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Editorial

Guidelines for submitting articles in JACP

Subhra Mitra

Professor, Pulmonary Medicine Department, Calcutta National Medical College, Kolkata

The Journal of the Association of Chest Physicians (JACP) is a peer-reviewed, open-access, bi-annual journal published in June and December. It is the official journal of the Association of Chest Physicians (ACP), West Bengal, India. The ACP is a body of chest physicians working together to increase awareness of chest diseases, induct preventive measures and foster good clinical practice in the state in particular and the country in general. The ACP not only performs regular clinical meets, CMEs and conferences but also generates knowledge through research and awareness, on important health issues like asthma, COPD, tuberculosis, hazards of smoking and air pollution.

The Journal welcomes manuscripts in the following categories: reviews and mini-reviews oriented towards the practicing internist; diagnostic puzzles from a variety of specialties; original scientific studies; short research reports; case reports of exceptional merit; analytic reviews such as meta-analyses and decision analyses; new methods and technologies; opinions on previously published literature; papers commenting on the clinical, scientific, social, political, and economic factors affecting health; letters to the editor. Our key aim is to engage, inform, and stimulate doctors, researchers and other health professionals in ways that will improve outcomes for patients and may facilitate hypothesis generation and development of further research to form the foundations of tomorrow's pulmonary medicine. The journal is devoted to the promotion of pulmonary medicine. Complimentary copies of the journal are sent to lifetime and associate life members of the ACP, West Bengal. The Editor-in-Chief and the editorial board do not necessarily subscribe to the views expressed by the author(s) in the articles published in this journal. The JACP accepts no liability for any inaccurate and misleading information, opinion or statement.

Author Guidelines:

A covering letter signed by all authors must state that the data have not been published elsewhere in whole or in part and all authors agree to their publication in the JACP. If the work has been conducted abroad then the article must be accompanied by a certificate from the Head of the institute where the work has been done.

The editorial board reserves the right to edit and, if necessary, shorten any material accepted for publication. The decision on the priority of publication would be strictly determined by the editorial board. All manuscripts will go through a double-blind peer-review process.

Manuscripts may be submitted by email to editor.jacp@gmail.com

Alternatively, manuscripts may be submitted in the following manner:

Type scripts:

Three typed copies of the article and one copy on a CD-ROM processed in MS Word (*.doc format only) should be submitted to the Editor. The text should be type-written in 12-point font Times New Roman, double spaced on one side of the paper not larger than ISO A4 (210 x 297 mm) with a 5 cm margin and pages should be numbered consecutively. The first page of the type script
should bear, in addition to the title of the paper, the names of the author(s) and the name and address of the institution or laboratory where the work has been carried out. The full address of the principal author to whom proofs will be sent should be given as footnote, as should any permanent change of address and/or appointment. Correspondence should also include e-mail address. A short (running) title of not more than 45 characters should be given. Please write as concisely as possible. Amendments should be made in the texts and not in the margins. All submitted manuscripts are reviewed by the editors and rejected manuscripts will not be returned. Ethical aspects will be considered in the assessment of the paper.

Type of manuscripts accepted for publication:

Original article (3000 words excluding references and structured abstract), case report (1000 words, 3 images, 10 references), letter to editor (750 words, 1 image), medical image (400 words in question and answer format, 2 image), review article (5000 words).

Arrangement:

Papers should be divided into: (a) Title page (b) Abstract (c) Introduction (d) Materials and methods (e) Results (f) Discussion (g) Acknowledgements (h) References (i) Tables (j) Figures and captions. The abstract should not exceed 250 words and should state concisely what was done, the main findings and how the work was interpreted. After the abstract, mention three to five keywords relevant to the article.

Style:

Abbreviations and symbols must be standard and SI units should be used throughout. Whenever possible, drugs should be given their approved generic name. Acronyms should be used sparingly. Statistical analysis must explain the methods used.

Reference should follow the Vancouver format. In the text, they should appear as numbers starting at 1 within parentheses in superscript.

Mitra S: Article Submission

At the end of the paper they should be listed (double spaced) in numerical order corresponding to the orders of citation in the text. All authors should be quoted for papers with up to six authors; for papers with more than six authors the first six only should be quoted followed by et al. Abbreviations for titles of medical periodicals should conform to those used in the latest edition of Index Medicus (found at www.ncbi.nlm.nih.gov/journals?tool=sidebar). The first and last page numbers for each reference should be provided. Abstracts and letter must be identified as such. Authors must check references against original sources for accuracy. Examples of reference are given below:

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Table and Figures:

Tables should be as few as possible and should present only essential data. Each table should be type-written on separate sheets, have a title or caption with Roman numbers. All photographs, graphs, diagrams should be referred to as figures and should be numbered consecutively in the text in Arabic numerical. The legends for illustrations should be typed on separate sheets. All illustrations must be in JPEG format at a resolution of 300 dots/inch (DPI) or higher. A separate file should be submitted for each Figure or Figure part. Photomicrographs should be un-mounted glossy prints. Photomicrographs should have internal scale markers; include in the legend the original magnification and the stain used. Line diagrams and graphs should be scanned at 600 DPI (or better) and submitted on separate sheets. The editorial board reserves the right to crop/trim any illustration to conform to the style of the text. Subject/patient must not be identifiable on the photograph. If this is unavoidable, written permission from the patient or legal guardian must be obtained.

