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Aspergillus in the Lung: The Spectrum of Diseases

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The infection caused by fungi associated with high mortality and morbidity rates. The frequency of pulmonary fungal infection is increasing over the past decades with the development of immuno-suppressed therapy, solid organ transplantation, steroid application and HIV-infection. Fungi causes the pulmonary infection include Candida, Cryptococcus, Aspergillus and others relatively uncommon fungus.[1] Although the treatment is difficult, but the results are encouraging. Hence, this is a need of today to know these diseases well so that we are able to manage them scientifically.

Aspergillosis is a mycotic disease caused by Aspergillus species, a genus of ubiquitous soil fungi. Although exposure to Aspergillus conidia through inhalation is common, only a minority of those exposed develop lung disease. The clinical features, course and prognosis of Aspergillus infections are largely depend on the host immune response and the number and virulence of the organisms.[2, 3]

Pulmonary aspergillosis can be subdivided into five categories: (a) saprophytic aspergillosis (aspergilloma), (b) hypersensitivity reaction (allergic bronchopulmonary aspergillosis), (c) tracheobronchial aspergillosis (d) chronic pulmonary aspergillosis, and (e) angioinvasive aspergillosis.

Saprophytic aspergillosis (aspergilloma) is an Aspergillus infection without tissue invasion. It consists of conglomeration of intertwined fungal hyphae admixed with mucus and cellular debris within a preexistent pulmonary cavity.[4] The common underlying causes are tuberculosis, cystic fibrosis and sarcoidosis. The most common clinical presentation of aspergilloma is hemoptysis, although patients may remain asymptomatic. On imaging, aspergilloma are characterized by the presence of a solid, round or oval mass with soft-tissue opacity within a lung cavity. Usually the mass is separated from the wall of the cavity by airspace of variable size and shape, and present as “air crescent” sign. Surgical resection is indicated for patients with severe life-threatening hemoptysis, and selective bronchial artery embolization can be performed in those with poor lung function.

In this issue of Journal Baseer and colleagues present their 12 years’ experience of surgical management of aspergilloma with excellent results with different surgical techniques. They also nicely review literature on this disease modality.

Allergic bronchopulmonary aspergillosis (ABPA) is caused by a complex hypersensitivity reaction to Aspergillus. ABPA is seen most commonly in patients with long-standing bronchial asthma. ABPA is characterized by the presence of plugs of inspissated mucus containing Aspergillus organisms and eosinophils. This results in bronchial dilatation and bronchiectasis in segmental and sub segmental bronchi. Patients usually cough up thick mucus plugs in which hyphal fragments can be demonstrated at culture or histologic analysis. Common clinical presentations include recurrent wheezing, malaise with low-grade fever, cough, sputum production, and a history of recurrent pneumonia. Radiologic manifestations include homogeneous, tubular, finger-in-glove areas of increased opacity in a bronchial distribution, usually predominantly involving the upper lobe and can migrate from one region to another. Treatment of ABPA aims to prevent progressive bronchiectasis. Corticosteroids are the main stay of treatment for several weeks or months. Iatraconaazole is used in patients with frequent exacerbations and to reduce the fungal burden and steroid dependence.[5]

Chronic Pulmonary Aspergillosis (CPA) has various patterns of presentation. Semi-invasive aspergillosis (SIA), also known as chronic necrotizing aspergillosis, is one of the commonest forms and characterized by the presence of tissue necrosis and granulomatous inflammation similar to that seen in reactivation of tuberculosis. Factors associated with the development

of this form of aspergillosis include diabetes mellitus, malnutrition, alcoholism, prolonged corticosteroid therapy, and chronic obstructive pulmonary disease.[3, 6] Another, more common pattern is chronic cavitary pulmonary aspergillosis (CCPA), characterized by slowly evolving, single or multiple lung cavities, usually with thick walls and with pleural fibrosis. In some cases of CCPA extensive pulmonary fibrosis may develop. These patients are classified as chronic fibrosing pulmonary aspergillosis.[3]

Clinical presentations of CPA are often insidious and include chronic cough, sputum production, fever, and constitutional symptoms. Management of patients with CPA is complicated and Azoles are the initial choice of treatment. Itraconazole, voriconazole and posaconazole can be used. The duration of treatment is usually prolong and associated with side effects of drugs. The relapse rate is also high in this form of aspergillosis.[3, 7]

Angioinvasive aspergillosis usually occurs in immunocompromised patients with severe neutropenia. The clinical diagnosis is difficult, and the mortality rate is high. Angioinvasive aspergillosis is characterized by the invasion and occlusion of small to medium-sized pulmonary arteries by fungal hyphae. This leads to the formation of necrotic hemorrhagic nodules or pleura-based, wedge-shaped hemorrhagic infarcts. Characteristic CT findings consist of nodules surrounded by a halo of ground-glass attenuation known as “halo sign” or pleura-based, wedge-shaped areas of consolidation.[8] Definite diagnosis is usually based on fungal culture, galactomannan, or PCR in blood and respiratory samples and on histopathology. Respiratory samples are better than blood for all tests except β-D-glucan. Voriconazole is the treatment of choice and has a significant mortality benefit. Duration of treatment in non-neutropenic patient is minimum of 12 weeks.[9]

Tracheobronchial aspergillosis or Aspergillus bronchitis is a less common form of aspergillosis and usually present in immunocompetent patients. These patients usually present with recurrent chest infections unsuccessfully managed with antibiotics and repeated isolation of Aspergillus from sputum or BAL and positive PCR but without pulmonary parenchymal disease.[3,10] They respond well to antifungals, but relapses are common.

In summary, the spectrum of disease caused by Aspergillus in the lung is wide, ranging from aspergilloma to invasive aspergillosis and can be viewed as a continuous spectrum of disease. The manifestations are depending on interaction between fungus and host. A broad knowledge of clinical presentation and high suspicion are required for timely diagnosis and treatment of aspergillus related lung diseases.

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MODS ASSAY FOR RAPID DIAGNOSIS OF TUBERCULOSIS AMONG HIV TB CO INFECTED INDIVIDUALS IN A TERTIARY CARE HOSPITAL, ANDHRA PRADESH.

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ABSTRACT

BACKGROUND: Rapid, reliable, economical methods are required for diagnosis of tuberculosis. The Microscopic Observation of Drug Susceptibility (MODS) assay is a relatively low-cost and simple liquid culture method. The objective of this study is to determine the sensitivity and specificity of MODS test in comparison to the Lowenstein- Jensen medium to diagnose tuberculosis among HIV seropositive individuals in GSL Medical College.

METHODS: Sputum specimens were evaluated using smear microscopy, culture on Lowenstein-Jensen medium and MODS assay. A study subject is considered to have tuberculosis if at least 1 culture on Lowenstein- Jensen medium or MODS technique showed growth for M. tuberculosis.

RESULTS: Spot Morning sputum samples were obtained from 873 HIV seropositive individuals. Two hundred and ninety seven (34%) [95% CI=30.8 – 37.2] patients were culture positive by MODS and 277 (32%) [95% CI=28.7 – 34.9] were culture positive on LJ slopes (P < 0.001). MODS sensitivity was 99.3% and specificity was 96.3%. Mean times for TB detection were 21 days (range 15 – 25 days) and 12 days (range 7- 15 days) for culture on Lowenstein-Jensen medium and MODS (including drug susceptible testing) respectively (P<0.001). Culture contamination was low in MODS assay than culture on Lowenstein-Jensen medium (1.35 vs. 15.6%; P<0.001). Drug resistance was 12.6% for both RIF and INH, 12.6 % for RIF and 15% for INH.

CONCLUSIONS: The MODS assay is a relatively simple test whose good performance for detection of pulmonary tuberculosis in HIV patients may make it suitable for resource-limited environments.

KEY WORDS: Tuberculosis, Sputum smear, HIV, MOD

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Introduction:

In India, ~ 5% of tuberculosis (TB) patients registered under Revised National tuberculosis Control Program (RNTCP) are co-infected with HIV. [1] The existence of HIV and TB together, greatly amplifies harmful effects of each other at individual level and contribute substantially to mortality among patients living with HIV (PLHIV). [2] The risk of developing TB is estimated to be between 20-37 times greater in PLHIV than among those without HIV infection.[3] Inadequate treatment, default behavior further result in Drug Resistance (DR) TB, HIV is one of the main predisposing factors.

Well equipped clinical laboratories can detect Mycobacterium tuberculosis (MTB) within 7-14 days, using sophisticated liquid culture systems such as BACTEC and Mycobacterium Growth Indicator Tubes (MGITs).[3,4] In most of the developing countries TB laboratories lack sophisticated, costly equipment and skilled technicians. Though ZN staining is a rapid test, sensitivity is relatively low, require about ten thousand bacilli per ml of the specimen.[5, 6] In half of the HIV TB patients sputum smears are negative for Acid Fast Bacilli (AFB) by ZN staining.[7, 8] This is the major limitation of ZN staining in PLHIV.

Most of the laboratories in developing countries use solid media such as Lowenstein Jensen (LJ). Under optimum conditions TB diagnosis takes 4 weeks and drug

susceptibility test (DST) takes additional 3 to 4 weeks using LJ medium.[9] To detect the TB rapid molecular tests like line probe assay have been developed.[10, 11] These molecular diagnostic tests are rapid and highly accurate. But cost, expertise and infrastructure are the major obstacles to offer these tests. Mycobacterium growth is more rapid in liquid medium as strings and tangles.[12] Based on this a new, rapid, reliable, inexpensive method[13-16] namely Microscopic Observation of Drug Susceptibility (MODS) is devised, which permits MTB detection and drug susceptibility in less than 2 weeks.

Hence in the current study the diagnosis and DST of TB in HIV patients is done by MODS and culture results are compared with gold standard LJ.

MATERIAL AND METHODS

The study was conducted from March 2009 to December 2013, in the department of Microbiology, GSL Medical College, Rajahmundry. Study was approved by the Institutional Research and Ethics committee. Study included PLHIV with clinical suspicion suggestive of TB. Children with HIV aged below 14 years, individuals who refused to give two consecutive samples of sputum and HIV sero negative individuals were excluded from the study. An informed written consent in the presence of witness was taken from all the volunteers who participated in the study. Sputum samples were collected from HIV sero-positive individuals by Spot Morning (SM) scheme.[18]

All the volunteers were explained regarding the importance of submission of good quality sputum sample. The visual difference between the sputum and saliva and the procedure for production of good quality sputum sample was demonstrated.[17] After collection of spot sample, the individuals were provided with pre labeled sample containers for collection of morning samples. Immediately after collection, sputum smears were prepared on new glass slide and were stained by ZN technique as per RNTCP guidelines.[18]

After smear preparation, decontamination and concentration of the sputum samples was done by standard N-acetyl -L-cysteine- Sodium hydroxide method.[19] Specimen with equal parts of N-acetyl-L-cysteine- Sodium hydroxide solution, mixed for 15 seconds on vertex mixture. Then enough phosphate buffer saline was added to reach within 1cm of the top of the test tube, cap was closed tightly and inverted to mix the solution. Then it was centrifuged at 3600xg for 15minutes. The supernatant was decanted and sediment was suspended in to 2ml of Middlebrook 7H9 broth.

