissemination of the guidelines, particularly the local one be done at the Chinese General Hospital. *Phil Journal of Chest Diseases. Vol. 12 No. 2 pp: 117 - 121*

Community-acquired pneumonia, treatment guidelines, physicians

Introduction

Pneumonia is an infection of the lung parenchyma that can be caused by bacteria, viruses, fungi and parasites. It affects millions of people worldwide, and accounts for significant mortality and morbidity, especially for the elderly and those with co-existing illnesses that may complicate or predispose the patient to pneumonia, such as congestive heart failure, diabetes mellitus, etc. Since pneumonia can be caused by a variety of agents, it should not be considered a single disease but a group of infections, each with a different epidemiology, pathogenesis, clinical presentation and clinical course. It is therefore very important to identify the etiologic agent in order to give the appropriate antibiotic. However, the clinical presentations and clinical course of the various etiologies are often quite similar.

Alternatively, the clinical presentation of patients infected with the same pathogen may also differ. Chest radiographs, although useful to diagnose pneumonia, rarely provide a specific etiology. Moreover, even when extensive laboratory testing is utilized, a definitive etiologic diagnosis is obtained in only about 50% of cases, and the data from these investigations are often delayed for hours or days. Due to the seriousness of the disease, and the evidence that there is an improved outcome with the earliest possible intervention, it is necessary to start empiric antibiotic therapy even before laboratory confirmation of the causative agent. Thus, guidelines to aid physicians in starting empiric therapy for community-acquired pneumonia (CAP) are needed. To date, the guidelines for the treatment of CAP that are widely accepted in the Philippines include those formulated by the American Thoracic Society (ATS), the Infectious Diseases Society of America (IDSA), the

[1] Chinese General Hospital

Table I. Demographic characteristics of respondents

	N (%)
Total	
In-training	15 (22)
Consultants	53 (78)
Specialty	
Internal Medicine	9 (15)
Pulmonology	10 (19)
Other specialties	35 (66)
Age	
27 – 40	49 (72)
41 – 50	17 (25)
51 – 60	1 (1.5)
61 – 70	1 (1.5)
Number of patients per day	
< 10	28 (41)
11 – 20	23 (34)
21 – 30	10 (15)
31 – 40	2 (2.9)
No answer	5
Percent of patients seen diagnosed as pneumonia	
< 10%	33 (49)
10 – 20%	10 (15)
21 – 30%	7 (10)
31 - 40%	6 (9)
41 – 50%	3 (4)
51 – 60%	2 (3)

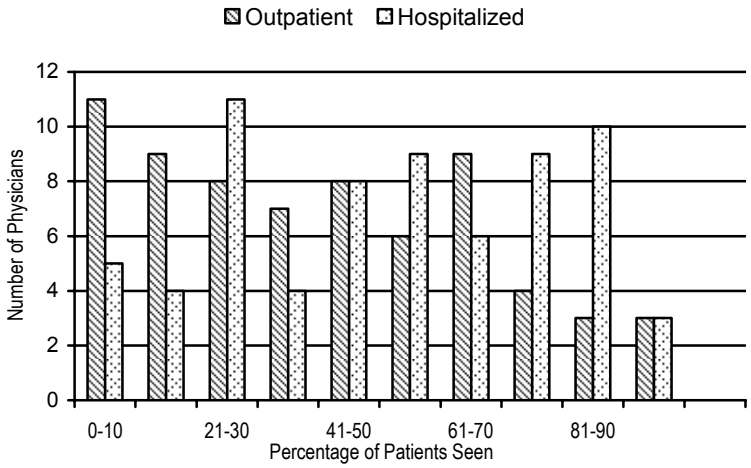

Figure 1 Distribution of patient disposition as reported by physician respondents

Philippine College of Chest Physicians (PCCP) and the Philippine Society for Microbiology and Infectious Diseases (PSMID).

The 2001 guideline of the ATS divide patients with CAP into one of four groups, depending upon the need for hospitalization, severity of illness, presence of coexisting disease, risk for infection with drug-resistant *Streptococcus pneumoniae* (DRSP) and risk or infection with *Pseudomonas aeruginosa*. DRSP risk is emphasized because *S. pneumoniae* is the most common pathogen in CAP. Risk factors identified for DRSP include antibiotic therapy within the last three months, age > 65 years, nursing home patient, immunosuppressive illness/therapy, multiple medical co-morbidities or history of alcohol abuse. Risk factors for infection with *P. aeruginosa* include structural lung disease, corticosteroid therapy, broad-spectrum antibiotic therapy for more than seven days in the month preceding the illness, and malnutrition.

Based on the above, the 2001 ATS guidelines for CAP; group I patients are those that have no cardiopulmonary disease and no modifying risk factors, and can be treated as outpatients with an advanced generation macrolide or doxycycline. Group II patients have cardiopulmonary diseases and/or other modifying risk factors that are controlled, and can be treated as outpatients with a B-lactam plus a macrolide or plus doxycycline or with an anti-pneumococcal fluoroquinolone alone. Group III patients have to be hospitalized, and are divided into group IIIa and group IIIb based on the presence of cardiopulmonary diseases and/or modifying risk factors (IIIa) or its absence (IIIb). Criteria for hospitalization were based on the Pneumonia Patient Outcome Research Team (Pneumonia PORT) study and the British Thoracic Society criteria. Group IIIa patients are treated with an intravenous (IV) anti-pneumococcal fluoroquinolone alone or with an IV B-lactam plus IV or oral macrolide or doxycycline. Group IV patients have to be admitted into the intensive care unit, and are categorized into group IVa if they have no risks for infection with *P. aeruginosa* or into group IVb if they have risks for *P. aeruginosa* infection. Group IVa patients should be given an IV B-lactam plus either an IV macrolide or IV f1uoroquinolone, whereas group IVb patients should be given an IV anti-pseudomonal B-lactam plus an IV anti-pseudomonal fluoroquinolone or an IV anti-pseudomonal B-lactam plus IV aminoglycoside plus either IV macrolide or IV non-pseudomonal fluoroquinolone.