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Mitra S: Article Submission

Submission Preparation Checklist:
As part of the submission process, authors are required to check off their submission's compliance with all of the following items, and submissions that do not adhere to these guidelines may be returned to authors. The manuscript must be accompanied by an undertaking that the submission has not been previously published, nor is it before another journal for consideration.

1. The submission file is in Microsoft Word document file format.
2. Where available, URLs for the references have been provided.
3. The text is double-spaced; uses a 12-point font; employs italics, rather than underlining (except with URL addresses); and all illustrations, figures, and tables are placed within the text at the appropriate points, rather than at the end.
4. The text adheres to the stylistic and bibliographic requirements outlined in the.
5. If submitting to a peer-reviewed section of the journal, the relevant instructions have been followed.
6. Statement on conflict of interest has been declared.

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The basics of biostatistics:

Although application of statistical methods to biomedical research began only some 150 years ago, statistics is now an integral part of medical research. Knowledge of statistics is also becoming mandatory to understand most medical literature.

Data (values of a variable) constitutes the raw material for statistical work. It is important to understand the different types of data and their mutual interconversion.

Biostatistics begins with descriptive statistics. This implies summarizing a data series from a sample or population. Categorical data are described in terms of percentages or proportions. With numerical data, individual observations within a sample or population tend to cluster about a central location, with more extreme observations being less frequent. The extent of this clustering is summarized by measures of central tendency such as the mean, median or mode, while the spread is described by measures of dispersion such as range, variance, standard deviation or coefficient of variation.

The confidence interval is an increasingly important measure of precision. When we observe samples, there is no way of assessing true population parameters. We can however, obtain a standard error from the sample and use it to define a range in which the true population value is likely to lie with a certain acceptable level of uncertainty. This is the confidence interval. Conventionally, the 95% confidence interval is used.

Patterns in data sets, called data distributions, are important component of descriptive statistics. The most common distribution is the normal distribution which is depicted as the well-known symmetrical bell-shaped Gaussian curve. Familiarity with other distributions, such as the binomial distribution and the Poisson distribution, would be also helpful.

![Box plot](image)

Figure 1: A horizontal box plot depicting the five number summaries of numerical data.

Note that this particular dataset is not symmetrical but is skewed to the left.

Various graphs and plots have been devised to summarize data and trends visually. Pie chart, line diagram, bar chart and the histogram are universally used. Some plots, such as the box-and-whiskers plot (Figure 1) and the stem-and-leaf plot are used less often but provide useful summaries in select situations. Error bars should be used to depict the variation or the precision of the measurements, wherever applicable.

Measuring disease frequency:

Incidence and prevalence are the two basic measures of disease frequency but they are often wrongly used and interpreted. The key to understanding measures of disease frequency is the three elements of N-E-T – number of persons who are observed for occurrence of the event (i.e. the population), the event (i.e. the disease, condition or outcome of interest) and the time period during which such events are observed. Incidence is the number of new cases occurring...
in a particular time period. In other words, it measures the rate at which people without a disease develop the same over a specified period of time. **Average annual incidence, incidence density, cumulative incidence, attack rate and attributable risk** are extensions of this concept. Prevalence is the count of existing disease at a single point in time or over a defined period of time. If over a period of time it will count both new and existing cases. Prevalence may be expressed as **point prevalence, period prevalence or cumulative** (e.g., lifetime) prevalence.

Mortality, incidence and prevalence may be stated as crude or specific rates. The **crude rate** refers to the number of occurrences for a whole population and is often expressed as rate per 1000, 10,000 or 100,000 members of the population. It may be more meaningful to state **specific rates** for factors like age, sex, ethnicity and others.

**Standardized rates** adjust for differences in structures between populations. Although age is normally used in this process, other factors (e.g., ethnicity) can also be employed. A single statistic is produced, allowing ready comparisons between populations. Standardization can be done by direct or indirect methods. Both compare a specific study population with a ‘standard population’ (often national population or the standard world population modeled by the World Health Organization). This may be carried out for both sexes individually. **Indirect standardization** is used more commonly and yields more stable results, than **direct standardization**, for small populations or small numbers of events. A **standardized mortality ratio** (SMR) is generated by this method.

**Determining sample size:**

An adequate sample ensures that a study yields reliable information, regardless of whether it ultimately suggests a clinically important association between the interventions or exposures and the outcomes being studied. The probability of **Type I and Type II errors**, the expected variance in the sample and the **effect size** are the essential determinants of **sample size** for interventional studies.

Any method for deriving a conclusion from experimental data carries some risk of drawing a false conclusion. Two types of false conclusion may occur, called **type I and type II errors**, whose probabilities are denoted by the symbols and . A type I error occurs when one concludes that a difference exists between the groups or data sets being compared when, in reality, it does not. This is akin to a false positive result. A type II error occurs when one concludes that a difference does not exist when, in reality, it does, and the difference is equal to or larger than the effect size defined by the alternative to the null hypothesis. This is a false negative result. When considering the risk of type II error, it is more intuitive to think in terms of power of the study or . Power denotes the probability of detecting a difference when it does exist. When calculating sample size, conventional acceptable values for and power are maximum 5% and minimum 80%, respectively. Smaller or larger power will increase sample size. Increasing variance in the sample tends to increase the sample size required to achieve a given power level. The effect size is the smallest clinically important difference that is sought to be detected and, rather than statistical convention, is a matter of past experience and clinical judgment. Larger samples are required if smaller differences are to be detected.