New, sterile flat bottom 24 well microtitre plates were used to test three sputum samples (eight wells per sample) by MODS technique. Five hundred and fourty ml of sputum medium solution was placed into each of four micro wells. Sixty ml of each drug solutions were added. The final drug concentrations are as follows:

a. Isoniazid (INH): 0.4& 0.1 mg/ml

b. Rifampcin (RIF): 1 & 0.5 mg/ml

In the remaining four wells first two were filled with sputum media mixture, acts as drug free control. In the other two wells, one was filled with media, this act as sterilization control. The last well was filled with known drug sensitive strain of MTB, by standardizing the turbidity with 0.5 Mc Farlands standard. Plates were sealed with scotch polyethylene tape, incubated at 37°C. Every day (except on Sundays and public holidays) wells were examined for the presence of MTB under an inverted light microscope under 40X objective.

A drop of processed sputum sample was also inoculated in blood agar and another drop was inoculated in Sabourauds Dextrose Agar. These were incubated at 37°C. If any bacteria or fungal growth was observed, another sample was collected from patient. Simultaneously samples were inoculated in LJ slopes, incubated at 37°C for 3 – 4 weeks. Regular decontamination of incubators was followed to avoid contamination of cultures.

Presence of pink colored bacilli in the ZN staining indicates sputum sample is positive for AFB. Presence of growth in microtiter well containing sputum media mixture was considered as TB positive. Individual was considered as non TB, if growth is absent in media sample containing well. Presence of growth in all the four drug containing wells (two RIF wells and two INH wells) along with media sample wells indicates DR. Presence of growth in drug free wells and absence in drug containing wells indicates that the clinical sample is TB positive and drug sensitive. LJ Media was home made.

Statistical methods:

Data were analyzed using of SPSS v. 16 (SPSS Inc., Chicago, IL, USA), with the patient as the unit of analysis. The Wilcoxon signed-rank test was used to compare the times to each end point among the two methods. A P value of less than 0.05 was used to indicate statistical significance. The concordance of susceptibility results was determined with the use of the sensitivity, specificity, and positive and negative predictive values for the detection of resistance (with 95% confidence intervals [CIs]). For sensitivity and speci-

ficity of detection and predictive-value calculations for each of the two methods, a positive reference result was defined as a positive culture according to at least one method for which cross-contamination had been conclusively ruled out. A negative reference result was defined as any sample in which both the culture methods yielded negative results. McNemar's $\chi 2$ test was used to compare the sensitivities of detection of the two methods.

RESULTS

During the study period a total of 873 patient's sputum samples were processed by both MODS and LJ slant techniques. Two hundred and ninety seven (34%) [95% CI= 30.8 – 37.2] patients were culture positive by MODS and 277 (32%) [95% CI= 28.7 – 34.9] were culture positive on LJ slopes (P<0.001) (Table 1). MODS sensitivity was 99.3% and specificity was 96.3% compared to the LJ slope as standard technique (P<0.001). Mean times for TB detection were 21 days (range 15–25 days) and 12 days (range 7- 15 days) for culture on LJ medium and MODS (including drug susceptible testing) respectively (P<0.001) (Table 1). The percentage of contaminated cultures was lower for the MODS assay than culture on LJ medium (1.35 vs. 15.6; P<0.001) (Table 2). Out of 297 MODS positivity, DR was 12.6% for both RIF & INH, 12.6% and 15% were resistant to RIF and INH respectively (Table 2). The recurring expenditures were Rs: 340/-, 120/- and 30/- respectively for MODS, LJ and ZN staining.

DISCUSSION:

In spite of the disadvantages like inability to detect DR, limited utility to diagnose TB in HIV individuals, sputum smear microscopy (ssm) is the only diagnostic method in the developing countries like India.[20] In a study by Ingred V et al[21] the sputum smear positivity was 9% among HIV seropositive individuals. Whereas in the current study 8.6% of HIV patients sputum smears were positive for TB. Simon waliusimbi et al in the meta analysis study on MODS stated that substantial proportion (35%) of TB cases were smear negative.[22]

Currently culture on solid media is the only feasible method for confirmed diagnosis of TB in developing countries. But MTB growth is rapid in liquid media than solid media. In liquid media MTB growth was observed in 7 to 15 days. On solid media MTB growth was observed in 15 to 27 days. As per the available literature, the average time period required to declare MODS results were 10 -12 days, in the current study it is 12 days. During this time period 30% of sputum samples only showed positive results on LJ slants and DST require additional time. This helps in large reduction of time, space and infrastructure in the laboratory. Early initiation of treatment is the major advantage of this method.

Table1: Sensitivity and specificity of MODS for TB diagnosis

		LJ culture		
		Positive	Negative	Total
MODS culture	Positive	275	22	297
	Negative	2	574	576
	Total	**277**	**296**	**873**

Sensitivity – 99.3%; 95% CI=0.989-0.996
Specificity – 96.3%; 95% CI=0.957-0.968
Positive Predictive Value (PPV) – 92.6%; 95% CI=0.915-0.936
Negative Predictive Value (NPV) – 99.7%; 95% CI=0.994-0.998

Table 2: Culture positivity cum contaminations

Variable	MODS				LJ-Medium				
	Pos	Tot	Prop	CI	Pos	Tot	Prop	CI	P
Culture	297	873	34.0	30.8 - 7.2	277	873	31.7	30.8 -37.2	0.001
Contamination	4	873	0.5	0.02-0.82	43	873	4.9	3.47 – 6.33	0.001
Median time to detection	12 (Inter Quartile Range=11.5 to 13.00); Standard Devination-2.99				21 (Inter Quartile Range=18 -31) Standard Devination-11				0.001

Pos: Positive
Tot: Total
Prop:Propotion
Cont: Contamination
CI: Confidence Interval
TAT: Turnaround Time

As per the Moore et al study,[15] the diagnostic yield of single sputum sample among the patients suspected with TB was 37%, 80% and 89% respectively for smear microscopy, LJ & MODS and with second sample the additional use is 11.6%, 7.5% and 8.2% respectively. In HIV patients, with single sputum sample diagnostic yield of PT was 42.9%, 78.6% and 92.9% and the incremental yield was 3.6%, 3.6% and 3.6% with second sputum sample respectively for sputum smear, LJ and MODS. In the current study the diagnostic yield of ssm was 7.9%, 8.6% respectively for spot and morning samples. Due to limited resources single sputum sample was only processed for culture.

In a meta analysis study by Jessica Minion et al,[23] DST of MODS has a sensitivity of 98% (95% CI 94·5 - 99·3), specificity 99·4% (95·7 - 99·9) for RIF resistance. For INH resistance, pooled sensitivity was 97·7% (94·4 - 99·1) and pooled specificity was 95·8% (88·1 - 98·6). In the current study, due to limited resources DST was not performed on LJ media. This could be the limitation of the current study.

In a study by Lazarnu[24] the authors reported that MODS is 94.12% sensitive and 89.39% specific when compared with LJ media and the concordance with DST by the proportion method on LJ media to RIF & INH was 91.5% & 90.8% respectively. In one of the south Indian studies on MODS assay for detecting TB among HIV individuals, the overall sensitivity and specificity was 89.1% & 99.1%. In the diagnosis of DR TB, MODS was 84.2% sensitive and the authors also reported that MODS has 87% and 100% sensitivity for INH and RIF mono resistant.[25]

In another south Indian study MODS was reported to be 78.9% sensitive and 96.7% specific and the authors also coated that the true positivity in 4/6 reference culture negative MODS positives.[26] Kashmira Limaye et al studied MODS on sputum smear positive TB cases and the investigators declared that culture positivity was 100% for both MODS assay as well as LJ medium.[27] In this study among sputum smear positive cases the sensitivity is 100% for MODS as well as LJ media.

In a study by Reddy etal [28] MODS test had 100% sensitivity to detect TB among HIV patients. In the current study MODS sensitivity is 99%. So MODS could be used as a diagnostic test to detect TB in HIV sero positive patients.

Culture contamination was low in MODS assay, compared to LJ. In the current study contamination rate was 1.35 vs 15.6% for MODS and LJ media respectively. In a study by Reddy et al[28] culture contamination was 7.3% vs 22% respectively for MODS and LJ.

Cord formation in MODS can be recognized more easily and rapidly than a ZN smear. With 2 weeks training, one can read MODS cultures easily. But DST on LJ may take several months of training. The other available rapid culture systems require computer attached incubators, in addition to the standard equipment. But MODS culture requires just an inverted microscope.

The recurring expenditure for MODS technique (both culture & DST) is 3 times more compared to LJ culture and 10 times high compared to ZN smears. So MODS is relatively expensive than the present routine techniques under the RNTCP conditions; Early detection and treatment would prevent spread of infection which is estimated to be 10 - 15 individuals per year per open case.[29] Due to misdiagnosis spread of PT can occur, for which national TB control programmes (NTPs) have to spend significant amount of money for anti TB treatment in the form of DOTS / DOTS plus. When compared to this, the expenditure on MODS is negligible.

Limitation of this study is that due to limited resources only one set of LJ media was used which deviation from the RNTCP rule. Another point is high contamination rate of LJ media but this is possibly due to long incubation period of this media.

CONCLUSION:

To conclude MODS test is rapid, economical, require minimum infrastructure, less contamination and the cord formation is read very easily than ZN smear. Like molecular techniques, MODS do not require any sophisticated equipment or skilled person, except biohazard safety cabinet and an inverted microscope. So, MODS is suggested as alternative method for the diagnosis of TB and DST in HIV patients.

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FACTORS DETERMINING THE DIAGNOSTIC YIELD OF CT-GUIDED CORE NEEDLE BIOPSY OF LUNG NODULES

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ABSTRACT

OBJECTIVE: The purpose of the study is to identify the factors determining the diagnostic yield of CT guided core needle biopsy of lung nodules.

MATERIALS AND METHODS: This study was conducted on 46 patients (from January to October 2013), who underwent CT guided core needle biopsy in the department of Radiology. All the patients were referred from Pulmonology, Medicine, and Cardiothoracic units of Lady Reading Hospital Peshawar that is a 1400 bedded tertiary care hospital of the province.

RESULTS: Amongst 46 patients, final diagnoses were twenty-three malignant lesions and fifteen benign lesions. The size of the mass was a significant factor contributing to diagnostic yield. Greater the size of the mass, the higher was the chances of yield. Lesions with a size between 1-2 cm., the yield were 87.9%, for lesions with a size between 2.1-3 cm., the yield was 86.7%, and beyond 3 cm., the yield was 100%. Ten patients developed small pneumothorax after the procedure.

CONCLUSION: Lesion size was a determining factor in diagnostic yield of CT guided core needle biopsy. Diagnostic yield increases with the increase in the lesion's size.