The IDSA guidelines differ from the ATS guidelines mainly in its greater emphasis on establishing the etiology for each case of pneumonia. Although it recognizes the fact that, as pointed out in the ATS guidelines, there is much difficulty in acquiring specific

Table II Knowledge of physicians about treatment guidelines according to specialty

Parameter	In-training	Consultants	Pulmonologists	Total
Awareness of treatment guidelines				
YES	15	32		47 (70)
NO	2	6		8 (12)
Not fully aware				13 (19)
Treatment guidelines being used				
ATS				34 (50)
IDSA				1 (1)
PCCP				14 (21)
None				20 (29)
Are guidelines applied to all patients?				
YES	5	9	0	14 (21)
NO	10	34	10	54 (70)

Table III Reasons for applying guidelines to patients

Reason Given	In-training	Consultants	Total
High treatment success rate	2	5	7 (50)
Cost-effective	0	1	1 (7)
Recommended by societies	2	1	3 (21)
Less adverse effects			1 (7)
Others: part of defensive management of patients	1	0	1 (7)

Table IV Primary reasons given for not applying guidelines to patients

Reasons Given	In-training	Consultant	Pulmonologist	TOTAL
High cost	9	10	3	22 (41)
Increased side effects	1	0	2	3 (6)
Reliance on clinical experience rather than guidelines	0	14	1	15 (28)
Treatment failure	1	0	1	2 (4)
Supports drug companies	0	0	1	1 (2)
Patient non-compliance	0	1	1	2 (4)
Not fully aware of guidelines	0	1	8	9 (17)

etiologic information, it advocates the routine use of sputum Gram stain (SGS) for outpatients, with an option of culturing for conventional bacteria.

Hospitalized patients should have a sputum Gram stain and culture of both sputum and blood. The IDSA algorithm for CAP-treatment helps define which patients would benefit from hospitalization based on the Pneumonia PORT study. Factors that influence decision-making include respiratory failure, ARDS, mechanical ventilation, bilateral infiltrates or a greater than 50% increase in infiltrates and a worsening chest radiograph within 48 hours of hospital admission. Other factors noted in the IDSA that indicate the severity of CAP include systolic or diastolic hypotension, profound sepsis with end-organ dysfunction, and tachypnea > 30 breaths/min. Moreover, it was pointed out that three parameters give the clinician the best opportunity to predict patient mortality: tachypnea > 30 breaths/min, BUN > 19.6 mg/dL and diastolic BP < 60 mm Hg.

The Philippine Clinical Practice Guidelines for CAP, which were developed by the PSMID, are similar to the ATS guidelines, in that patients are divided into four groups. Also, Like the ATS and unlike the IDSA, it does not recommend SGS for routine use particularly for patients who do not need hospitalization.

Although there are many guidelines for the treatment of CAP available, not all physicians involved in the care of patients with this disease are aware of these, nor are these guidelines universally practiced. According to Pearson, "publishing a guideline document is not a guarantee that it will ever be read and still less that it will be acted on. Many members of the medical profession jealousy guard their right to treat each individual as an individual…"[3] It is therefore the objective of this paper to determine if the physicians practicing in Chinese General Hospital and Medical Center are aware of any of the guidelines mentioned above, which aspect of the guidelines they are aware of, and which, if any, they utilized in their practice, and finally, why they do or do not use these guidelines.

Methodology

Physicians practicing Internal Medicine in Chinese General Hospital and Medical Center were requested to fill up a form designed specifically for this study. The results were then tabulated, and statistical analyses were subsequently applied.

Results

A total of 68 physicians practicing Internal Medicine in Chinese General Hospital were surveyed. Fifteen were residents in training, and the rest were consultants (those who had completed their training). Of these consultants, eight (15 %) were purely internists, 10 (19%) were subspecialists in Pulmonology, and the rest (66%) were subspecialists in fields other than Pulmonology. Ages of respondents ranged from 27 - 70 years; median age was 27-70 years. Most physicians saw, on the average, less than or equal to 20 patients per

Table V Other reasons given for not applying guidelines to all patients

High Cost	11 (22)
Increased side effects	5 (10)
Relies on clinical experience rather than guidelines	13 (27)
Treatment failure	7 (15)
Supports drug companies	2 (4)
Patient non-compliance	9 (19)
Not fully aware of guidelines	1 (2)

Table VI Percentage of patients on whom guidelines are applied (for those who do not apply it to all)

Percent of patients	No. of physicians (%)
< 20%	17 (25)
30%	3 (4)
40%	5 (7)
50%	7 (10)
60%	10 (15)
70%	11 (16)
80%	11 (16)
90%	4 (9)

day, and of these, less than or equal to 10% had pneumonia.

Most of the respondents (69%) were aware of the treatment guidelines, while some (19%) were not ful1y conversant with these guidelines, and the rest were completely unaware of any guidelines. Of those knowledgeable of the guidelines, most (50%) utilized the ATS guidelines; 21% utilized the PCCP guidelines, 1% utilized the IDSA guidelines, while the rest did not utilize .any guidelines at all. Although majority of the respondents were aware of these guidelines, most 79% did not apply these to all patients. Statistical analysis using *chi-square test* showed that there was no significant difference as to whether the respondent were in-training, consultants in other subspecialties of Internal Medicine or Pulmonologists.

Of those who applied the guidelines to all their patients, the primary reason given was that these guidelines led to a high treatment success rate. On the other hand, those who did not use these guidelines on all their patients gave as their primary reason their perception that the medications being recommended are expensive. Again, using the *chi-square test*, there were no significant differences in the perceptions of the respondents in-training versus the consultants in other subspecialties and the pulmonologists.

Discussion

There are a variety of guidelines for CAP in the medical journals that advocate treatment targeted against the most common etiologic microorganisms to be found in a given population of patients. Although according to Campbell, "adherence to the ATS guidelines proved to be associated with improved outcome and reduced cost of treatment,"[4] many physicians, as evidenced by this survey, though knowledgeable about these guidelines, still do not apply these to their patients because of a variety of reasons, foremost of which is due to the perception of the expensiveness of medications.

However, these guidelines have been formulated in such a way that the most appropriate and cost effective initial empiric regimens be given to patients in order to reduce morbidity or mortality and the high costs attendant to these.

Another prominent reason that was found for non-compliance to guidelines is that physicians would rather rely on their own clinical experience. Indeed, as mentioned by Pearson, "implementation of guidelines requires that the medical profession is willing to conform to patterns of diagnostic and treatment behavior set down by others."[2] He further continues to say that many physicians may "regard the imposition of guidelines as a threat. Others argue that it is helpful to set out the best practice but to recognize that for exceptional patients, doctors may deviate from the guidelines ..."[2] However, since evidence is available to show that these guidelines can improve clinical outcome and therefore lessen the costs associated with prolonged hospitalization, and the loss of income consequent to hospitalization and morbidity, then it behooves the medical profession to comply with them rather than on individual opinion.