In the past, sample size determination was difficult due to the need to learn relatively complex mathematics and numerous formulae. However, the task has become much easier of late, owing to improving availability, capability and user-friendliness of power and sample size determination software. Many can execute routines for a wide variety of research designs and statistical tests. Therefore, researchers must now concentrate on applying the principles...
appropriately and achieving calculated sample size targets so that study conclusions are truly meaningful.

**Correlation and linear regression:**

Correlation and linear regression are commonly used techniques for quantifying the association between two numeric variables. **Correlation** quantifies the strength of the linear relationship between a pair of variables, expressing this as a correlation coefficient. If both variables $x$ and $y$ are normally distributed, we calculate **Pearson’s correlation coefficient** ($r$). The value $r^2$ denotes the proportion of the variability of $y$ that can be attributed to its linear relation with $x$, and is called the **coefficient of determination**. If normality assumption is not met for one or both variables in a correlation analysis, a rank correlation coefficient, such as **Spearman’s rho** ($\rho$) or **Kendall’s tau** ($\tau$), may be calculated. A hypothesis test of correlation tests whether the linear relationship between the two variables holds in the underlying population, in which case it returns $p < 0.05$. A 95% confidence interval for the population correlation coefficient can also be calculated.

**Linear regression** is a technique that attempts to link the two variables $x$ and $y$ in the form of a mathematical equation ($y = a + bx$), such that given the value of one variable the other may be predicted. Generally, the method of least squares is applied to obtain the equation of the regression line.

Correlation and linear regression analyses are based on certain assumptions and misleading conclusions may be drawn if these are not met. The first assumption is that of linear relationship between the two variables. A **scatter plot** is essential before embarking on any correlation-regression analysis to show that this is indeed the case. Clustering (subgroups) or outliers within data sets can distort the correlation coefficient value. Finally, it is vital to remember that though strong correlation can be a pointer towards causation, the two are not synonymous.

**Hypothesis testing:**

Hypothesis testing (or **inferential statistics**) is one of the major applications of biostatistics. Most studies have a research question that can be framed as a hypothesis. Inferential statistics begins with the **null hypothesis** that reflects the conservative position of no change or no difference in comparison to baseline or between groups. Usually the researcher has reason to believe that there is some effect or some difference, that is believes in an alternative hypothesis. The researcher therefore proceeds to study samples and measure outcomes in the hope of generating evidence strong enough for the statistician to be able to reject the null hypothesis.

The $p$ value concept is almost universally used in hypothesis testing. It denotes the probability of obtaining by chance a result at least as extreme as that observed; even when the null hypothesis is true and no real difference exists. Usually, if $p$ is $< 0.05$ the null hypothesis is rejected and sample results are deemed **statistically significant**. The **two-tailed** $p$ value is used more commonly, implying that the results would be accepted irrespective of whether they are favoring the test or the control intervention, as against a **one-tailed** $p$ value that is used when change, if any, would be one direction only for certain.

With the universal availability of computers and increasing access to specialized statistical software, the drudgery involved in inferential statistics calculations is now gone. The researcher is free to devote time to optimally designing the study, carefully selecting the hypothesis tests to be applied and taking care in conducting the study well. Thinking of the research hypothesis in terms of generic research questions helps in selection of the right hypothesis test. In addition, it is important to be clear about the nature of the variables.
(e.g. numerical vs. categorical; parametric vs. non-parametric) and the number of groups or data sets being compared (e.g. two or more than two) at a time.

Finally, it is becoming the norm that an estimate of the size of any effect, expressed with its 95% confidence interval, is required for meaningful interpretation of results. A large study is likely to have a small (and therefore ‘statistically significant’) p value, but a ‘real’ estimate of the effect would be provided by the 95% confidence interval. If the intervals overlap between two interventions, then the difference between them is not so clear-cut even if p < 0.05.

Comparing groups: numerical variables:

Numerical data that are normally distributed can be analyzed with parametric tests, that is tests based on the parameters that define a normal distribution curve. If the distribution is uncertain, the data can be plotted as a normal probability plot and visually inspected, or tested for normality using one of a number of goodness of fit tests, such as the Kolmogorov-Smirnov test or the Shapiro-Wilk test.

The widely used Student’s t test has three variants. The one-sample t test is used to assess if a sample mean (as an estimate of the population mean) differs significantly from a given population mean. The means of two independent samples may be compared for a statistically significant difference by the unpaired or independent samples t test. If the data sets are related in some way, their means may be compared by the paired or dependent samples t test.

The t test should not be used to compare the means of more than two groups. Applying the t test to compare groups in pairs in such a situation will increase the probability of type I error. The one-way analysis of variance (ANOVA) is employed to compare the means of three or more independent data sets that are normally distributed. However, multiple measurements from the same set of subjects cannot be treated as separate unrelated data sets. Comparison of means in this scenario requires repeated measures ANOVA. It is to be noted that while a multiple group comparison test such as ANOVA can point to a significant difference, it does not identify exactly between which two groups the difference lies. To do this, an appropriate post hoc test is necessary. Examples are the Tukey’s test, Student-Newman-Keuls test or Dunnett’s test following ANOVA.

If the assumptions for parametric tests are not met, there are non-parametric alternatives for comparing data sets. These include Mann-Whitney U test instead of unpaired Student’s t test, Wilcoxon’s matched pairs signed ranks test in lieu of paired Student’s t test, Kruskal-Wallis test as the non-parametric counterpart of ANOVA and the Friedman’s test instead of repeated measures ANOVA. The Dunn’s test is used as a post hoc test following Kruskal-Wallis or Friedman’s ANOVA.