KEY WORDS: Lung nodules, CT guided core needle biopsy

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INTRODUCTION

Transthoracic CT-guided percutaneous fine-needle biopsy has been a reliable means of differentiating benign and malignant pulmonary lesions. Success rates have been well documented, with diagnostic accuracy rates in excess of 93%and sensitivity rates in excess of 95%.[1, 2] Aside from pneumothorax (16.0%–44.6%), reported complications are uncommon for image-guided fine needle aspiration biopsy[3]. Successful biopsy of lesions as small as 3 mm in diameter has been reported.[4]

As imaging techniques and technology advance our ability to detect smaller lesions, our definition of small pulmonary nodules continues to change. This results in increased demand for sampling lesions 1.0 cm or smaller. These lesions are usually difficult to detect with fluoroscopy and typically require computed tomography (CT) to guide any biopsy attempt. On rare occasions, pleural-based lesions can be identified and biopsy performed with ultrasonographic guidance.[5] Investigators in several studies have reported a decline in the accuracy of percutaneous biopsy to less than 75% for lesions 1.0 cm or smaller.[6] Newer techniques with respiratory gating and CT fluoroscopy have been used to improve success rates.[7] This study is intended to identify the factors determining the diagnostic yield of such lesions in the department of Radiology of Lady Reading Hospital Peshawar with special emphasis over the size of lesion whether benign or malignant.

MATERIAL & METHODS

Forty-six CT guided core needle biopsies were performed in patients referred from Pulmonology, Medical and Cardiothoracic units of Lady Reading Hospital Peshawar from January to October 2013.

Toshiba Astion CT scanner scanned all the lesions and measurements were taken with the help of pulmonary windows. Depth of the lesion from the nearest skin surface was also measured. All biopsies were performed by consultant radiologists assisted by senior resident or another radiologist. The patient was placed in such a position to allow penetration of the lesion from the position closest to the skin surface. Laser lights were used for localization of lesions on the skin surface. All biopsies were done using 18 gauge core needle biopsy systems. The position of the needle tip

Table 1: (Age-wise distribution of participants in the study)

S. No	Ages (in years)	Number of participants	Percentage
1	28-45	6	13
2	46-65	25	54
3	66-83	15	33
Total		**46**	**100**

Table 2: (size of lesion and accuracy rate in the CT guided core needle biopsy)

Size of lesion	Success group	Failure group	Yield rate
1-2 cm	15	4	78.9 %
2.1-3 cm	13	2	86.7%
3.1-5 cm	5	0	100 %
5.1-7 cm	**2**	**0**	**100 %**

in the lesion was checked again on CT. All 46 biopsies were sent for histological examination.Upright postero-anterior expiratory chest radiographs were obtained immediately after biopsy in all patients.

RESULTS

The study included 28 men and 18 women. Mean age was 66 years (Ranging from 28-83 years and SD+_8.3). More than 50% of patients were in the age range of 46-65 years (Table-1). Regarding the size of lesions on CT scan, there were 7 lesions of 1-2 cm, 15 lesions 2.1-3cm, 17 lesions of 3.1-5cm, 07 lesions of 5.1-7cm. Final diagnoses were twenty-three malignant lesions and fifteen benign lesions. The size of the mass was a significant factor contributing to diagnostic yield. Greater the size of the mass, the higher was the chances of yield. Lesions with a size between 1-2 cm., the yield were 87.9%, for lesions with a size between 2.1-3 cm., the yield was 86.7%, and beyond 3 cm., the yield was 100% (Table-2). Post biopsy small pneumothorax occurred in 10 cases (22%) and post biopsy hemoptysis occurred in 01 case (2.2 %).

DISCUSSION

Computed Tomography is better than plan X-ray for detecting small pulmonary nodules. Once a nodule is detected the most important is to determine whether the lesion is malignant or benign. In this regards CT guided core needle biopsy is the best modality for conforming the diagnosis of pulmonary nodules. There are various factors determining the diagnostic yield of CT guided core needle biopsies of the lung nodules whether these are benign or malignant. In this study, nodule size was significant criteria (factor) for diagnostic yield in CT guided core needle biopsy of the lung. Diagnostic yield is increased with an increase in size[8]. In a series of CT guided aspiration biopsies, Van Sonnesbergreported diagnostic yield of 90% for lesion 3-4cm in size, 89.3% for lesion 2.1-3cm in size, 83.9% for lesions 1.1-2cm in size and 73.9% for lesion 0.3-1cm in diameter recognizing a decrease in diagnostic accuracy with decrease in size.[9]

Kaziroonireported that the presence of pneumothorax before the biopsy decreases diagnostic yield. It is due to the fact that pneumothorax with partial lung collapse displaces the lesion from the point of initial localization.[10]

Pulmonary lesion changes position with respiration. Thus patient`s cooperation is very crucial for core needle biopsy. Minimal movement or unstable respiration during biopsy causes the initial localization of the lesion inaccurate. If the lesion is under a rib, then patient cooperation is very important as reported by Moore.[11]

The experience of the physician performing the procedure must also be included when success rates are compared. Similarly, sub-pleural pulmonary nodules are often more challenging than deeper lesions. In the literature, factors discussed in relation to increased risk of pneumothorax include smaller lesion size, increasing lesion depth, number of passes, pleural surfaces crossed, and underlying lung disease.[12] Rizo et al. described a higher incidence of pneumothorax in smaller and deeper lesions on which biopsies were performed in 121 procedures, with a mean lesion diameter of 1.7 cm.[13] Our study revealed pneumothorax in 22% of cases, and are possiblythe result of these factors described.

CONCLUSION

The most important factors in predicting the diagnostic yield in pulmonary nodules are tumor size, pre-existing pneumothorax, preprocedural pulmonary

function tests and location of lesions. Our study is a small one but the first of its kind in the country to identify the factors, which will predict the success of the procedure. Similar studies are needed in other centers to increase the reliability of this procedure and identify some other yet unknown factors predicting the diagnostic yield of pulmonary lesions.

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12 YEARS EXPERIENCE OF SURGICAL MANAGEMENT OF PULMONARY ASPERGILLOMA

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ABSTRACT

OBJECTIVE: To analyze the results of surgery in the management of Pulmonary Aspergilloma.

METHODOLOGY: Computerized records of 450 cases of diagnosed Pulmonary Aspergilloma were retrospectively analyzed from Jan 2003 to May 2014. Patients of all ages, both sexes, medically fit and unilateral Pulmonary Aspergilloma were included in the study. Medically unfit and bilateral pulmonary aspergilloma were excluded from the study. Routine investigations, serology for aspergillus, sputum culture, Computed Tomography, Pulmonary Function Tests and Bronchoscopy were performed in all cases. Type of pulmonary resection done according to extent of the disease. All patients underwent preoperative anesthetic evaluation by anesthetist and one lung ventilation during surgery and specimen sent for histopathology in all cases.

RESULTS: Out of 450 patients, 255 patients were male and 195 were female, age ranges from 16 years to 70 years, mean age was 35.6 years. The most common symptom was hemoptysis (92%) followed by persistent chest pain (30.7%) and recurrent cough with sputum (23%). The most common underlying lung disease was tuberculosis in 407 (90.44%), whereas lung abscess was present in 42 (9.33%) and lung cancer in 1(.22%) case. Simple Mycetoma was observed in 22 (4.88%) cases whereas complex Mycetoma was diagnosed in 428 (95.11%) cases. The procedures performed were Lobectomy in 380 (84.44%) cases, Bilobectomy 36 (8%), wedge resection 22 (4.8%) and Pneumonectomy in 12 (2.66%) cases. Postoperative complications occurred in 32 (7.11%) patients, of which 15 (3.33%) had prolonged air leak, 4 (.88%) had significant postop bleeding out of which two required re-exploration, 2 (0.44%) patients developed Empyema and wound infection occurred in 11 (2.44%) patients. Mortality was 10 (2.2%) of which 09 patients died due to respiratory failure and one patient due to pulmonary embolism.

CONCLUSION: Even surgical resection for complex aspergilloma can be done with low morbidity and mortality rate in a high volume center with harmonic and intercostal muscle flap utilization.

KEYWORDS: Pulmonary Aspergilloma, Tuberculosis, Surgery.

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INTRODUCTION

Pulmonary aspergilloma, the so-called fungus ball or mycetoma, refers to colonization of pre-existing lung cavities with the Aspergillus fungus, most commonly the fumigatus species, and the lesion itself consists of a tangled mass of fungal hyphae, fibrin, epithelial cells, mucus, debris and blood cells.[1,2] Tubercular lesions are the most common cause of such cavities although aspergillomas may occur within cavities of diverse etiologies including lung abscesses, bronchiectasis, cysts and bullae, necrotic malignant cavities, pleural spaces.[3,4] Other rare etiologies include ankylosing spondylitis, Wegener's granulomatosis, and pulmonary infarction.[5-8]

Clinical spectrum of this pathology ranges from an incidental radiologic finding to life threatening hemoptysis. Several mechanisms for hemoptysis have been proposed including erosion of vascular cyst wall, elaboration of endotoxin, Fibrinolytic substance produced by aspergillus micelles induces caseous necrosis of tissues, and this is the cause of haemoptysis by the fungus and the patient's underlying disease.[3-8] As pul-

monary Aspergilloma may cause life-threatening hemoptysis, the disease has been brought to the attention of chest physicians and thoracic surgeons.

Medical treatment has little role in the management and surgery offers significant benefit for the patient diagnosed with pulmonary aspergilloma. However, high mortality and morbidity rates of the operation have been reported in literature.[5,9,10] Surgery of aspergilloma has been known to be a technical challenge because of its high intra- and postoperative complication rate.[11,12] Patients with the so-called simple aspergilloma (thin-walled cavity; no parenchymal/pleural disease) are offered surgical treatment liberally because operation carries low risk. However, surgical resection for complex aspergilloma (thick-walled cavity; associated parenchymal/pleural disease) carries significant morbidity and mortality rates [13] which must be weighed against the clinical benefits. In particular, notoriously high morbidity rates have been reported when patients with complex aspergilloma undergo a Pneumonectomy.

The purpose of the present study is to analyze the results of open surgery in the management of Pulmonary Aspergilloma.

METHODOLOGY:

Computerized records of 450 cases of diagnosed Pulmonary Aspergilloma were retrospectively analyzed from Jan 2003 to May 2014. Patients of all ages, both sexes, medically fit and unilateral Pulmonary Aspergilloma were included in the study. The most common symptom was hemoptysis (92%) followed by persistent chest pain (30.7%) and recurrent cough with sputum (23%).Routine investigations, serology for aspergillus, sputum culture, Computed Tomography, Pulmonary Function Tests and Bronchoscopy were performed in all cases. Specimen sent for histopathology in all cases.

Procedure: The surgery was performed under general anesthesia e one lung ventilation via the use of a double-lumen endobronchial tube. The chest was opened via a posterolateral thoracotomy. Pleural space was often obliterated with fibrous and vascular adhesions. Lung was mobilized by extra pleural dissection; avoiding entry to the infected cavity Harmonic scalpel was used to dissect adhesions to minimize the blood loss. Bleeding from the chest wall was checked and stopped .Lung was visualized for the diseased areas and surgical resections done in the form of wedge resection.lobectomy, bilobectomy or pneumonectomy with the aim to preserve healthy lung as much as possible with complete resection of the mycetoma cavity. The extent of lung resection was determined by the amount of involvement by the aspergilloma and the degree of lung function. At the end of surgery, bronchial stump was checked for any air leak. Pleural flap /intercostals muscle flaps were used to prevent Bronchopleural fistulas .Two Chest Drains (apical and basal) were kept in the pleural cavity in cases of wedge resection, lobectomy and bilobectomy while single basal drain were kept in cases of pnemonectomies. Chest cavity was closed in two layer with Vicryl 2. All patients were put on low pressure suction to avoid air space problem post operatively. Patients were encouraged to have incentive spirometry, physio therapy postoperatively with judious use of analgesia.