Moreover, many physicians, as evidenced in this survey may have an idea that there are clinical guidelines being advocated but still they are not completely knowledgeable about them. In this regard, there may be a problem with guideline dissemination and education.

Heffner et. al.[5] have suggested ways to ensure proper implementation of Guidelines in clinical practice, Firstly, ways by which these guidelines may be disseminated to the majority should be sought. This may be done by producing user-friendly and problem oriented materials and manuals not only for physicians but also for patients, health-care organizations, and pharmaceutical industry representatives. These should be made readily available through various media, including the Internet.

Secondly, continuing medical education programs are stated as important venues for the dissemination of guidelines, and may help to clarify any confusion and questions regarding these.

Thirdly, Heffner et al. states that, "all guidelines are local, meaning that guidelines are successful only if they are supported and adopted by physicians in their local practice environment." Thus, local opinion leaders need to be identified and their participation in guideline implementation obtained.

Lastly, Heffner et al also notes that adult learning can be possible only if the individual is ready to learn. Thus, the Societies involved, for example, the Phil. College of Chest Physicians, as well as the Philippine Society of Microbiology and Infectious Diseases, should seek out ways to assist physicians in identifying whatever knowledge gaps that they may have.

Once there is widespread use of clinical practice guidelines, a potential outcome would be that variations in clinical practice and irrationality of therapeutic decisions be minimized.[2] In this manner, a standard of care could be set for all patients. It is therefore recommended that the guidelines for CAP, especially that of the PSMID, which is tailored to the local setting, should be better disseminated among the physicians of the Chinese General Hospital.

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Profile of Nosocomial Pneumonia in Non-vented Adult Patients at the Manila Doctors Hospital

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Objective: To determine the clinical profile of patients who develop nosocomial pneumonia at the Manila Doctors Hospital (MDH).
Design: Descriptive, retrospective
Setting: In patients, pay and service, of MDH, a private tertiary hospital.
Patients: All adult non-vented patients admitted at MDH from January 1, 2002 to December 31, 2002 who develops signs and symptoms of pneumonia 48 hours or more after admission.
Results: There was an almost equal male to female ratio (1.16:1) with an increased incidence for those on the seventh decade of life (61.53%). Initial symptoms were productive cough (46.15%), fever (30.74%) and difficulty of breathing (23.08%) with most presenting after the fourth hospital day (58.85%). Piperacillin-Tazobactam was initially given to 46.15% of the patients. The organisms isolated were *K. pneumoniae* (53.85%), *E. coli* (26.92%) and *P. aeruginosa* (19.23%).
Conclusion: Patients on the seventh decade of life presenting with two or more co-morbidities and those with hospitalization of more than four days have an increased chance of acquiring nosocomial pneumonia. Those presenting initially with sudden difficulty of breathing have a higher mortality rate (83.33%). Piperacillin-tazobactam seems to be an effective drug for nosocomial pneumonia. *Phil Journal of Chest Diseases. Vol. 12 No. 2 pp: 122 - 125*

Keywords: Nosocomial pneumonia, mechanical ventilator, antibiotic therapy

Introduction

Hospital acquired infections have emerged as a new challenge to the clinician with regard to their diagnosis and treatment. This is especially true in the diagnosis and treatment of lower respiratory tract infections.[2]

Nosocomial infections are those that develop in a hospitalized patient after 48 hours which was neither present nor incubating at the time of admission.[1] The diagnosis of nosocomial pneumonia is based on (1) the evidence of parenchymal lung involvement with new infiltrate on chest radiograph; (2) new onset of fever > 38°C; (3) presence of purulent tracheobronchial secretions (> 25 WBC/hpf with < 10 epithelial cells/hpf) and (4) increased WBC count (> 10,000/mm^3) or leucopenia (< 4,000/mm^3).

This study was done to describe the clinical profile of patients who develop nosocomial pneumonia at MDH. Hopefully, a better understanding of nosocomial pneumonia, particularly at the MDH could help clinicians manage this condition better.

Methods

This is a descriptive retrospective study. Subjects are non-vented adult patients admitted at MDH from January 1, 2002 to December 31, 2002 who acquired nosocomial pneumonia. They were classified as such if they developed signs and symptoms, physical examination findings, chest radiographs and/or white cell count elevation indicative of pneumonia after 48 hours of confinement.[1,2] A sputum culture and sensitivity or tracheal aspirate culture and sensitivity should have been done.

Inclusion Criteria: 1. All adult patients admitted at MDH from January 1, 2002 to December 31, 2002 who develop signs and symptoms of pneumonia 48 hours after being admitted. 2. There must be no pneumonia upon admission. 3. The subjects should not have been intubated at any time, during the admission, or prior to acquiring nosocomial pneumonia. 4. A tracheal and/or sputum culture and susceptibility should have been done. 5. A chest radiograph must have been done.

[1] Manila Doctors Hospital

Table I Age and Sex Distribution of Adult Non-Vented Patient who Develop Nosocomial Pneumonia at Manila Doctors Hospital from January 1, 2002 to December 31, 2002.

Age	Male	Female	Total
>75	3(11.52)	3(11.52)	6(23.08)
70-75	3(11.52)	1(3.85)	4(15.38)
65-69	5(19.23)	7(26.92)	12(46.15)
60-40	3(11.52)	1(3.85)	4(15.38)
Total	14(53.85)	12(46.15)	26

Table II Number of Co-morbid Factors of Adult Non-Vented Patients who Developed Nosocomial Pneumonia at Manila Doctors Hospital from January 1, 2002 to December 31, 2002

No. of co-morbid factors	N (%)
1	4(15.38)
2	10(38.46)
3	6(23.08)
4	6(23.08)

Table III Co-morbidity of Adult Non-Vented Patients who developed Nosocomial Pneumonia at Manila Doctors Hospital from January 1, 2002 to December 31, 2002

Co-morbid Conditions	N (%)
Coronary Artery Disease	12(46.15)
Hypertension	12(46.15)
Diabetes Mellitus Type 2	10(38.46)
Pulmonary	8 (30.75)
CVD	8 (30.75)
Liver disease	6 (23.08)
Abdominal surgery	2 (7.69)

The subjects will be identified using the records of the Department of Medicine and of the Microbiology Section of the laboratory. Charts of patients with tracheal and/or sputum culture and sensitivity requested after the second hospital day will be reviewed based on the other inclusion criteria.