Comparing groups: categorical variables:

Categorical variables are commonly represented as counts or frequencies. For analysis, such data are conveniently arranged in contingency tables (tables in which counts in individual cells are independent of one another and their sum denotes the total sample). Conventionally, such tables are designated as r X c tables, with r denoting number of rows and c denoting number of columns.

The chi-squared probability distribution is particularly useful in analyzing categorical variables. A number of tests yield test statistics that fit, at least approximately, a chi-squared distribution and hence are referred to as chi-squared tests. Examples include Pearson’s chi-squared test (or simply the Chi-squared test), McNemar’s chi-squared test, Mantel-Haenszel chi-squared test and others. The Pearson’s chi-squared test is the most commonly used test for assessing difference
in distribution of a categorical variable between two or more independent groups. If the groups are ordered in some manner, the **chi-squared test for trend** should be used. The **Fisher's exact probability test** is a test of the independence between two dichotomous categorical variables. It provides a better alternative to the chi-squared statistic to assess the difference between two independent proportions when numbers are small, but cannot be applied to a contingency table larger than 2 X 2. The **McNemar’s chi-squared test** assesses the difference between paired proportions. It is used when the frequencies in a 2 x 2 table represent paired (dependent) samples. The **Cochran's Q test** is a generalization of the McNemar’s test that compares more than two related proportions.

The $p$ value from the Chi-squared test or its counterparts does not indicate the strength of the difference or association between the categorical variables involved. This information can be obtained from the relative risk or the odds ratio statistics. Both are measures of dichotomous association obtained from 2 X 2 tables.

**Statistics of diagnostic tests:**

Crucial therapeutic decisions are based on diagnostic tests. Therefore it is important to evaluate such tests before adopting them for routine use. Tests on blood or other biological fluids, radiological imaging and microbial cultures are obvious diagnostic tests. However, even things like specific clinical examination procedures, scoring systems based on physiological or psychological evaluation, ratings based on questionnaires are also diagnostic tests and therefore merit similar evaluation.

In the simplest scenario, a diagnostic test will give either a positive (disease likely) or negative (disease unlikely) result. Ideally, all those with the disease should be classified by a test as positive and all those without the disease as negative. Unfortunately, in practice, no test gives 100% accurate results. Therefore, leaving cost aside, the performance of diagnostic tests is evaluated on the basis of at least four statistical parameters – sensitivity, specificity, positive predictive value and negative predictive value. **Likelihood ratios** combine information on specificity and sensitivity to expresses the likelihood that a given test result would occur in a subject with a disorder compared to the probability that the same result would occur in a subject without the disorder.

Not all tests can be categorized simply as ‘positive’ or ‘negative’. Test results may come on a numerical scale and in such cases judgment is required in choosing a cut-off point to distinguish normal from abnormal. Naturally a cut-off value should provide the greatest predictive accuracy but there is a trade-off between sensitivity and specificity here - if the cut-off is too low, it will identify most patients who have the disease (high sensitivity) but will also incorrectly identify many who do not (low specificity). A **receiver operator characteristic (ROC) curve** plots pairs of sensitivity versus (1 – specificity) values, and helps in selecting an optimum cut-off – the one lying on the ‘elbow’ of the curve.

The **Bland-Altman plot** is a graphical method of assessing agreement between two diagnostic tests that measure on a numerical scale. It plots the difference between pairs of observations against their arithmetic mean. **Cohen's kappa statistic** is a measure of inter-rater agreement for categorical variables. It is also used to assess how far two tests agree with respect to diagnostic categorization. It is generally thought to be a more robust measure than simple percent agreement calculation since it takes into account the agreement occurring by chance.
Assessing risk:
A basic measurement of risk is the probability of an individual developing an outcome when exposed to a risk factor. This can be simply expressed as proportion (percentage) of those exposed to the risk factor who develop the outcome, along with its 95% confidence interval. However, to assess the importance of an individual risk factor, it is necessary to compare the risk of the outcome in the exposed group with that in the non-exposed group. A comparison between risks in different groups can be made by examining either their ratio or the difference between them. The 2 X 2 contingency table comes handy in the calculation of ratios.

**Odds** is the ratio of the probability of occurrence of an event to the probability of non-occurrence of the same event. **Odds ratio (OR)** or cross-product ratio is the ratio of the odds of an event in the exposed group, to the odds of the same event in the non-exposed group. It can range from zero to infinity. OR > 1, indicates exposure increases risk while OR < 1 indicates that exposure is protecting against risk. The OR should be presented with its 95% CI to enable more meaningful interpretation – if this interval includes 1, then even a relatively large OR will not carry much weight. The **relative risk (RR)** or risk ratio denotes ratio of probability of event in exposed group to probability of same event in the non-exposed group. Its interpretation is similar (but not identical) to the OR. If the event in question is relatively uncommon, values of OR and RR tend to be similar. However, for common events the value of RR is constrained while the OR may become very large.