RESULTS:

Out of 450 patients, 255 patients were male and 195 were female, age ranges from 16 years to 70 years, mean age was 35.6 years. The most common symptom was hemoptysis (92%) followed by persistent chest pain (30.7%) and recurrent cough with sputum (23%). The most common underlying lung disease was tuberculosis in 407 (90.44%), whereas lung abscess was present in 42 (9.33%) and lung cancer in 1(.22%) case. Simple Mycetoma was observed in 22 (4.88%) whereas complex Mycetoma was diagnosed in 428 (95.11%) cases. The procedures performed were Lobectomy in 380 (84.44%) cases, Bilobectomy 36 (8%),wedge resection 22 (4.8%) and Pneumonectomy in 12 (2.66%) cases.Postoperative complications occurred in 32 (7.11%) patients, of which 15 (3.33%) had prolonged air leak, 4 (.88%) had significant postop bleeding out of which two required re-exploration, 2 (0.44%) patients developed Empyema and wound infection occurred in 11 (2.44%) patients. Mortality was 10 (2.2%) of which 09 patients died due to respiratory failure and one patient due to pulmonary embolism.

DISCUSSION:

Pulmonary aspergilloma is an opportunist infection of the lung complicating necrotic cavitary lesions.Soubani, Regnard, and Lin et al pointed out that fungi grow in a pre-existing cavity, either in the lung or a dilated bronchus. Patients with aspergilloma are usually non typical and have chronic underlying lung diseases including advanced tuberculosis, bronchiectasis, interstitial fibrosis or emphysema, solid or cavitating neoplasm, abscess cavity containing necrotic tissue.[17-19]

Tuberculosis is the most common underlying disease which ranges from 50% to 90% of the patients.[1-3, 8, 13] In our series, we found that open healed tuberculosis cavity contributed 90.44% of the patients. The British Thoracic and Tuberculosis Association reported 6% of patients with open healed tuberculous cavity developing an aspergilloma within three years.[20]

The high mortality from aspergilloma is related to the underlying disease and to the frequent occurrence

of hemoptysis.As pulmonary aspergilloma may cause life-threatening hemoptysis, symptomatic patients with aspergilloma are deemed candidates for therapy.[10] Efficacy of medical treatment for aspergilloma is still limited, and definitive treatment is surgical removal of the affected lung.[14]

Belcher and Plummer[15] divided aspergilloma into two groups: simple aspergilloma and complex aspergilloma, according to the nature and extent of the underlying disease of the lung. Simple aspergilloma develops in isolated thin walled cysts of bronchial origin with little or no abnormality in the surrounding lung. On the other hand, complex aspergilloma develops in cavities with gross disease in the surrounding lung tissue. Patients with simple Aspergilloma are considered good candidates for pulmonary resection, because surgery carries little risk. However, surgical removal of complex aspergilloma is associated with a high incidence of complications following operation.[4-16]

Hemoptysis is the most common presenting symptom, occurring in 48% to 100% of patients,[1-3,8,10] which may be mild, severe, or even exsanguinating; especially in the intracavitary type. Ninety two percent (92%) of patients presented with recurrent hemoptysis in our study. Bronchial artery embolization rarely results in control of hemoptysis because of the massive collateral blood vessels.[2, 8, 14] However, it should be considered as a temporary treatment in patients with life-threatening hemoptysis.[14]

Serological diagnosis has reasonably good sensitivity and specificity but has limited clinical importance in a typical scenario. Serum precipitating antibodies (Ig G) are almost always present, initially in high concentration, but become weaker and even negative, if the fungus ball is taken out.[11] In our series, as is usually the case, radiology formed the basis of diagnosis. Chest X-ray shows the typical 'air-crescent' sign in patients with Aspergilloma and CT gives you the extent of the disease.

In patients with pulmonary aspergilloma, surgical resection is generally performed through a standard posterolateral thoracotomy because of severe adhesions and the risk for massive hemorrhage.[21] In the past decade, video-assisted thoracic surgery (VATS) has undergone significant evolution and refinement, and continues to change the way thoracic conditions are managed.[22] However, the safety and feasibility of a thoracoscopic approach to lung resection for pulmonary aspergilloma have not been well evaluated. Gossot D et al.[23]

Use of the harmonic scalpel for the control of vessels during open thoracic surgical procedures is safe, shortens operative time by almost 30 minutes and minimize blood loss by almost 200mls compared with the conventional technique. This represents a refinement of technique, with decreased anesthesia and operating time, minimal blood loss, less post-operative complication and significant cost savings.[24] In our study we have used harmonic scalpel for dissection during surgical resection of complex Mycetoma and find it very effective in hemostasis and better surgical outcome.

Surgery offers three potential benefits: control of symptoms; prevention of hemoptysis; and prolongation of life.[2, 3] The ideal operative procedure should be a formal pulmonary resection. However, the technique involved ranks among the most complex in thoracic surgery due to severe intra pleural adhesion and many patients already have a poor pulmonary reserve that is a contraindication of pulmonary resection. When surgical resection is performed, lobectomy is the most common procedure.[2-8, 25] Pneumonectomy is preferred over less aggressive procedures for patients with multiple lobes affected by aspergilloma or with a totally destroyed underlying lung. However, previous studies have reported that pneumonectomy for complex aspergilloma is associated with extremely high complication rates.[26] During the Pneumonectomy procedure for complex aspergilloma, surgeons encounter dense fibrosis with obliteration of the pleural space, extension beyond the extra pleural plane of dissection, and distortion of hilar structures.[25-27] These structural alterations due to the inflammatory disease process make dissection extremely difficult. Many investigators experience excessive blood loss in patients undergoing a pneumonectomy for complex aspergilloma.[1,3,5] In our series Simple Mycetoma was observed in 22 (4.88%) whereas complex Mycetoma was diagnosed in 428 (95.11%) cases, the procedures performed were Lobectomy in 380 (84.44%) cases, Bilobectomy 36 (8%), and Pneumonectomy in 12 (2.66%) cases for complex mycetoma whereas wedge resection was done in 22 (4.8%) cases for simple Mycetoma cases.

The overall complication rate in our study was 7.11% which is comparable to recent reports.[1–3,8] The most common complications included prolonged air leak in 15 cases (3.33%),which was conservatively treated with low pressure suction .Wound infection occurred in 11 (2.44%) patients was treated according to culture sensitivity. Four patients (0.88%) had significant postop bleeding out of which two required re-exploration and empyema occurred in two (0.44%) patients whom operated again.

Recent reports show mortality rates of 1% to 9.5 %.[2,28] In our study mortality was 10 (2.2%) of which 09 patients died due to due to respiratory failure and one patient due to pulmonary embolism. Though surgical resection for complex Mycetoma carry high morbidity and mortality, in our series the results of surgical resec-

tion for complex Mycetoma are good and low compare to other series mainly because:

1) high volume center in which all the team members are gear up for pre op, per op and post-operative management.

2) use of harmonic for dissection reduces blood loss and post-operative complications.

3) use of intercostal muscle flap to prevent Broncho pleural fistulas.

CONCLUSION:

Even surgical resection for complex aspergilloma can be done with low morbidity and mortality rate in a high volume center with harmonic and intercostal muscle flap utilization.

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TREATMENT OUTCOME OF MULTI-DRUG RESISTANT TUBERCULOSIS (MDR-TB).

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ABSTRACT

OBJECTIVE: To assess the treatment outcome of multi-drug resistant tuberculosis (MDR-TB).

PLACE AND DURATION: People's University and Medical Health Sciences, Nawabshah during the period of four years from January 2007 to December 2010.

MATERIAL AND METHOD: Patients were selected from Pulmonology outpatient department and ward, after having confirmed MDR-TB by Laboratory AFB culture and DST (Drug Sensitivity Test). Patients were admitted in Pulmonology ward till sputum conversion was achieved. The details of demographic data, chemotherapy, adverse reactions to drugs, follow-up assessment as well as regular sputum bacteriology and chest radiograph result were recorded.

Medical records were reviewed of patients treated for MDR-TB from January 2007 to 2010 and monitored three years after initiation of treatment. Initial treatment outcomes and survival rates were analyzed.

RESULTS: 14 out of 36 patients (38.44%) treatment success rate was found at the end of treatment and 8 patients (22.24%) were failed to achieved sputum conversion by smear and culture at the end of MDR-TB treatment. Where as eight patients (22.24%) were defaulter and 4 patients (11.22%) were died and 2 patients (5.56%) were relapsed after completing their treatment.

CONCLUSION: Adequate TB control polices should be implemented to prevent the further spread of drug resistance.

KEY WORDS: MDR-TB, XDR-TB, AFB Sputum Smear, AFB Culture, Treatment Failure, DST.

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INTRODUCTION

Multi-drug resistant tuberculosis is a growing hazard to human health worldwide and a threat to tuberculosis control, the management of MDR-TB is difficult, more expensive challenging and quite often leads to treatment failure.[1] Drug resistance is the end result of poor TB control, drug resistant form of tuberculosis is poised to kill tens of millions people across the world.[2]

MDR-TB is an iatrogenic problem (Man made error). MDR-TB is one of the earth's deadliest infection with resistant strain of mycobacterium tuberculosis. MDR-TB is defined as resistance to Rifampicin and Isoniazid with or without resistance to other anti-tuberculosis drug.[3] Increased prevalence of MDR-TB is due to incorrect regimens and poor patient's adherence.[4] Pakistan is one of the most adversely affected country by MDR-TB it is caused by incorrect prescription, poor compliance, poor drug quality, irregular drug supply, inadequate TB control program, lack of DOTS results in MDR-TB. MDR-TB is more difficult and more expensive to treat; treatment of this disease can take up to 24 months with a combination of toxic, less potent drugs.

According to a recent W.H.O report, approximately 490,000 MDR-TB cases occur globally every year, corresponding to approximately 4.8% of the world's TB cases. MDR-TB is an increasing health problem in Pakistan. W.H.O report 2008 Geneva, the estimated cases of MDR-TB in Pakistan are 3.4% and 36% in new and previously treated cases of tuberculosis respectively. Globally Pakistan is ranked 8th in terms of estimated number of tuberculosis (TB) cases with an incidence of 181/100,000 persons.[5] Patients infected with MDR strains are not only difficult to cure but also more likely to remain sources of infection for a longer period of

time than those drug susceptible organism.[6] Uprising problem of treatment failure in pulmonary tuberculosis cases needs to find out the treatment outcome of MDR-TB patients with second line anti-tuberculosis drugs, whether the MDR-TB patients are treatable or not with second line anti-TB drugs.

XDR-TB is the occurrence of TB in person whose M. Tuberculosis isolates are resistance to Isoniazid and Rifampin Plus resistant to any Fluoroquinolone and at least one of three Kanamycin, Amikacin or Capreomycin. XDR is an extremely serious, emerging threat to public health and TB control. XDR-TB (Extensively Drug Resistant Tuberculosis) which cannot be cure by either first line or second line drugs.[7]

MATERIAL AND METHODS

PLACE OF STUDY:

This prospective study was conducted on thirty six MDT-TB patients between January 2007 to 2010 at People's University of Medical & Health Sciences Nawabshah.