The profile is described as to: age and sex distribution, co-morbid factors, incubation period and initial symptom, initial empiric therapy and step down medication, the organisms isolated and the sensitivity pattern, white cell and differential count.

Table IV Selected characteristics of Nosocomial Pneumonia in Non-Vented Adult Patient at Manila Doctors Hospital from January 1, 2002 to December 31, 2002

Characteristics	N (%)
Incubation Period (days)	
3	3 (11.54)
4	9 (34.61)
>4	14(58.85)
Total	26
Symptom	
Fever	8 (30.74)
Cough	12(46.15)
Difficulty of Breathing	6 (23.08)
Antibiotic Used	
3rd gen cephalosporin	3(11.54)
3rd gen cephalosporin + aminoglycoside	2 (7.69)
Meropenem	7(26.92)
Cefipime	2 (7.69)
Piperacillin-tazobactam	12(46.15)
Isolate	
K. pneumoniae	14 (53.85)
E. coli	7 (26.92)
P. aeruginosa	5 (19.23)
Total	26
WBC Count	
>20,000/mm^3	2 (7.69)
15,000-20,000/mm^3	1 (3.85)
10,000-15,000/mm^3	20(76.93)
5,000-10,000/mm^3	3 (11.54)
White cell differential count	
90 or greater	2
80-89	15
70- 79	7
60-69	2
Total	26
Increase in the WBC count	
greater than 5000	8(30.77)
4000-4999	4(15.38)
3000-3999	1 (3.85)
2000-2999	2 (7.69)
1000-1999	2(7.69)
less than 1000	9(34.62)
Total	26

Results

Age and Sex Incidence. A total of 26 non-vented patients were documented to have acquired nosocomial pneumonia. Of these, 14 were males and 12 were females (*Table I*) occurring most commonly in the seventh decade of life (61.53%) particularly those 65-69 years old (46.15%).

This is consistent with the findings of Greenway et. al. with a mean age of 63 $\pm$ 17 years,[3] and by Alora et. al. where those in the fifth to seventh decades accounted for 55% with nosocomial infections.[4] The oldest patient was 93 years old while the youngest was 63 years old.

Co-morbidity. Only four patients had one co-morbid condition (*Table II*). Three had pulmonary disease (COPD predominantly Chronic Bronchitis) while the other had CVD Infarct. The rest had two to four co-morbid factors: Coronary Artery Disease, Hypertension, Diabetes Mellitus, CVD, Pulmonary (PTB, COPD), Liver disease (Hepatic Encephalopathy), and abdominal surgery (*Table III*).

Incubation period and initial symptom Majority of patients (58.85%) developed nosocomial pneumonia after the fourth hospital day (three on day 5; five on day 6; one on day 7; two on day 8; two on day 12 and; one on day 20). Only three patients (11.54%) developed nosocomial pneumonia within 48-60 hours of admission. A study by Gomez et al, noted that the incidence of nosocomial pneumonia in non-vented patients increased with hospitalization of more than fourteen days.[5] (*Table IV*)

The most common presenting symptom was a productive cough (46.15%) of white to yellow phlegm. A fever of 38°C or more was found to be the initial symptom

Empiric Treatment Twelve (46.15%) were started on piperacillin-tazobactam 2.25 gm IV every eight hours (Table IV) Meropenem 1 gm IV every eight hours was given in seven patients while cefipime 1 gm IV every 12 hours was started in two patients.

The third generation cephalosporin used was ceftazidime (given in five patients) with or without an aminoglycoside (amikacin in one and netilmycin in another).

Culture and Sensitivity. All organisms isolated were gram negative bacilli with *K pneumoniae* (53.85%) as the most common isolate. The National Nosocomial Infection Study (NNIS) in the United States isolated gram negative bacilli (58.7%) with *K. pneumoniae* accounting for 17.2%.[6] Alora et al. in their nosocomial surveillance done at UST isolated *K pneumoniae* in 48.89% (22 out of 45 isolates) of tracheal secretions and 15.79% (3 out of 19 isolates) of sputum specimen.[4]

Cefipime had the best sensitivity profile for *K. pneumoniae* and *E. coli* with 85.71% of the isolates showing sensitivity. Amikacin had an average of 70.08% sensitivity for all isolates. The sensitivity to piperacillin-tazobactam of the three isolates ranged from 64.28% to 80%. A study which included all nosocomial infections in UST[4] and in PGH[7] showed that all were sensitive to cefipime.

White cell and differential count. Leucocytosis is one of the clinical parameters included in the diagnosis of nosocomial pneumonia.[1,2,8] All of the patients had a CBC prior to onset of symptoms pertaining to nosocomial pneumonia and all had a repeat of the WBC count with differential or a CBC done when the patient presented with symptoms of nosocomial pneumonia. About a third (34.62%) of the patients had minimal increase in the WBC count (less than 1000/mm^3) and 30.77% with an increase of more than 5000/mm^3. Only 3 patients (11.54%) had a normal WBC count (*Table IV*) but most had an increased segmenter count (65.38%).

Morbidity and mortality. Five of the 26 patients expired with the cause of death attributed to sepsis. All of the five patients initially presented with sudden difficulty of breathing and were subsequently intubated and transferred to the ICU. None of the five had positive blood cultures. Three of these patients were initially given ceftazidime while the other two were given ceftazidime in combination with an aminoglycoside. Those started on ceftazidime were later shifted to piperacillin-tazobactam after the sensitivity report came out and there was still no clinical improvement. Isolates from all five patients was *K. pneumoniae.* The overall mortality rate was 19.23% (5/26) which is consistent with a study done by Greenway et al.[3]

Table V Sensitivity pattern of bacterial isolates from Non-Vented Adult Patient at Manila Doctors Hospital from January 1, 2002 to December 31, 2002

Antibiotic	*K. pneumoniae*		*E. coli*		*P. aeruginosa*	
	Sensitive	Resistant	Sensitive	Resistant	Sensitive	Resistant
Cefipime	12(85.71)	2	6 (85.71)	1		
Amikacin	9 (64.28)	5	6 (85.71)	1	4 (80)	1
Tazocin	9 (64.28)	5	5 (71.43)	2	4 (80)	1
Ceftazidime	5 (35.71)	9		7	1 (20)	4
Gentamycin	4 (28.57)	10	5 (71.43)	2	4 (80)	1
Meropenem	4 (28.57)	10		7		5
Imipenem	4 (28.57)	10		7		
Netilmycin	3 (21.43)	11		7		
Moxifloxacin	2 (14.28)	12		7		5
Co Amoxiclav	1 (7.14)	13		7		5
Ceftriaxone	1 (7.14)	13				5
Ampi-Sulbactam		14		7		5
Chloramphenicol		14		7		5
Gatofloxacin		14		7		
Cotrimoxazole		14		7		5
Cefuroxime		14				

The rest of the patients recovered and antibiotic therapy was given from 10 to 14 days.