**Absolute risk reduction (ARR)** is a measure of the effectiveness of an intervention with respect to a dichotomous event. It is calculated as proportion experiencing the event in control group minus the proportion experiencing the event in treated group. It is often used to denote the benefit to the individual. The reciprocal of ARR is the **number needed to treat (NNT)** and this denotes the number of subjects who would need to be treated in order to obtain one more success than that obtained with a control treatment. Alternatively (e.g. in vaccine trials), this could also denote the number that would need treatment in order to prevent one additional adverse outcome as compared to control treatment. Extended to toxicity, the NNT becomes a measure of harm and is then called **number needed to harm (NNH)**. NNT and NNH are important concepts from the policy maker’s perspective.

**Survival analysis:**
Survival analysis is concerned with ‘time to event’ data. Traditionally it dealt with cancer death as the event in question, but it can handle any event occurring over a time frame such as complication, recovery, failure, success, etc. When the outcome of a study is the time to an event, a likely problem is that it is often not possible to wait until events have happened in all the subjects (e.g. till all are dead). Additionally, many subjects may leave the study prematurely or simply be lost to follow-up. Such situations lead to what is called **censoring** as complete information is not available for these subjects. The data set is thus a mixture of times to the event in question and times after which no more information on the individual is available. Survival analysis methods make no assumption regarding normal distribution of time data and are the only techniques capable of handling censored observations without treating them as missing data.

Descriptive methods for estimating the distribution of survival times from a sample include **life table**, **survival distribution fitting**, and **Kaplan-Meier survival function** estimation. The last is exemplified by the **Kaplan-Meier survival plot** (Figure 2), which plots the cumulative probability of survival against time. Several techniques are available for comparing survival experience in two or more groups – the **log-rank test** is popularly used. An advantage of the log rank test is that it can also be used to produce...
an odds ratio as an estimate of risk of the event: this is called a hazard ratio.

Figure 2: A basic Kaplan-Meier survival plot.
Note the staircase pattern. Note also that it is a ‘crazy’ staircase since neither the height nor the width of the ‘stairs’ fixed.

Finally, survival analysis offers different regression models for estimating the relationship of multiple variables to survival. Cox proportional hazards model is a popular regression method that allows the hazard function to be modeled on a set of explanatory variables without making restrictive assumptions concerning the nature or shape of the underlying survival distribution. It can accommodate any number of covariates, whether they are categorical or continuous. Like the adjusted odds ratios in logistic regression, this multivariate technique produces adjusted hazard ratios for individual factors that may modify survival.

The general linear model and other multivariate methods:
Multivariate analysis refers to statistical techniques that look at a number of variables simultaneously, with a view to clarifying the relationships between them. Many of them try to build mathematical models that can be used for prediction. The general linear model is not a discrete statistical technique in itself, but rather a strategy for analysis. Its goal is to determine whether and how one or more independent variables relate to or affect one or more dependent variables, assuming that the relationships between them are linear.

Hazra A: Biomedical Statistics

It is an umbrella concept, that in addition to simple linear regression and one-way analysis of variance (ANOVA), includes several multivariate techniques.

Multiple linear regression models a situation where a single numerical dependent variable is to be predicted from multiple independent variables. Logistic regression is an analogous technique that is used when the outcome variable is dichotomous in nature. In this, the natural logarithm of odds ratios is modeled as a linear function of the explanatory variables. The log-linear technique models count type of data and can be used to analyze cross-tabulations where more than two variables are included. It can look at three or more variables at the same time to determine associations between them and also show just where these associations lie.

Factor analysis and principal component analysis are a group of related techniques that seek to reduce a large number of predictor variables to a smaller number of factors or components, which are linearly related to the original variables.

Analysis of covariance (ANCOVA) is an extension of ANOVA, in which an additional independent variable of interest for which data is available, the covariate, is brought into the analysis. It tries to examine whether a difference still persists after ‘controlling’ for the effect of the covariate that can impact the numerical dependent variable of interest. MANOVA and MANCOVA, are multivariate extensions of ANOVA and ANCOVA respectively, and are used when multiple numerical dependent variables have to be incorporated in the analysis.

Structural equation modeling includes a number of advanced statistical techniques and is referred to by a variety of other names. It is the most flexible approach under the general linear model, and is able to deal with multiple dependent and independent variables, whether numerical or
categorical in nature. Two analytic techniques that use structural equation modeling, **path analysis** and **confirmatory factor analysis**, are considered distinct techniques in their own right.

**Path analysis** may be regarded as a multivariate statistical technique that makes use of multiple regression to explore causal relationship among variables and depicts this relationship in graphical form called the path diagram. The path diagram can only be constructed if one has formulated a 'causal hypothesis', that is some hypothesis regarding which variables may be related and in what manner. Path diagram conventions allow relationships to be shown with their directions and strengths.

**Classification and regression tree (CART) analysis** is an alternative to procedures like multiple regression and logistic regression for investigating the relationship between a response or outcome variable and a set of predictor or explanatory variables. The goal is to determine subsets of explanatory variables most important for prediction of the response variable. Rather than fitting a mathematical model to the sample data, the observations are divided recursively into a number of groups, each division being chosen so as to maximize some measure of the difference in the response variable in the resulting two groups. The resulting CART dendrogram often provides easier interpretation than a regression equation, and those variables most important for prediction can be quickly identified. Binary response variables lead to classification trees, while continuous numerical response variables lead to regression trees.