SELECTION OF PATIENTS:

Patients were selected from out patients department and Pulmonology ward after having confirmed MDR-TB by Laboratory identification and susceptibility test were enrolled.

INCLUSION CRITERIA:

Adult patients of TB with sputum for AFB culture and sensitivity report showing resistant to at least Rifampicin and Isoniazid.

EXCLUSION CRITERIA:

Pregnancy, Mental illness.

All Patients who were included in this study were admitted and treated with ofloxacin and at least three other second line anti-tuberculosis drugs based on drug susceptibility test. Patients were admitted in TB Ward till sputum conversion was achieved. Radiological examination was done by serial chest x-rays at least once every three months. Radiological severity was estimated by using the recommendation of the National Tuberculosis Association of the United States.[8] We used the modified six treatment outcome categories recommended by WHO (Cure, Default Death, Treatment Failure, Relapse and transfer out).[9]

Guidelines for the Programmatic Management of Drug- Resistant Tuberculosis, Geneva, Switzerland Publication No: WHO/HTM/TB/2006. 361. The duration of adequate treatment was defined as 18 months or more and 12 months or more after culture conversion.

Treatment was given daily and directly observed during the intensive phase (3-5 months) patients were closely observed for any side effects of second line drugs. During this period bacteriological monitoring was done by smear and culture monthly for 6 month then quarterly till the end of treatment (18-24 months). LFT, Urea, creatinine were also done at a monthly interval.

DEFINITION OF TREATMENT OUTCOME

Cured: A patient who has completed treatment for at least for 18 months and has been culture negative for the final 12 consecutive months of treatment.

Death: A patient who dies during the course of treatment.

Failure: A patient who remains culture positive at least 6 months or those who become consistently positive subsequently during treatment and require change treatment.

Default: A patient who had interrupted treatment for two or more consecutive months.

Relapse: A patient previously treated for TB or treatment completed and is diagnosed with bacteriologically positive (smear or culture) tuberculosis.

RESULTS

Demographic data of MDR-TB patients are presented in Table- 1

There were twenty three (63.88%) males and thirteen (36.12%) females with mean age of 37.42 $\pm$ 7.72 years (Range 16-75 years) and mean weight 40.65 $\pm$ 7.70 kg (Range 25-58 kg) nine (25%) out of thirty six patients were smoker and all of them were males.
All the patients were having a definite history of anti-tuberculosis therapy varying from 5 months to 3 years. In this study all patients were acquired drug resistance MDR-TB.

Associated medical problem were seen in four patients, two of them had diabetes mellitus where as one was hypertensive and other one had pericardial effusion.

Resistant pattern of MDR-TB listed in Table-2.

Two drugs resistance were found in two patients (5.56%), three drugs seen in ten patients (27.78%), four drugs resistance were seen in ten patients (27.78%), five drugs resistance were found in ten patients (27.78%) and six drugs seen in four patients (11.12%) and remaining four patients were resistance to six drugs.

Table 1: Demographic Data of MDR-TB

Patients Characteristics	Number of Cases (n=36)	Percentage
Age		
Mean	37.42 + 7.72	
Range	(16-75 years)	
Sex		
Male	23	63.88 %
Female	13	36.12 %
Body weight	40.65 + 7.70	
(Kg)	25-58 Kg	
Smoker	9	25 %
History of contact with TB Patients	27	75 %
Previous History	5 month to 3 years	

Table 2:

Resistance to	Drugs	No. of Patients n=36	Total percent of Patients n=36
Two drugs	RH	2	2 (5.56%)
Three drugs	RHZ	3	10 (27.78%)
	RHE	3	
	RHS	4	
Four drugs	RHEZ	4	10 (27.78%)
	SRHE	6	
Five drugs	SREHZ	6	10 (27.78%)
	KSRH OFX	4	
Six drugs	KSRH OFX Z	2	4 (11.12%)
	KSRH OFX ETO	2	

R= Rifampcin, H= Isoniazid, E= Ethambutol, S=Streptomycin, K= Kanamycin,
Z= Pyrazinamide, ETO= Ethionamide, OFX=Ofloxacin.

Table 3: Outcomes of MDR-TB n=36

	Cure	Treatment Failure	Default	Died	Relapse
MDR-TB	14 (38.89%)	8 (22.24%)	6 (16.68%)	2 (5.56%)	2 (5.56%)
XDR-TB	-	-	2 (5.56%)	2 (5.56%)	-

28 patients (77.8%) out of 36 sputum smear and conversion rate was found, where as 8 (22.2%) patients were failed to achieved sputum smear and culture at the end of 5 months therapy. (P-value= 0.001, Chi Square = 44.44).

Finally the treatment outcome after two year of anti-tuberculosis treatment for MDR-TB was obtained in 36 patients, cure rate favourable clinical and bacteriological response was recorded in 14 (38.4%) out of 36 patients and treatment failure was found in 8 patients (22.24%) where as 8 patients (22.24%) defaulted and treatment restarted, after 2 months they lost to follow up and failed to keep their OPD appointment, and 4 patients (11.12%) defaulted and 4 patients (11.12%) died before treatment completion and 2 patients (5.56%) were relapsed after completing their treatment.

DISCUSSION

MDR-TB has a high mortality rate even with treatment. Treatment of MDR-TB is both difficult and expensive even in industrialized countries. The treatment success rate in this study was 38.89% (14/36) LOCK-

MAN reported cure rate (defined as completed > 6 months of therapy and had negative AFB smear result at the end of treatment of 37% (17/46), which is compatible to our study.[10] Default rate 22.24% (8/36) was high in our study. Authors have reported high default rates 28.9%.[11, 12] In resource limited countries, where default during treatment is high. We believe that the reason for default in our study was because of side effects of second line drugs and economic constraint i.e poverty. It has been reported patients who received initial therapy in Hospital had significantly higher treatment completion rate (79%) than those treated as outpatient alone (48%). Our treatment completion rate was low in spite of all patients being admitted in the initial phase. The relapse rate is quite low in this study. This could be because of the patients who benefitted from their own purchased good quality drugs. Relapse rate during the study period 2 patients (5.6%) reported with positive sputum among those who were successfully completed the treatment. The gap between completion of treatment and relapse was between 4-6 months (attempts were made to contact but failed to traced them) due to non availability of facilities for follow up.

The limitation of this study was that the patients were followed up with sputum smear and chest X-ray only as the facility for AFB culture on a large scale was not possible. The other limitation was lack of follow up after completion of treatment.

CONCLUSION:

MDR-TB is a treatable disease with proper management and strategy. Adequate TB polices should be implemented to prevent the further development and spread of drug resistance.

RECOMMENDATION

The top priority is not the management, but the prevention of MDR-TB by implementation of good National TB Program (NTP) using shout course chemotherapy (SCC) by directly observed treatment shout course (DOTS).

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INCIDENTAL FINDING OF COLOPLEURAL FISTULA DURING PLEUROCUTANEOUS WINDOW SURGERY FOR EMPYEMA THORACIS

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ABSTRACT

We report a 35 year old male patient with a 43 day history of left sided chest pain, shortness of breath and fever. Before presenting to us, he was admitted at a local hospital, where left sided tube thoracostomy was performed for empyema thoracis. After failure of pus to resolve, he was referred to the Department of Thoracic Surgery at Dow University of Health Sciences, Karachi, Pakistan. Pus for gram stain and culture grew multiple organisms and antibiotics were started promptly. The patient's condition did not improve, hence surgery was planned. During surgery, undigested food particles were found in the pleural cavity along with foul smell, suggesting a diagnosis of enteropleural fistula. Barium studies confirmed the diagnosis of colo-pleural fistula. Adopting a staged approached, laprotomy and fistulectomy with primary closure of bowel was attempted. Patient's recovery was unremarkable and he was discharged after eight days.

KEY WORDS: Colopleural fistula, diaphragmatic hernia, empyema

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INTRODUCTION

Fistulas are abnormal communications between two epithelial-lined surfaces. Gasterointestinal fistulas include all such connections that involve the alimentary tract. Gasterointestinal fistulas can be external if they communicate with the skin surface i.e. entercutaneous fistula & internal if they connect to another internal organ, system or space. Colopleural fistula is a rare entity. Possible cause include hepato gastrointestinal surgery, fistula secondary to diaphragmatic hernia[1] malignancy, complication of pneumonectomy[2] and diverticular disease.[3]

CASE REPORT

We report a case of 35 year old male patient referred from a local hospital in Sindh. He was received in a cachexic, septic condition with a left sided chest tube in place discharging foul smelling pus. According to the patient, around 2 months back, he developed abdominal pain with constipation and vomiting. He received conservative management at a local hospital and was discharged after a week. About 12 days later, he started spiking a fever and developed left sided chest pain. He was diagnosed with left hydropneumothorax with possible empyema formation and a tube thoracostomy was performed.Chest tube bottle collected more than a litre of frank pus, so antibiotics were started and the patient was referred to our department.

We sent Culture and sensitivity of pus which reported growth of Ecoli, Proteus mirabilis and Streptococci. Despite appropriate antibiotics, the patient's condition continued to deteriorate rapidly. As his condition did not permit any major surgical interventions, we decided to create a pleurocutaneous window to drain the foul smelling pus. During the procedure, the lung was found to be collapsed and there were no pleural adhesions. We were surprised to find undigested food particles in the pleural cavity at the diaphragmatic site and a small opening was seen at the diaphragm.

Suspecting a possible enteropleural fistula ,patient was kept NPO and total parenteral nutrition started. It was observed that while patient was NPO his pus discharge decreased significantly which was suggestive of Sister Leena's Sign.[2] The fistulous communication was confirmed on barium enema which showed contrast entering the pleural cavity. After confirmation of fistulous communication, elective laparotomy was planned. During surgery, the splenic flexure of colon was found entrapped within the left dome of diaphragm with underlying diaphragmatic hernia. The colon appeared healthy on assessment, so the fistula tract was excised and the intestine was repaired in two layers. The defect in diaphragm was also closed. Colonic tissue specimen was sent for histopathology which revealed

a nonspecific inflammatory infiltrate without any obvious pathology. Patient's post-op recovery was smooth and he was orally allowed on the 6th postoperative day.