Summary

Nosocomial pneumonia occurred most commonly in the seventh decade of life (61.53%) with an almost equal sex predilection (1.16:1). Twenty-three (86.06%) presented with two or more co-morbidities. The incubation period, for 58.85% of the patients, was more than four days and only 11.54% developed pneumonia within 48-60 hours of admission. The most common initial presenting symptom is productive cough (46.15%). Those who presented with sudden difficulty of breathing (23.08%) were all intubated. Upon diagnosis of nosocomial pneumonia, most patients (46.15%) were given piperacillin-tazobactam with a 100% cure rate. The predominant isolate was *K. pneumoniae* (53.85%). The three isolates *(Klebsiella, Escherichia* and *Pseudomonas)* had sensitivity only towards meropenem, imipenem, cefepime, piperacillin-tazobactam, amikacin and ceftazidime. Most patients (88.46%) had increased WBC count with 92.3% showing a predominance of segmenters. The overall mortality was 19.23%

Patients on the seventh decade of life presenting with two or more co-morbidities and those with hospitalization of more than four days have an increased chance of acquiring nosocomial pneumonia. Those presenting initially with sudden difficulty of breathing have a higher mortality rate (83.33%). Piperacillin-tazobactam seems to be an effective drug for nosocomial pneumonia.

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A meta-analysis on the effectiveness of fixed dose combination (FDC) therapy compared to separate drug therapy in the treatment of pulmonary tuberculosis

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Research Question Among newly diagnosed patients with pulmonary tuberculosis, how effective is fixed dose combination (FDC) therapy compared to separate drug therapy in terms of rate of cure, sputum AFB smear or culture conversion, completion of treatment and incidence of adverse events?

Background: The World Health Organization (WHO) and International Union against Tuberculosis and Lung Disease (IUALTD) have advocated the use of Fixed-Dose Combination (FDCs) in the treatment of tuberculosis because of the following potential benefits: (1) simplification of treatment, (2) simplification of drug supply management and (3) decrease emergence of drug resistance.

Objectives: To compare the effectiveness of FDC and separate drug therapy in the treatment of tuberculosis in terms of the following endpoints: (1) rate of sputum AFB smear and/ or TB culture conversion after 2 months of intensive phase, (2) rate of completion of treatment, (3) rate of cure defined as AFB smear and/ or TB culture negativity after treatment and (4) incidence of adverse events.

Inclusion Criteria: Randomized Controlled Trials (RCTs) , in English, in full text that compare FDCs and separate drugs in the treatment of pulmonary tuberculosis were included. Trials with patients 15 years or older, newly-diagnosed, sputum AFB smear and/ or TB culture positive before start of treatment were included. Endpoints of the studies should include those mentioned in the objectives.

Search Strategy: Literature search was done using the following search engines, databases and libraries from 1980 to June 2003: Cochrane Library, Medline Search, PubMed, MD Consult, Ovid Library, University of the Philippines College of Medicine Library, World Health Organization Library, Quezon Institute Library. Pharmaceutical companies with manufacturing FDCs were also asked for assistance in retrieving published and unpublished articles. Cross-references were checked from the initially retrieved trials and reviews.

Study Maneuvers: Full text versions of the studies were appraised by 3 independent reviewers. Differences were resolved by consensus. Quality assessment of the trials was performed using the Cochrane approach to allocation and concealment and the 5 point Jaded Scale.

Statistical Analysis: Data were analyzed using the Review Manager Version 4.2 software and were expressed as pooled odds ratio.

Results: Eight trials were identified, all of which were retrieved and appraised. Five studies were included in the meta-analysis. All included trials were Grade B as the manner of randomization were not fully disclosed. There was no significant differences in both treatment arms in terms of the following outcomes: (1) rate of completion of treatment with pooled OR 0.92 (0.61, 1.40), N = 864 patients, (2) rate of sputum AFB smear or TB culture conversion after 2 months with pooled OR 1.26 (0.87, 1.81), N = 1607 patients, (3) rate of sputum AFB smear or TB culture negativity at end of treatment with pooled OR 0.83 (0.41, 1.72), N = 791 patients, and (4) rate of interruption of treatment due to adverse drug reactions with pooled OR 0.80 (0.53, 1.22), N = 1798.

Conclusion: Based on the meta-analysis, there is lack of substantial evidence to assess whether FDCs are more effective than separate drugs in the treatment of pulmonary tuberculosis based on completion of treatment, sputum AFB smear or TB conversion after 2 months, sputum smear or TB culture negativity after treatment and incidence of adverse events.

Recommendation: Studies with larger populations comparing FDC therapy and separate drugs are needed. These should be based on standardized formulations and treatment protocols with emphasis on clinically relevant endpoints. *Philippine Journal of Chest Diseases. Vol. 12 No. 2 pp: 126-132*

Keywords: Pulmonary tuberculosis, therapy, FDC

Introduction

Pulmonary tuberculosis is almost always curable if patients are given sufficient uninterrupted therapy. Cure rates are estimated to range from 95-98% (Bastian et al. 2003). However, this disease continues to be a major health problem in many developing countries like the Philippines. Tuberculosis is consistently among the top five diseases causing morbidity and mortality in the country (Philippine Clinical Practice Guidelines 2000).

Based on the 1997 National Prevalence Survey, there are 200,000-600,000 infected individuals and about 75 Filipinos die of tuberculosis each day.

An emerging problem in the treatment of tuberculosis is the increasing incidence of multi-drug resistance (MDR-TB). In a study done at the University of the Philippines-Philippine General Hospital, a tertiary hospital and training institution, the rate of MDR-TB is 26% among 126 evaluated patients (Mendoza et al. 2003). MDR-TB is mainly due to poor patient compliance to intake of medications as well as improper and inadequate treatment practices of physicians (Mitchinson 1998). Efforts have been undertaken to address these problems. The first and the most effective strategy espoused by the World Health Organization (WHO) and International Union in Tuberculosis and Lung Disease (IUTLD) and adopted by the Philippine government is the Directly Observed Therapy Short Course (DOTS). Another strategy being recommended by the WHO and IUTLD is the use of fixed-dose combinations (FDCs) in the treatment of tuberculosis (Blomberg et al. 2001 and Laing and McGoldrick 2000).