**FURTHER READING:**

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INTRODUCTION:
Patients with chronic kidney disease (CKD) have increased risk of tuberculosis (TB). According to NICE guidelines, the relative risk (RR) of developing active TB is 10-25 in patients with CKD and those on hemodialysis and 37 for post renal transplant where immunity is depressed due to immunesuppressive therapy.[1]

One population based study screening of 4972 persons in new Delhi revealed prevalence of CRF in adult population was 0.785% or 7852/million.[2]

Advanced CKD is associated with an acquired immunodeficiency which results in reduced function of neutrophils, T and B cell, monocytes and natural killer cells.[3],[4] So, every physician should have an idea of managing TB in presence of CKD.

Aims are
1. Avoidance of nephrotoxic drugs.
2. Modification of dose of drugs depending on the degree of renal failure.
3. Attention to interaction between immunosuppressive drugs used in post renal transplant patients and antitubercular drugs.

So, management of TB infection and disease depends according to
- Stages of CKD.
- Whether on peritoneal dialysis or haemodialysis.
- After renal transplantation.

Before going to the subject proper we must know the Grades of Renal Impairment in Chronic Kidney Disease (CKD).[5]

Recommended equation for Glomerular Filtration rate (GFR) is by Cockcroft-Gault Equation

\[
\text{Estimated Creatinine clearance (ml/min)} = \frac{(140 - \text{Age}) \times \text{Wt in kg}}{72 \times \text{Serum Creatinine}} 
\]

(multiplied by 0.85 in case of female)

- Stage 1 CKD: Normal creatinine clearance and function but having urinary tract abnormality, for example polycystic kidney, structural abnormality.
- Stage 2: Creatinine clearance 60-90 ml/min.
- Stage 3: Creatinine clearance 30-60 ml/min.
- Stage 4: Creatinine clearance 15-30 ml/min.
- Stage 5: Creatinine clearance <15 ml/min with or without dialysis.

In stage 3-5 CKD there is deficiency of 25 hydroxy vitamin D which may cause impaired monocyte function, reduced production of Cathelicidin, a peptide capable of destroying Mycobacterium tuberculosis.[6]

BRIEF OUTLINE OF ATD PHARMACOKINETICS IN PRESENCE OF CKD:

**Isoniazid:**

It is metabolized by the liver into less active compounds which is then excreted by the kidneys. It is dialyzable only in very small amounts. In CKD when thrice weekly high dose is used, there is increased risk of neurotoxicity. There is no clear data on INH elimination during peritoneal dialysis. There is high risk of neuropsychiatric disturbances including encephalopathy in patients on dialysis. Usually within the first few weeks of therapy patient may develop grand
Kundu S: Tuberculosis Management in CKD

Ethambutol:
Around 80% of ethambutol is excreted unchanged by the kidneys. In patients with CKD, excretion of ethambutol is significantly reduced (with dose 15mg/kg). Its ocular toxicity is largely dose-dependent. Even it can cause blindness. So monthly vision check up is necessary. It is dialysable. It has improved efficacy when administered intermittent high doses than lower daily dose.[7] Serum monitoring should be done and trough levels should be < 1.0 mg/ml at 24 hour post dose without dialysis, Streptomycin is better than ethambutol in CKD.

Aminoglycosides:
Approximately 80% of Streptomycin, Kanamycin, Amikacin and Capreomycin are excreted unchanged in urine. Streptomycin causes significant vestibular toxicity but less nephrotoxicity compared to other aminoglycosides. Elimination times increases in advanced age and impaired renal function. Approximately 40% of Streptomycin Amikacin, Capreomycin and Kanamycin are removed by haemodialysis when these drugs are given just before haemodialysis. No data is available on peritoneal dialysis. Like Ethambutol and Pyrazinamide, the dosing interval should be increased rather than dose reduction as the drugs exhibit concentration-dependent bactericidal action and lower dose may reduce drug efficacy. ATS recommends 12-15mg/kg/dose 2 or 3 times/week for all of these drugs and drug levels should be monitored.

Fluoroquinolones:
Both Ofloxacin and Ciprofloxacin are dependent on renal clearance and doses should be reduced accordingly. Levofoxacin undergoes greater renal clearance than Moxifloxacin. Fluoroquinolones decrease metabolism of Ciclosporin A and displace it from the bound form, thus increasing its toxicity.
**Cycloserine:**

Up to 70% is excreted by the kidneys and 56% removed by hemodialysis.[8],[9],[10] Dose related neurological and psychiatric side effects are reported in up to 50% of patients.

The ATS recommends increasing the dose interval in CKD and suggesting 250 mg once daily or preferably 500 mg 3 times/week. It should be given after haemodialysis to avoid under dosing and monitored for neurotoxicity.

**Para-amino Salicylic acid (PAS):**

A modest amount of PAS (6.3%) is cleared by haemodialysis but its metabolite acetyl-PAS, is substantially removed. A dose of 4 mg twice daily should be adequate.

**Ethionamide / Prothionamide:**

They are not cleared by kidneys nor are they removed by haemodialysis, so no dose adjustment is required.

**Clofazimine:**

It can accumulate in CKD and causes skin and hair discoloration, photosensitivity and ocular problems. The normal dose is 100 - 300 mg daily and dose should be reduced to 3 times/week in CKD and in haemodialysis.

**Linezolid:**

Higher incidence of blood disorder and optic neuropathy are seen when it is used for more than 28 days. It is reversible MAO inhibitor. Normal dose 600mg BID. The ATS uses a creatinine clearance of < 30 ml/min as cut off point below which dose adjustment is necessary. It creatinine clearance is >30 ml/min then standard dose with regular serum level estimation is advised.