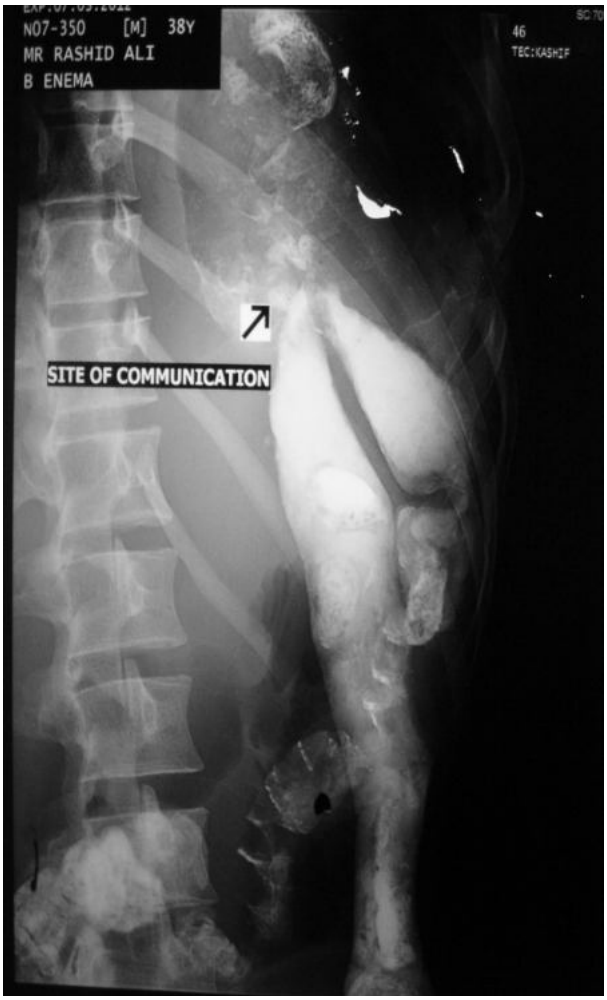

Figure 1: Barium enema showing splenic flexure communicating with left thoracic cavity

DISCUSSION

Feculent empyma thoracis is a very uncommon presentation of diaphragmatic hernia. Our literature review revealed similar cases in which colopleural fistula was diagnosed as an incidental finding secondary to diaphragmatic hernia repair,[1] due to sigmoid perforation[4] or resulting as a complication post pneumonectomy.[2,5] While traumatic diaphragmatic hernia is a well-recognized complication of blunt and penetrating injuries to the abdomen and thorax,[6] strangulation of the large bowel that migrates through that hernia into the thorax with subsequent rupture and the development of fecal pneumothorax is most unusual.[6] The clinical presentation of traumatic diaphragmatic hernia maybe acute or delayed in its appearance. Late presentations may be dramatic if they occur months or years after the initial

Figure 2: Fistulectomy being performed

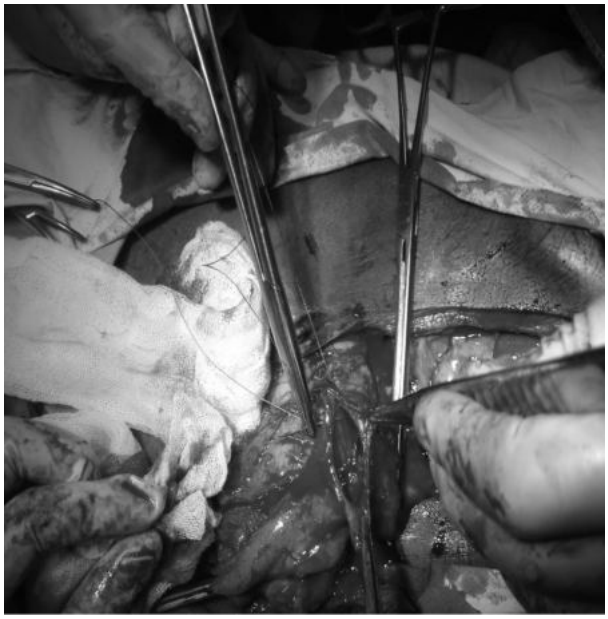

Figure 3: Large bowel repair being done

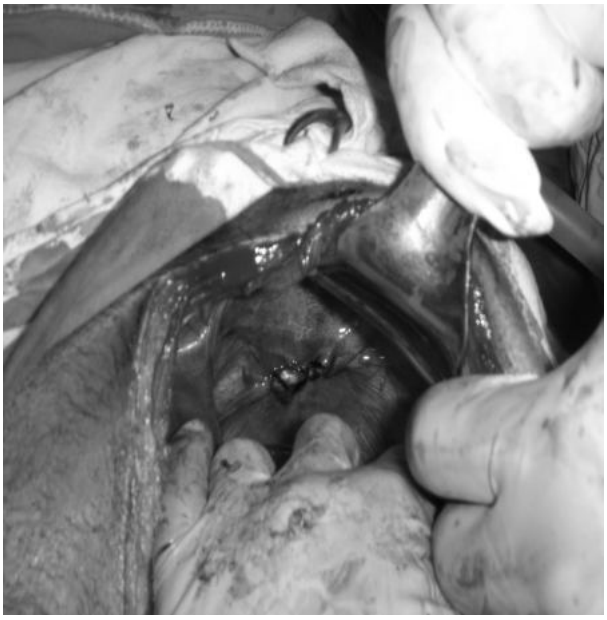

Figure 4: Diaphragmatic repair

injury.[4,6] During history taking, our patient recalled two injuries from adolescence, one inflicted with a knife on the left side of his chest, managed by primary closure and another injury that resulted after a fall from the back seat of a loader vehicle but he did not recieve any treatment for it.

Patients with colopleural fistula usally present like empyema thoracis, with fever, chest discomfort and dyspnea.[1] Diagnosis requires a high degree of suspicion. Presence of a foul smelling thickened discharged should raise the possibility of fistula formation.[3] Observing sister leena's sign may aid in diagnosis.[2] In our case, the detection of coliforms in culture, polymicrobial flora on gram stain[6] and presence of fecal pyopneumothorax along with the correlation of amount of pus with food intake was highly suggestive of colopleural fistula. Definite diagnosis requires barium imaging. Recommended method of treatment of this pathology is a laparotomy or thoracotomy either as urgent surgery once diagnosed[3] or a staged procedure after stabilization of the patient with TPN and antibiotics and definitive surgery.

CONCULSION

Diagnosis of colopleural fistula is a challenge. It is important to diagnose it early to avoid patient morbidity. Presence of foul smelling discharge with pyopneumothorax, growth of polymicrobial flora on gram stain with E coli detection and a decrease in discharge following reduction in food intake should raise the suspicion of a colopleural fistula.

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SIX- VS. EIGHT-MONTH ANTI-TUBERCULOSIS REGIMEN FOR PULMONARY TUBERCULOSIS UNDER PROGRAMME CONDITIONS

SETTING: One urban tertiary care and one rural secondary care hospital in Nigeria.

OBJECTIVE: To compare the epidemiological characteristics and treatment outcomes of tuberculosis (TB) patients treated with an 8-month or 6-month anti-tuberculosis regimen in a low-resource setting.

DESIGN: Retrospective cohort study.

RESULTS: A total of 928 newly diagnosed smear-positive TB patients were treated with either daily ethambutol (EMB), isoniazid (INH), rifampicin (RMP) and pyrazinamide (PZA) for 2 months followed by EMB and INH for 6 months (2RHZE/6EH), or the same intensive phase as the first regimen followed by 4 months of daily RMP and INH (2RHZE/4RH). The proportion of successful outcomes was 381/490 (77.8%) with 2RHZE/6EH and 373/438 (85.2%) with 2RHZE/4RH (P = 0.004). Defaulting was significantly more frequent in patients who received 2RHZE/6EH (14.3% vs. 5.5%; P < 0.001). Treatment failure was not significantly higher in patients who received 2RHZE/6EH (2.9% vs. 1.6%; P = 0.15). After adjusting for confounders, older age (adjusted odds ratio [aOR] 1.7), 2RHZE/6EH treatment (aOR 1.6) and male sex (aOR 1.5) independently predicted unsuccessful outcomes in human immunodeficiency virus negative TB patients.

CONCLUSIONS: Newly diagnosed TB patients on 2RHZE/4RH have a higher treatment success rate than those treated with 2RHZE/6EH under programme conditions in a low-resource, high-burden setting. Current World Health Organization recommendations should be maintained.

BRONCHOSCOPE INSERTION ROUTE AND PATIENT COMFORT DURING FLEXIBLE BRONCHOSCOPY

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SETTING: Diagnostic flexible bronchoscopy performed in hospitalised and ambulatory patients in a tertiary care academic hospital in Monterrey, Mexico.

OBJECTIVE: To determine the effect of the route of insertion of the bronchoscope (oral or nasal) on patient comfort, vocal cord visualisation, local anaesthetic and sedation requirements and possible complications.

DESIGN: Prospective study carried out in patients aged >18 years with an indication for flexible bronchoscopy. The route of insertion was randomly assigned. Symptoms related to the procedure were evaluated using a questionnaire.

RESULTS: Sixty-three patients were included: 32 in the oral insertion group and 31 in the nasal insertion group. There was no statistically significant difference in patient discomfort (1.91 ± 2.95 vs. 2.39 ± 3.56 points on a scale of 1 to 10, P = 0.74) or procedural complications (4 vs. 0 events, P = 0.12) between study groups. Oral insertion was associated with less time to vocal cord visualisation (25.5 ± 156 s vs. 56 ± 61 s, P < 0.01), lower requirement for lidocaine (15 ± 7.50 vs. 16 ± 4 ml, P = 0.01) and fewer insertion failures (0 vs. 6 cases, P < 0.01).

CONCLUSIONS: With intravenous sedoanalgesia, route of insertion did not affect patient comfort. However, the oral route was associated with faster vocal cord visualisation, less use of lidocaine and no insertion failure.

SUBSTITUTING OR ADDING FLUOROQUINOLONES TO ESTABLISHED FIRST-LINE ANTITUBERCULOUS DRUG REGIMENS GIVES NO ADDITIONAL BENEFIT OR RISKS

BACKGROUND: Currently the World Health Organization only recommend fluoroquinolones for people with presumed drug-sensitive tuberculosis (TB) who cannot take standard first-line drugs. However, use of fluoroquinolones could shorten the length of treatment and improve other outcomes in these people. This review summarises the effects of fluoroquinolones in first-line regimens in people with presumed drug-sensitive TB.

OBJECTIVES: To assess fluoroquinolones as substitute or additional components in antituberculous drug regimens for drug-sensitive TB.

Search strategy: We searched the Cochrane Infectious Diseases Group Specialized Register; CENTRAL (The Cochrane Library 2013, Issue 1); MEDLINE; EMBASE; LILACS; Science Citation Index; Databases of Russian Publications; and metaRegister of Controlled Trials up to 6 March 2013.

SELECTION CRITERIA: Randomized controlled trials (RCTs) of antituberculous regimens based on rifampicin and pyrazinamide and containing fluoroquinolones in people with presumed drug-sensitive pulmonary TB.

DATA COLLECTION AND ANALYSIS: Two authors independently applied inclusion criteria, assessed the risk of bias in the trials, and extracted data. We used the risk ratio (RR) for dichotomous data and the fixed-effect model when it was appropriate to combine data and no heterogeneity was present. We assessed the quality of evidence using the GRADE approach.

MAIN RESULTS: We identified five RCTs (1330 participants) that met the inclusion criteria. None of the included trials examined regimens of less than six months duration.

Fluoroquinolones added to standard regimens

A single trial (174 participants) added levofloxacin to the standard first-line regimen. Relapse and treatment failure were not reported. For death, sputum conversion, and adverse events we are uncertain if there is an effect (one trial, 174 participants, very low quality evidence for all three outcomes).

Fluoroquinolones substituted for ethambutol in standard regimens

Three trials (723 participants) substituted ethambutol with moxifloxacin, gatifloxacin, and ofloxacin into the standard first-line regimen. For relapse, we are uncertain if there is an effect (one trial, 170 participants, very low quality evidence). No trials reported on treatment failure. For death, sputum culture conversion at eight weeks, or serious adverse events we do not know if there was an effect (three trials, 723 participants, very low quality evidence for all three outcomes).