In a meeting of experts and researchers organized by the WHO in 2001, the following potential advantages of FDCs were enumerated: (1) simplification of treatment, (2) simplification of drug supply management and (3) decrease emergence of drug resistance.

In the Philippine setting, the National Tuberculosis Program currently uses separate drugs available in blister packs. There have been anecdotal reports of problems in drug supply management and administration of anti-tuberculosis medications this formulation. This study aims to evaluate whether there is substantial evidence to adapt the use of FDCs locally because of the "alleged" potential advantages of these formulations as proposed by the WHO.

It is therefore the objective of this meta-analysis to search and critically appraise the relevant literature, in order to determine the strength of evidence on the effectiveness of fixed dose combination therapy compared to separate drug therapy in the treatment of pulmonary tuberculosis. The following endpoints will be compared as measures of effectiveness: (1) Rate of sputum AFB smear and/ or TB culture conversion after 2 months of intensive phase; (2) Rate of completion of treatment; (3) Rate of cure defined as AFB smear and/ or TB culture negativity after treatment; (4) Incidence of adverse events that caused discontinuation or modification of treatment.

Methodology

Criteria for considering studies for review:

Definitions used in the study: Fixed-dose combinations (FDCs) – defined as formulations of at least 3 of the first-line oral anti-tuberculosis agents (isoniazid, rifampicin, pyrazinamide and ethambutol) in one tablet or preparation. The dosing or number of tablets taken by the patient depends on actual body weight.

Directly Observed Therapy (DOT) – defined as administration of anti-tuberculosis drugs under the supervision of a health care personnel.

Cure – defined as sputum AFB smear and/ or tuberculosis culture negativity at the end of treatment.

Types of studies Articles that are parallel group studies, randomized controlled trials that compare FDCs with separate or individual drugs in the treatment of pulmonary tuberculosis were included. All articles included were written in English.

Types of participants. Newly-diagnosed cases of pulmonary tuberculosis, aged 15 years old and above, sputum AFB smear and/ or culture positive before start of treatment were included in the study.

Types of interventions. Studies comparing fixed-dose combinations (FDCs) and separate or individual drugs were included. The intensive phase of the included studies used at least 3 drugs for at least 2 months while the maintenance phase utilized at least 2 drugs for at least 4 months. Data from trials of continuous daily therapy and intermittent therapy as the manner of drug administration were combined. Trials utilizing directly observed therapy (DOT) and unsupervised treatment were analyzed together as well as separately.

Types of outcome measures. End points were mainly clinical, pertaining to compliance, clinical improvement, rate of sputum AFB smear and/ or TB culture conversion after 2 months, completion of therapy, cure, relapse and incidence of adverse events.

Search strategy:

Literature search was done using the following search engines, databases and libraries from 1980 to June 2003: Cochrane Library, Medline Search, PubMed, MD Consult, Ovid Library, University of the Philippines College of Medicine Library, World Health Organization Library, Quezon Institute Library. Pharmaceutical companies with manufacturing FDCs were also asked for assistance in retrieving published and unpublished articles. Cross-references were checked from the initially retrieved trials and reviews. The following

Table I. Methodological Quality of Included Studies:

	Randomized	Method of randomization described/ appropriate	Double Blind	Method of blinding described/ appropriate	Withdrawals/ drop-outs described
Gravendeel et al. 2003	Yes	Not stated	No	Not stated	Yes
Su and Perng 2002	Yes	Not stated	No	Not stated	Yes
Teo, 1999 Singapore Tuberculosis Service/ British Medical Research Council	Yes	Not stated	No	Not stated	Yes
Wolde et al. 1992	Yes	Not stated	No	Not stated	Yes
Hong Kong Chest Service/ British Medical Research Council 1991	Yes	Not stated	No	Not stated	Yes

Table II. Summary of Included Studies

Study ID	Methods	Participants	Interventions	Outcomes	Allocation Concealment
Gravendeel et al. 2003	Parallel group, Randomized1 6 centers Indonesia	New AFB smear positive patients, BW 33-50 kg 360 patients	DOT INTENSIVE PHASE NTP (National TB program) - 2HRZE separate drugs 4FDC - 2HRZE combination tabs CONTINUATION PHASE NTP – 4H3R3 4FDC – 4H3R3	Sputum AFB smear at start of study then 2, 5 and 6 months; Sputum conversion rate; Cure rate; Tx completion rate; Tx failure rate; Defaulter rate; Death rate; Adverse events; Follow-up until 3 years after end of Tx	Grade B; Manner of randomization not explained
Su and Perng 2002	Parallel group, Randomized; Taiwan	New AFB smear and/ or culture positive patients, 18 years old and above; 105 patients	Self-administered; **INTENSIVE PHASE;** Separate drugs – 2HRZE; Rifater+E – 2HRZE; **CONTINUATION PHASE;** Separate drugs – 4HRE; Rifinah+E – 4HRE;	Sputum AFB smear and culture, CXR at start of study ; Sputum AFB smear and culture monthly until end of Tx; Sputum conversion rate, radiographic improvement; Cure rate ; Tx failure rate; Tx completion rate; Relapse rate; Defaulter rate; Resistance rate; Adverse events; Follow-up until 1 year after end of Tx	Grade B; Manner of randomization not explained
Teo, 1999; Singapore Tuberculosis Service/ British Medical Research Council	Parallel group, Randomized Singapore	New AFB smear and/or culture positive, 15 years old and above; 310 patients	DOT; **INTENSIVE PHASE; 2 month-regimen;** 1) Separate drugs - 2SHRZ; 2) Rifater+S – 2SHRZ; 3) Separate drugs – 2HRZ; 4) Rifater – 2HRZ; **1 month-regimen;** 1) Separate drugs- 1SHRZ; 2) Rifater+S – 1SHRZ; **CONTINUATION PHASE;** 4H3R3 (for those given 2 month regimen in the intensive phase); 5H3R3 (for those given 1 month regimen in the intensive phase)	Sputum AFB smear and culture, CXR at start of study ; Sputum AFB smear and culture monthly until end of Tx ; CXR repeated 3, 6, 30, 60 months and if suspicion of relapse; Follow-up until 5 years after end of Tx; Sputum conversion rate; Cure rate ; Tx failure rate; Tx completion rate; Relapse rate; Tx interruption, Defaulter rate; Resistance rate ; Acceptability to patients; Adverse events	Grade B ; Manner of randomization not explained
Hong Kong Chest Service/ British Medical Research Council 1991	Parallel group, Randomized; Hong Kong	New AFB smear and/or culture positive, 15 years old and above; 1386 patients	DOT; Separate drugs; 6H3R32Z34S3; 6H3R34Z34S3; 6H3R36Z34S3; 6H3R36Z3noS; Combination (Rifater); Rifater+4S3 - 6H3R32Z34S3; Rifater+4S3 - 6H3R34Z34S3; 6H3R36Z34S3; 6H3R36Z3noS	Sputum AFB smear and culture, CXR at start of study ; Sputum AFB smear and culture monthly until end of Tx ; Follow-up until 5 years after end of Tx; Sputum conversion rate; Cure rate ; Tx failure rate; Tx completion rate; Relapse rate; Defaulter rate; Resistance rate; Acceptability to patients; Adverse events	Grade B ; Manner of randomization not explained
Wolde et al. 1992	Parallel group, Randomized; Ethiopia	New smear positive, 15 to 65 years old, no previous treatment	DOT for the first 2 months; Group A; 2S HRZ (Rifater)/ 6 TH (combined preparation); Group B; 2SHRZ/ 6 TH (separate preparations); Group C; 2SHRZ/ 4 TH (separate preparations); Group D; 2STH/ 10 TH (standard regimen)	Sputum AFB and culture before starting treatment, 2 months; Sputum AFB and culture; 12 month regimen - also done at 6,8,10,11,12 months; 8 month regimen - also done at 4,5,6,7,8 months; 6 month regimen – also done at 3,4,5,6 months; CXR before treatment	Grade B; Manner of randomization not explained;