**Treatment of Tuberculosis in patients with CKD not on dialysis:**

For patients with stages 4 and 5 CKD, dosing intervals should be increased to three times weekly for ethambutol, pyrazinamide and the aminoglycosides.

Although R, H and Z can be used in normal doses in renal impairment several studies have shown thrice weekly treatment with pyrazinamide is therapeutically better.[7],[11],[12] Pyridoxine supplementation should be given to prevent peripheral neuropathy those who are on INH.

Ethambutol is mainly excreted through kidneys, increasing the dose interval with monitoring of drug level is essential.

Recent reports show that gatifloxacin and moxifloxacin are at least equivalent and possibly better than ethambutol as the fourth drug.[13],[14] But moxifloxacin is suitable for daily regimen only.

**Haemodialysis:**

For hemodialysis patients dosing interval of ATT and timing (predialysis or postdialysis) is very important. Dosing interval should be three times weekly to reduce toxicity. If drugs are given predialysis there is chance of early removal of drugs and reduced therapeutic efficacy. If drugs are given after dialysis, then drugs administration will be supervised, so there is advantage of DOTS with improved adherence but definitely there is chance of drug toxicity.

Majority of respiratory physicians prefer ATD to be given after dialysis.

**On peritoneal dialysis:**

One study has shown those who are suffering from pulmonary TB and on chronic ambulatory peritoneal dialysis (CAPD) no dose adjustment is needed for INH, R or Z.

Rifampicin has a high molecular weight, lipid solubility and protein binding capacity and so it is less dialysable through peritoneal membrane. So, oral therapy with rifampicin may not be adequate for treatment of peritoneal tuberculosis. Intraperitoneal administration of rifampicin may be considered in treating peritoneal TB patients.[15]
Renal Transplantation:

Renal function usually improves after transplantation. Dose modification may be necessary depending upon the function of transplant kidney.

In general standard therapy for 6 months of RHZE/M followed by 4 RH can be used.[16] Antitubercular drug interaction with immunosuppressive drugs can lead to graft rejection. Rifampicin induces a number of liver enzymes. The daily corticosteroid dose should be doubled in patients taking rifampicin. Rifampicin lowers blood levels of cyclosporine, which should be monitored and dose adjusted. Information regarding rifampicin tacrolimus interaction is limited but dose of tracrolimus may need to be increased.

Similarly doses of mycophenolate mofetil should be increased. Once rifampicin has been stopped, liver enzyme induction usually takes 2 weeks to return to normal.

Table: Dosage of 1st line ATDs in CKD

<table>
<thead>
<tr>
<th></th>
<th>Stage 1-3 CKD</th>
<th>Stage 4 and 5 CKD/MHD</th>
<th>Renal transplant recipients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isoniazid</td>
<td>300 mg daily</td>
<td>300 mg daily</td>
<td>300 mg daily</td>
</tr>
<tr>
<td>Rifampicin</td>
<td>&lt;50 kg: 450 mg daily</td>
<td>&lt;50 kg: 450 mg daily</td>
<td>&lt;50 kg: 450 mg daily</td>
</tr>
<tr>
<td></td>
<td>&gt;50 kg: 600 mg daily</td>
<td>&gt;50 kg: 600 mg daily</td>
<td>&gt;50 kg: 600 mg daily</td>
</tr>
<tr>
<td>Pyrazinamide</td>
<td>&lt;50 kg: 1.5 g daily</td>
<td>25-30 mg/kg, 3/week</td>
<td>&lt;50 kg: 1.5 g daily</td>
</tr>
<tr>
<td></td>
<td>&gt;50 kg: 2 g daily</td>
<td></td>
<td>&gt;50 kg: 2 g daily</td>
</tr>
<tr>
<td>Ethambutol</td>
<td>15 mg/kg daily</td>
<td>15-25 mg/kg, 3/week (max 2.5 g)</td>
<td>15 mg/kg daily</td>
</tr>
<tr>
<td>Moxifloxacin</td>
<td>400 mg daily</td>
<td>Not suitable for 3 weekly regimen</td>
<td>400 mg daily</td>
</tr>
</tbody>
</table>

Secondline Drugs in CKD

<table>
<thead>
<tr>
<th>Drug</th>
<th>GFR</th>
<th>Dose</th>
<th>Dialysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Streptomycin</td>
<td></td>
<td>20-50% daily (7.5-15mg/kg every 24h)</td>
<td>HD as for GFR &lt;10ml/min CAVH as for GFR 10-20ml/min</td>
</tr>
<tr>
<td></td>
<td></td>
<td>10-20% every 24-72 h (7.5-15mg/kg every 24-72h)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>&lt;10</td>
<td>50-100% every 72-96 h (7.5-15mg/kg every 72-96h)</td>
<td></td>
</tr>
<tr>
<td>PAS (manufacturer States)</td>
<td>&gt;50 ml/min</td>
<td>100%</td>
<td>HD: give after HD</td>
</tr>
<tr>
<td></td>
<td>10-50</td>
<td>50-75%</td>
<td>PD: as &lt;10ml/min</td>
</tr>
<tr>
<td></td>
<td>&lt;10</td>
<td>50%</td>
<td>CAVH: as &lt;10ml/min</td>
</tr>
<tr>
<td>Ethionamide</td>
<td></td>
<td>&gt;50</td>
<td>No Change</td>
</tr>
<tr>
<td></td>
<td>10-50</td>
<td>No Change</td>
<td></td>
</tr>
<tr>
<td></td>
<td>&lt;10</td>
<td>50%</td>
<td></td>
</tr>
<tr>
<td>Capreomycin (adjust dose to give steady state concentrations of 10µg/ml)</td>
<td>&gt;50</td>
<td>24 h dose interval</td>
<td>HD: give after HD</td>
</tr>
<tr>
<td></td>
<td>10-50</td>
<td>48 h dose interval</td>
<td>PD: no Change</td>
</tr>
<tr>
<td></td>
<td>&lt;10</td>
<td>48 h dose interval</td>
<td>CAVH dose as 10-50ml/min</td>
</tr>
<tr>
<td>Cycloserine (blood monitoring levels &lt;30mg/l)</td>
<td>&gt;50</td>
<td>12 h dose interval</td>
<td>HD: no change</td>
</tr>
<tr>
<td></td>
<td>10-50</td>
<td>12-24 h</td>
<td>PD: no change</td>
</tr>
<tr>
<td></td>
<td>&lt;10</td>
<td>24 h dose interval</td>
<td>CAVH: dose as 10-50ml/min</td>
</tr>
</tbody>
</table>
Latent Tubercular Infection (LTBI)