Fluoroquinolones substituted for isoniazid in standard regimens

A single trial (433 participants) substituted moxifloxacin for isoniazid. Treatment failure and relapse were not reported. For death, sputum culture conversion, or serious adverse events the substitution may have little or no difference (one trial, 433 participants, low quality evidence for all three outcomes).

Fluoroquinolines in four month regimens

Six trials are currently in progress testing shorter regimens with fluoroquinolones.

NOT ENOUGH EVIDENCE ON THE ROUTINE USE OF SURGERY IN ADDITION TO DRUG TREATMENT FOR PEOPLE WITH TUBERCULOSIS OF THE SPINE

BACKGROUND: Tuberculosis is generally curable with chemotherapy, but there is controversy in the literature about the need for surgical intervention in the one to two per cent of people with tuberculosis of the spine.

OBJECTIVES: To compare chemotherapy plus surgery with chemotherapy alone for treating people diagnosed with active tuberculosis of the spine.

SEARCH STRATEGY: We searched the Cochrane Infectious Diseases Group Specialized Register (February 2010), CENTRAL (The Cochrane Library 2010, Issue 1), MEDLINE (1966 to February 2010), EMBASE (1974 to February 2010), LILACS (1982 to February 2010), conference proceedings, and reference lists. A search update in November 2012 revealed no new studies.

SELECTION CRITERIA: Randomized controlled trials with at least one year follow up that compared chemotherapy plus surgery with chemotherapy alone for treating active tuberculosis of the thoracic and/or lumbar spine.

DATA COLLECTION AND ANALYSIS: Two authors independently assessed trial eligibility, methodological quality, and extracted data. We analysed data using odds ratio with 95% confidence intervals.

MAIN RESULTS: Two randomized controlled trials (331 participants) met the inclusion criteria. They were conducted in the 1970s and 1980s with follow-up reports available after 18 months, three years, and five years; one trial also reported 10 years follow up. Completeness of follow up varied at the different time points, with less than 80% of participants available for analysis at several time points. There was no statistically significant difference for any of the outcome measures: kyphosis angle, neurological deficit (none went on to develop this), bony fusion, absence of spinal tuberculosis, death from any cause, activity level regained, change of allocated treatment, or bone loss. Neither trial reported on pain. Of the 130 participants allocated to chemotherapy only, 12 had a neurological deficit and five needed a decompression operation. One trial suggested that an initial kyphosis angle greater than 30° is likely to deteriorate, especially in children.

CHEST PHYSIOTHERAPY FOR PNEUMONIA IN ADULTS

BACKGROUND: Despite conflicting evidence, chest physiotherapy has been widely used as an adjunctive treatment for adults with pneumonia.

OBJECTIVES: To assess the effectiveness and safety of chest physiotherapy for pneumonia in adults.

SEARCH STRATEGY: We searched CENTRAL 2012, Issue 11, MEDLINE (1966 to November week 2, 2012), EMBASE (1974 to November 2012), Physiotherapy Evidence Database (PEDro) (1929 to November 2012), CINAHL (2009 to November 2012) and CBM (1978 to November 2012).

SELECTION CRITERIA: Randomised controlled trials (RCTs) assessing the efficacy of chest physiotherapy for treating pneumonia in adults.

DATA COLLECTION AND ANALYSIS: Two authors independently assessed trial eligibility, extracted data and appraised trial quality. Primary outcomes were mortality and cure rate. We used risk ratios (RR) and mean difference (MD) for individual trial results in the data analysis. We performed meta-analysis and measured all outcomes with 95% confidence intervals (CI).

MAIN RESULTS: Six RCTs (434 participants) appraised four types of chest physiotherapy (conventional chest physiotherapy; osteopathic manipulative treatment (which includes paraspinal inhibition, rib raising and myofascial release); active cycle of breathing techniques (which include active breathing control, thoracic expansion exercises and forced expiration techniques); and positive expiratory pressure).

None of the physiotherapies (versus no physiotherapy or placebo) improved mortality rates of adults with pneumonia.

Conventional chest physiotherapy (versus no physiotherapy), active cycle of breathing techniques (versus no physiotherapy) and osteopathic manipulative treatment (versus placebo) did not increase the cure rate or chest X-ray improvement rate.

Osteopathic manipulative treatment (versus placebo) and positive expiratory pressure (versus no physiotherapy) reduced the mean duration of hospital stay by 2.0 days (mean difference (MD) -2.0 days, 95% CI -3.5 to -0.6) and 1.4 days (MD -1.4 days, 95% CI -2.8 to -0.0), respectively. Conventional chest physiotherapy and active cycle of breathing techniques did not.

Positive expiratory pressure (versus no physiotherapy) reduced fever duration (MD -0.7 day, 95% CI -1.4 to -0.0). Osteopathic manipulative treatment did not.

Osteopathic manipulative treatment (versus placebo) reduced the duration of intravenous (MD -2.1 days, 95% CI -3.4 to -0.9) and total antibiotic treatment (MD -1.9 days, 95% CI -3.1 to -0.7).

Limitations of this review are that the studies addressing osteopathic manipulative treatment were small, and that six published studies which appear to meet the inclusion criteria are awaiting classification.

EARLY (LESS THAN 30 DAYS AFTER THE START OF CHEMOTHERAPY) OR LATE (MORE THAN 30 DAYS AFTER THE START OF CHEMOTHERAPY) CHEST RADIOTHERAPY FOR PATIENTS SUFFERING FROM LIMITED SMALL CELL LUNG CANCER

BACKGROUND: This is an update of the original review published in Issue 1, 2005. It is standard clinical practice to combine chemotherapy and chest radiotherapy in treating patients with limited-stage small cell lung cancer. However, the best way to integrate both modalities is unclear.

OBJECTIVES: To establish the best timing of chest radiotherapy with chemotherapy for patients with limited-stage small cell lung cancer in order to improve long-term survival.

SEARCH STRATEGY: We ran a new search in January 2009. We searched MEDLINE (through PubMed), EMBASE (through Ovid), CINAHL (through EBSCO), the Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library 2009, Issue 1) and reference lists, handsearched journals and conference proceedings, and contacted experts to identify potentially eligible trials, published and unpublished.

SELECTION CRITERIA: Randomised controlled clinical trials comparing different timing of chest radiotherapy in patients with limited-stage small cell lung cancer.

DATA COLLECTION AND ANALYSIS: Seven randomised trials were included. There were differences in the timing and overall treatment time of chest radiotherapy, and the type of chemotherapy used.

MAIN RESULTS: We found no significant differences in overall survival, whether chest radiotherapy was delivered within 30 days after the start of chemotherapy or later, even after exclusion of the only study that delivered chest radiotherapy during cycles of non-platinum chemotherapy (HR 0.86 in favour of early radiation, P = 0.11). The same was observed for studies having early chest radiotherapy delivered in an overall treatment time of less than 30 days compared to a longer treatment time (HR 0.82, P = 0.13). These results should be interpreted with caution because the largest trial has follow-up data up to three years only. The outcome of longer follow up for overall survival remains to be seen. Local tumour control was not significantly different between early and late chest radiotherapy, nor the incidence of severe pneumonitis or severe oesophagitis. However, we observed a trend towards a higher chance of developing oesophagitis and pneumonitis when early chest radiotherapy was delivered during chemotherapy, which remained for oesophagitis, but not pneumonitis, after exclusion of studies with non-platinum based chemotherapy.

EFFECTIVENESS AND SAFETY OF INHALERS CONTAINING THE DRUG ACLIDINIUM BROMIDE FOR MANAGING PATIENTS WITH STABLE COPD

BACKGROUND: Bronchodilators are the mainstay for symptom relief in the management of stable chronic obstructive pulmonary disease (COPD). Aclidinium bromide is a new long-acting muscarinic antagonist (LAMA) that differs from tiotropium by its higher selectivity for M3 muscarinic receptors with a faster onset of action. However, the duration of action of aclidinium is shorter than for tiotropium. It has been approved as maintenance therapy for stable, moderate to severe COPD, but its efficacy and safety in the management of COPD is uncertain compared to other bronchodilators.

OBJECTIVES: To assess the efficacy and safety of aclidinium bromide in stable COPD.

SEARCH STRATEGY: We identified randomised controlled trials (RCT) from the Cochrane Airways Group Specialised Register of trials (CAGR), as well as www.clinicaltrials.gov, World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP), US Food and Drug Administration (FDA) website and Almirall Clinical Trials Registry and Results. We contacted Forest Laboratories for any unpublished trials and checked the reference lists of identified articles for additional information. The last search was performed on 7 April 2014 for CAGR and 11 April 2014 for other sources.

SELECTION CRITERIA: Parallel-group RCTs of aclidinium bromide compared with placebo, long-acting beta2-agonists (LABA) or LAMA in adults with stable COPD.

DATA COLLECTION AND ANALYSIS: Two review authors independently selected studies, assessed the risk of bias, and extracted data. We sought missing data from the trial authors as well as manufacturers of aclidinium. We used odds ratios (OR) for dichotomous data and mean difference (MD) for continuous data, and reported both with their 95% confidence intervals (CI). We used standard methodological procedures expected by The Cochrane Collaboration. We applied the GRADE approach to summarise results and to assess the overall quality of evidence.

MAIN RESULTS: This review included 12 multicentre RCTs randomly assigning 9547 participants with stable COPD. All the studies were industry-sponsored and had similar inclusion criteria with relatively good methodological quality. All but one study included in the meta-analysis were double-blind and scored low risk of bias. The study duration ranged from four weeks to 52 weeks. Participants were more often males, mainly Caucasians, mean age ranging from 61.7 to 65.6 years, and with a smoking history of 10 or more pack years. They had moderate to severe symptoms at randomisation; the mean post-bronchodilator forced expiratory volume in one second (FEV1) was between 46% and 57.6% of the predicted normal value, and the mean St George's Respiratory Questionnaire score (SGRQ) ranged from 45.1 to 50.4 when reported.

There was no difference between aclidinium and placebo in all-cause mortality (low quality) and number of patients with exacerbations requiring a short course of oral steroids or antibiotics, or both (moderate quality). Aclidinium improved quality of life by lowering the SGRQ total score with a mean difference of -2.34 (95% CI -3.18 to -1.51; I2 = 48%, 7 trials, 4442 participants) when compared to placebo. More patients on aclidinium achieved a clinically meaningful improvement of at least four units decrease in SGRQ total score (OR 1.49; 95% CI 1.31 to 1.70; I2 = 34%; number needed to treat (NNT) = 10, 95% CI 8 to 15, high quality evidence) over 12 to 52 weeks than on placebo. Aclidinium also resulted in a significantly greater improvement in pre-dose FEV1 than placebo with a mean difference of 0.09 L (95% CI 0.08 to 0.10; I2 = 39%, 9 trials, 4963 participants). No trials assessed functional capacity. Aclidinium reduced the number of patients with exacerbations requiring hospitalisation by 4 to 20 fewer per 1000 over 4 to 52 weeks (OR 0.64; 95% CI 0.46 to 0.88; I2 = 0%, 10 trials, 5624 people; NNT = 77, 95% CI 51 to 233, high quality evidence) compared to placebo. There was no difference in non-fatal serious adverse events (moderate quality evidence) between aclidinium and placebo.