;

search terms were used: Fixed-dose combination OR Fixed-drug combination OR Rifater, Myrin, Myrin-P AND Tuberculosis Pulmonary tuberculosis

Methods of Review:

The retrieved articles will be systematically reviewed. Full text versions of the retrieved studies were assessed separately by 3 independent reviewers in terms of quality and type of interventions. Differences were resolved by consensus. Quality assessment was graded

Table III Summary and Characteristics of Excluded Studies:

Punnotok et al. 1995	Parallel group, Randomized Thailand	New smear and/or culture positive, 15-60 years old, no previous treatment 199 patients	Unsupervised Group A 2HRZ (Rifater)/4HR (Rifinah) Group B 2HRZ (Rifater)+EMB/6HT	Sputum AFB smear and culture every 2nd week during the first 2 months, then monthly until end of treatment, the every 6 months until 36 months CXR 2 months, end of treatment, then every 6 months until 36 months Sputum conversion Radiological improvement Adverse events Relapse rate	Grade B Manner of randomization not explained **Reason for exclusion:** Fixed dose combination used in both treatment groups in the intensive phase
Cowie RL, BA Brink. 1990	Parallel group, Randomized	New smear and culture positive 150 patients	DOT HRZ (Rifater) – daily 5x/week for 90 doses HRZS (separate) – daily 5x/week for 90 doses	Follow-up 2, 5, 12 and 24 months after start of therapy Timing of repeat AFB and/or TB culture not stated	Use of random numbers table **Reason for exclusion:** Total treatment duration less than 6 months
Macnab et al. 1994	Parallel group randomized Cape Town, South Africa	New culture positive, 15 years old and above 319 patients	Rifater 5 days a week 130 doses HRZE (Schedule II) 5 days a week 130 doses	Sputum AFB and culture and sensitivity before treatment CXR before treatment After 90 doses – repeat CXR and TB CS After 130 doses – TB CS Treatment was discontinued if 90 dose culture result is negative Non-compliance rate Side effects	Odd numbers received Rifater, Even numbers received schedule II (separate drugs) **Reason for exclusion:** Total treatment duration less than 6 months

using the Cochrane approach to allocation concealment and the 5-point scale of Jadad. The data were pooled and analyzed using Review Manager Version 4.2.

Grading:

Grade A: adequate

Grade B: uncertain

Grade C: clearly inadequate

Five point scale of Jadad 1996:

Study was described as randomized (yes:1, no: 0)

Method of randomization was described and was appropriate (yes:1, no: -1)

Study was described as double blind (yes:1, no:0)

Method of blinding was described and was appropriate (yes:1, no:-1)

Description of withdrawals and drop outs stated (yes:1, no:0)

Results

A total of 8 studies comparing FDCs and separate drugs in the treatment of tuberculosis were identified. Among the 8 studies in English, five were included for final analysis while 3 were excluded. The included studies were of good quality with grade B. The method of randomization was not fully described in all the studies.

There were 4 outcomes pooled for analysis: (1) rate of completion of treatment, (2) rate of sputum AFB smear or TB culture conversion after 2 months of treatment, (3) rate of cure defined as sputum AFB smear or TB culture negativity at end of treatment, and (4) rate of interruption or modification of treatment due to adverse drug reactions. Other clinical endpoints such as relapse rate and resistance rate were not included because of insufficient data and definitions were varied among the studies.

Rate of completion of treatment. Four studies with a total of 864 patients showed data on completion of treatment. There was no significant difference between the groups with a pooled OR 0.92 (0.61, 1.40). There was significant heterogeneity (I^2 = 49.6%) which decreased as the study of Wolde et al was excluded. There was likewise no significant difference in both groups when the study using unsupervised therapy (Su and Perng) was excluded with a pooled OR 0.99 (0.61, 1.62), also showing significant heterogeneity (I^2 = 65.0%).

Rate of Sputum AFB and/ or TB culture conversion after 2 months. Five studies with a total of 1607 patients showed data on sputum AFB smear or TB culture conversion after 2 months. There data was homogeneous with no significant difference between the

groups with a pooled OR of 1.26 (0.87, 1.81). There was likewise no significant difference between treatment groups when the study with unsupervised or non-DOT therapy (Su and Perng) was excluded with a pooled OR 1.25 (0.86, 1.81), also showing homogeneous data.