Compared to tiotropium, aclidinium did not demonstrate significant differences for exacerbations requiring oral steroids or antibiotics, or both, exacerbation-related hospitalisations and non-fatal serious adverse events (very low quality evidence). Inadequate data prevented the comparison of aclidinium to formoterol or other LABAs.

INSTRUCTIONS TO AUTHOR

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Describe your selection of the observational or experimental subjects (patients or laboratory animals, including controls) clearly. Identify the age, sex, and other important characteristics of the subjects. Because the relevance of such variables as age, sex, and ethnicity to the object of research is not always clear, authors should explicitly justify them when they are included in a study report. The guiding principle should be clarity about how and why a study was done in a particular way. For example, authors should explain why only subjects of certain ages were included or why women were excluded. Authors should avoid terms such as "race," which lacks precise biological meaning, and use alternative descriptors such as "ethnicity" or "ethnic group" instead. Authors should specify carefully what the descriptors mean, and tell exactly how the data were collected (for example, what terms were used in survey forms, whether the data were self-reported or assigned by others, etc.). Identify the methods, apparatus (give the manufacturer's name and address in parentheses), and procedures in sufficient detail to allow other workers to reproduce the results. Give references to established methods, including statistical methods (see below); provide references and brief descriptions for methods that have been published but are not well known; describe new or substantially modified meth-

ods, give reasons for using them, and evaluate their limitations. Identify precisely all drugs and chemicals used, including generic name(s), dose(s), and route(s) of administration. Reports of randomized clinical trials should present information on all major study elements, including the protocol (study population, interventions or exposures, outcomes, and the rationale for statistical analysis), assignment of interventions (methods of randomization, concealment of allocation to treatment groups), and the method of masking (blinding). Authors submitting review manuscripts should include a section describing the methods used for locating, selecting, extracting, and synthesizing data. These methods should also be summarized in the abstract.

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When reporting experiments on human subjects, indicate whether the procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional or regional) and with the Helsinki Declaration of 1975, as revised in 1983. Do not use patients' names, initials, or hospital numbers, especially in illustrative material. When reporting experiments on animals, indicate whether the institution's or a national research council's guide for, or any national law on, the care and use of laboratory animals was followed. Send the copy of approval certificate from *Institutional review board for bioethics/ research ethical committees.*

f Statistics

Describe statistical methods with enough detail to enable a knowledgeable reader with access to the original data to verify the reported results. When possible, quantify findings and present them with appropriate indicators of measurement error or uncertainty (such as confidence intervals). Avoid relying solely on statistical hypothesis testing, such as the use of P values, which fails to convey important quantitative information. Discuss the eligibility of experimental subjects. Give details about randomization. Describe the methods for and success of any blinding of observations. Report the complications of treatment, if any. Give numbers of observations and report losses to observation (such as dropouts from a clinical trial). References for the design of the study and statistical methods should be to standard works when possible (with pages stated) rather than to papers in which the designs or methods were originally reported. Specify any general-use computer programs used. Put a general description of methods in the Methods section. When data are summarized in the Results section, specify the statistical methods used to analyze them. Restrict tables and figures to those needed to explain the argument of the paper and to assess its support. Use graphs as an alternative to tables with many entries; do not duplicate data in graphs and tables. Avoid nontechnical uses of technical terms in statistics, such as "random" (which implies a randomizing device), "normal," "significant," "correlations," and "sample." Define statistical terms, abbreviations, and most symbols.

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i Acknowledgments

List all contributors who do not meet the criteria for authorship, such as a person who provided purely technical help, writing assistance, or a department chair who provided only general support. Financial and material support should also be acknowledged. Groups of persons who have contributed materially to the paper but whose contributions do not justify authorship may be listed under a heading such as "clinical investigators" or "participating investigators," and their function or contribution should be described for example, "served as scientific advisors," "critically reviewed the study proposal," "collected data," or "provided and cared for study patients." Because readers may infer their endorsement of the data and conclusions, all persons must have given written permission to be acknowledged.

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Articles in Journals

1. Standard journal article

Up to six authors: Zafar I, Ali S, Basit A, Ziaullah, Khan MY, Javaid A. Comparison of treatment outcome of tuberculosis before and after the introduction of daily DOTS in TB clinic at Lady Reading Hospital Peshawar. Pak J Chest Med 2014; 20(2): 54-60

More than six authors: List the first six authors followed by et al. Basit A, Khan MA, Dost M, Ahmad M, Ziaullah, Zafar I, et al. Need for establishing a linkage between tertiary care hospital and peripheral DOTS centres. Pak J Chest Med 2013;19(3): 54-60

2. Organization as author

The Cardiac Society of Australia and New Zealand. Clinical exercise stress testing. Safety and performance guidelines. Med J Aust 1996; 164: 282-4.

3. No author given

Cancer in South Africa [editorial]. S Afr Med J 1994; 84:15.

4. Article not in English

(Note: NLM translates the title to English, encloses the translation in square brackets, and adds an abbreviated language designator.) Ryder TE, Haukeland EA, Solhaug JH. Bilateral infrapatellar seneruptur hostidligere frisk kvinne. Tidsskr Nor Laegeforen 1996; 116: 41-2.

5. Volume with supplement:

Shen HM, Zhang QF. Risk assessment of nickel carcinogenicity and occupational lung cancer. Environ Health Perspect 1994;102 Suppl 1:275-82.

6. Issue with supplement

Payne DK, Sullivan MD, Massie MJ. Women's psychological reactions to breast cancer. Semin Oncol 1996; 23 (1 Suppl 2):89-97.

7. Volume with part

Ozben T, Nacitarhan S, Tuncer N. Plasma and urine sialic acid in non-insulin dependent diabetes mellitus. Ann Clin Biochem 1995; 32(Pt 3): 303-6.

8. Issue with part

Poole GH, Mills SM. One hundred consecutive cases of flap lacerations of the leg in ageing patients. N Z Med J 1994; 107 (986 Pt 1): 377-8.

9. Issue with no volume

Turan I, Wredmark T, Fellander-Tsai L. Arthroscopic ankle arthrodesis in rheumatoid arthritis. Clin Orthop 1995; (320): 110-4.

10. No issue or volume

Browell DA, Lennard TW. Immunologic status of the cancer patient and the effects of blood transfusion on antitumor responses. Curr Opin Gen Surg 1993: 325-33.

11. Pagination in Roman numerals

Fisher GA, Sikic BI. Drug resistance in clinical oncology and hematology. Introduction. Hematol Oncol Clin North Am 1995 Apr;9(2):xi-xii.

12. Type of article indicated as needed

Enzensberger W, Fischer PA. Metronome in Parkinson's disease [letter]. Lancet 1996;347:1337. Clement J, De Bock R. Hematological complications of hantavirus nephropathy (HVN) [abstract]. Kidney Int 1992; 42: 1285.

13. Article containing retraction

Garey CE, Schwarzman AL, Rise ML, Seyfried TN. Ceruloplasmin gene defect associated with epilepsy in EL mice [retraction of Garey CE, Schwarzman AL, Rise ML, Seyfried TN. In: Nat Genet 1994; 6: 426-31]. Nat Genet 1995; 11: 104.

14. Article retracted

Liou GI, Wang M, Matragoon S. Precocious IRBP gene expression during mouse development [retracted in Invest Ophthalmol Vis Sci 1994; 35: 3127]. Invest Ophthalmol Vis Sci 1994; 35: 1083-8.

15. Article with published erratum

Hamlin JA, Kahn AM. Herniography in symptomatic patients following inguinal hernia repair [published erratum appears in West J Med 1995;162:278]. West J Med 1995;162:28-31.

Books and Other Monographs

(Note: Previous Vancouver style incorrectly had a comma rather than a semicolon between the publisher and the date.)

16. Personal author(s)

Ringsven MK, Bond D. Gerontology and leadership skills for nurses. 2nd ed. Albany (NY): Delmar Publishers; 1996.

17. Editor(s), compiler(s) as author

Norman IJ, Redfern SJ, editors. Mental health care for elderly people. New York: Churchill Livingstone; 1996.

18. Organization as author and publisher

Institute of Medicine (US). Looking at the future of the Medicaid program. Washington: The Institute; 1992.

19. Chapter in a book

(Note: Previous Vancouver style had a colon rather than a p before pagination.) Phillips SJ, Whisnant JP. Hypertension and stroke. In: Laragh JH, Brenner BM, editors. Hypertension: pathophysiology, diagnosis, and management. 2nd ed. New York: Raven Press; 1995. p. 465-78.

20. Conference proceedings

Kimura J, Shibasaki H, editors. Recent advances in clinical neurophysiology. Proceedings of the 10th International Congress of EMG and Clinical Neurophysiology; 1995 Oct 15-19; Kyoto, Japan. Amsterdam: Elsevier; 1996.

21. Conference paper

Bengtsson S, Solheim BG. Enforcement of data protection, privacy and security in medical informatics. In: Lun KC, Degoulet P, Piemme TE, Rienhoff O, editors. MEDINFO 92. Proceedings of the 7th World Congress on Medical Informatics; 1992 Sep 6-10; Geneva, Switzerland. Amsterdam: North-Holland; 1992. p. 1561-5.

22. Scientific or technical report

Issued by funding/sponsoring agency: Smith P, Golladay K. Payment for durable medical equipment billed during skilled nursing facility stays. Final report. Dallas (TX): Dept. of Health and Human Services (US), Office of Evaluation and Inspections; 1994 Oct. Report No.: HHSIGOEI69200860. Issued by performing agency: Field MJ, Tranquada RE, Feasley JC, editors. Health services research: work force and educational issues. Washington: National Academy Press; 1995. Contract No.: AHCPR282942008. Sponsored by the Agency for Health Care Policy and Research.

23. Dissertation

Kaplan SJ. Post-hospital home health care: the elderly's access and utilization [dissertation]. St. Louis (MO): Washington Univ.; 1995.

24. Patent

Larsen CE, Trip R, Johnson CR, inventors; Novoste Corporation, assignee. Methods for procedures related to the electrophysiology of the heart. US patent 5,529,067. 1995 Jun 25.

25. In press

(Note: NLM prefers "forthcoming" because not all items will be printed.) Leshner AI. Molecular mechanisms of cocaine addiction. N Engl J Med. In press

1996.

26. Journal article in electronic format

Morse SS. Factors in the emergence of infectious diseases. Emerg Infect Dis [serial online] 1995 Jan-Mar [cited 1996 Jun 5];1(1):[24 screens]. Available from: URL: http://www.cdc.gov/ncidod/EID/eid.htm

27. Monograph in electronic format

CDI, clinical dermatology illustrated [monograph on CD-ROM]. Reeves JRT, Maibach H. CMEA Multimedia Group, producers. 2nd ed. Version 2.0. San Diego: CMEA; 1995.

28. Computer file

Hemodynamics III: the ups and downs of hemodynamics [computer program]. Version 2.2. Orlando (FL): Computerized Educational Systems; 1993.

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A systematic review paper should have a structured Abstract of no more than 250 words using headlines as Objective, Data Sources, Study Selection, Data Extraction, Data Synthesis and Conclusions and with 3-10 key words for indexing.

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The *Introduction* of the paper could be similar to an original report, but without any longer literature survey, only reviewing shortly previous structural reviews and stating the reason and aim of the present review.

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Conclusions of the article also highlighting the problems, or areas for future research may be included.

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