Rate of cure defined as Sputum AFB smear or TB culture negativity at end of treatment. Four studies with a total of 791 patients showed data on AFB smear or TB culture negativity after treatment. There was no significant difference between the groups with a pooled OR of 0.83 (0.41, 1.72) with low level heterogeneity. There was likewise no significant difference when the study with unsupervised or non-DOT therapy (Su and Perng) was excluded with a pooled OR 0.95 (0.44, 2.01), also showing homogeneous data.

Rate of interruption or modification of treatment secondary to adverse drug reactions. In terms of discontinuation or modification of treatment due adverse reactions, 3 studies were included. There was no significant difference between the two groups with a pooled OR 0.80 (0.53, 1.22) with significant heterogeneity (I^2 = 45.6%). There was likewise no significant difference noted when the study with unsupervised or non-DOT therapy was excluded with a pooled OR 0.78 (0.51, 1.20), with significant heterogeneity (I^2 = 70.8%). The total number of patients analyzed was 1798.

Discussion

In 2001, the WHO organized a meeting of experts and researchers with particular knowledge of FDCs and TB control. The main objective was to accelerate the use of WHO recommended 4-drug fixed dose combinations (4FDCs) for TB control in both public and private health care sectors. It must be emphasized that the 4FDCs being recommended are those formulations with efficacy proven by standardized bioavailability studies. The strengths of FDCs and dosage schedules are presented in the Appendix B.

The WHO report (2001) stated 3 main reasons for recommending FDCs in the treatment of tuberculosis. First, FDCs simplify the delivery of treatment. FDCs reduce the number of tablets to be taken per day. This can potentially minimize prescription errors, increases patient and health care worker compliance and enable reduction of supervision. However, based on the dosing regimens, the number of tablets prescribed to a patient below 50 Kg may not vary considerably whether FDC or separate drug formulations are used. This advantage of reduction of tablets to be taken is more evident for patients more than 70 Kg.

Second, FDCs can simplify drug supply management in terms of calculating drug needs, ordering, procurement, distribution and storage of supplies. Third, FDCs can potentially decrease emergence of drug resistance by means of ensuring correct dosing of all drugs and by preventing monotherapy.

The potential advantages of FDCs can be measured indirectly by comparing effectiveness of FDCs and separate drugs. However, this meta-analysis was not able to give substantial evidence to fully recommend FDCs in terms of completion of treatment, sputum or TB culture conversion after intensive phase and at end of treatment, and incidence of adverse reactions. These clinical endpoints did not show statistically significant differences between the two treatment arms. This may be due to explained by 3 factors: 1) the pooled sample size of the studies may not have been sufficient, (2) the lack of standardization in both the quality, dosing and strength of the formulations used, and (3) the differences in the manner by which the drugs were administered. Only the latest study by Gravendeel et al (2003) that used the brand 4FDC was compliant with WHO recommendations for FDCs. The other studies used rifater as FDC also mentioned bioavailability studies but the dosing were varied.

In terms of drug administration, the study of Gravendeel et al (2003) was the only one that strictly followed the Five Element Directly Observed Therapy Short Strategy adopted by National Tuberculosis Programs. The trial of Su and Perng (2002) was carried out by unsupervised or self-administered therapy. The Hong Kong Chest Service/ British Medical Research Council (1992) study was the only trial that employed intermittent therapy even in the intensive phase. When the non-DOT study (Su and Perng 2002) was excluded, pooled data of the trials done under DOT still did not show significant differences between FDC and separate drugs.

At this point, it should be emphasized that the Five Element DOTS strategy is still the most important and cost-effective tool at hand for control of tuberculosis as supported by high cure rates as the main clinical endpoint (WHO Treatment of Tuberculosis: Guidelines for National Programmes. 2nd edition. 1997). Presently, the role or FDCs remains unclear if clinical end points are solely taken into account, but its benefit maybe in terms of the public health perspective or administrative issues on drug supply management.

Conclusion

Based on the meta-analysis, there is lack of substantial evidence to assess whether FDCs are more effective than separate drugs in the treatment of pulmonary tuberculosis based on completion of treatment, sputum AFB smear or TB conversion after 2 months, sputum smear or TB culture negativity after treatment and incidence of adverse events.

Limitations of the study

1) Non-English studies were not included in the meta-analysis as these could not be adequately appraised by the authors. During the literature search, a total of 6 non-English articles were identified comparing FDCs and separate drugs in the treatment of tuberculosis.

2) Some data on the desired clinical endpoints from the included studies were not presented clearly such that these could not be included in the meta-analysis.

Recommendation

Studies with larger populations comparing FDC therapy and separate drugs are needed. These should be based on standardized formulations and treatment protocols with emphasis on clinically relevant endpoints.

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Appendix A

Table 1 The recommended strengths of fixed-dose combination formulations of essential anti-tuberculosis drugs (WHO Model List of Essential Drugs, 1999)

For Daily Use		
Drugs	Form	Strengths
RHZE	Tablet	R 150mg + H 75mg + Z 400mg + E 275mg
RHZ	Tablet	R 150mg + H 75mg + Z 400mg
RHZ		R 60mg + H 30mg + Z 150mg (paediatric)
RH	Tablet	R 300mg + H 150mg
RH		R 150mg + H 75mg
RH		R 60mg + H 30mg (paediatric)
EH	Tablet	H 150mg + E 400mg
TH	Tablet	T 50mg + H 100mg
TH		T 150mg + H 300mg
For intermittent use 3 times weekly		
RHZ	Tablet	R 150mg + H 150 + Z 500mg
RH	Tablet	R 150mg + H 150mg
RH		R 60mg + H 60mg (paediatric)

E= etahmbutol, H= isoniazid, R= rifampicin, S= streptomycin, T= Thiacetazone, Z= pyrazinamide

Table 2 Dosage schedule for FDCs of WHO recommended strengths for adults*

Patient's body weight (kg)	Initial phase 2 months			Continuation phase 4 months		
	RHZE Daily 150mg + 75mg + 400mg + 275mg	RHZ Daily 150mg + 75mg + 400mg	RHZ 3x/wekk 150mg + 150mg + 500mg	RH Daily 150mg + 75mg	RH 3x/week 150mg + 150mg	HE daily 150mg + 400mg
30-37	2	2	2	2	2	1.5
38-54+	3	3	3	3	3	2
55-70+	4	4	4	4	4	3
71 and more	5	5		5	5	3

* R= rifampicin, H= isoniazid, Z= pyrazinamide, E= ethambutol

+ The composition of the 4FDC also ensures adequate doses of the drugs when 50kg is chosen as cut-off point for changing between 3 and 4 tablets per day.