According to NICE guidelines the relative risk for active TB is 10-25 times in patients with CKD or MHD and 37% for Renal transplant recipients

ATS/CDC recommends targeted tuberculin skin testing (TST) for all patients with chronic kidney disease. The Spanish group for the study of infection in transplant recipients recommends TST as a part of the evaluation of all potential candidates for solid organ transplantation.

Maintenance hemodialysis (MHD) patients receiving INH prophylaxis 16.7% developed active TB disease compared to 32.7% in the controlled group.[17] In a randomized, double blind, placebo controlled, prospective trial of INH prophylaxis in patients on MHD from India has shown some degree of protection.[18]

Method of Screening:

TST- It is unreliable in advanced CKD and on immunosuppressive agents. A positive test may be useful but a negative test may not be true negative. Because in advanced CKD reported energy may be up to 50%.

The new Interferon Gramma Release Assay (IGRA) test has two commercially available tests

1. T-SPOT TB assay
2. QuantiFERON-TB gold.

The second one is easier to perform but T-SPOT TB assay is more sensitive.

Chemoprophylaxis in LTBI

1. T. INH 300mg once daily for 6 months + Pyridoxine 10-25 mg daily

   OR

2. RH daily for 3 months + Pyridoxine 10-25 mg daily

   OR

3. Only Rifampicin daily for 4-6 months.

INH longer than 6 months has minimal additional advantage rather it increases the risk of drug-induced hepatitis.

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Case Report
Foreign Body in Bronchus with Normal Chest X-ray
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ABSTRACT:
Foreign body aspiration is a dreaded emergency in children below three years of age. There are cases where foreign body does not cause airway obstruction. Delay in diagnosis can occur when the foreign body does not cause airway obstruction. Our patient is a 7-year child presented with chest discomfort and cough. His chest x-ray was normal but there was presence of fixed rhonchi on auscultation. Fibre optic bronchoscopy revealed a foreign body in the right intermediate bronchus and it was removed successfully.

KEY WORDS: Foreign body, bronchus, chest x-ray

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INTRODUCTION:
Foreign body aspiration is commonly encountered in children particularly less than three years in age. History is suggestive in 67% of the children while radiological findings supported the diagnosis in 83%.[1, 2] Although history and radiological findings lead to early diagnosis in many cases, delay in diagnosis leading to severe complications is not rare either. Delay is especially prominent when the foreign body does not cause airway obstruction thereby not disturbing respiratory physiology. One case with aspiration of a foreign body that allows passage of air and therefore not obstructing ventilation and not causing significant clinical and radiological findings is discussed below.

CASE REPORT:
An 11-year male presented to pediatric medicine outdoor with history of ingestion of upper part of pen. He complained of cough and chest discomfort. He denied any history suggestive of spontaneous expulsion of foreign body through stool or by mouth. A screening chest x-ray was done to rule out lodgment of any foreign body within the respiratory tract [Figure 1].

Figure 1: Normal chest x-ray of the patient.
Patient was referred to chest outdoor with the chest x-ray. On examination of respiratory system, there was presence of fixed rhonchi in right infraclavicular and interscapular area. Patient was admitted for evaluation of fixed rhonchi. Fibre optic bronchoscopy showed a black foreign body with central opening in right main bronchus [Figure 2].

Figure 2: FOB showing black foreign body obstructing the right main bronchus.
Saha K: Foreign Body in Bronchus

Foreign body was removed by holding its edge with biopsy forceps while patient was asked to cough [Figure 3a & b].

![Figure 3](image)

**Figure 3**: Removed black foreign body with central opening (a) and carina with clear right and left main bronchus after removal of foreign body (b).

After removal of foreign body, fixed rhonchi disappeared.

**DISCUSSION:**

Foreign body aspiration that is most commonly encountered in pre-school children is a life threatening emergency; however, it may go unrecognized for prolonged periods of time due to vague clinical and radiological findings in some cases.[3],[4] Considering the fact that most commonly aspirated foreign bodies in children include organic material like peanuts not causing complete obstruction, careful evaluation is especially important for prompt diagnosis.[3] Aspiration of a foreign body may result in immediate choking when lodged in larynx or may lead to complete obstruction of air entry into a lung segment.[5],[6] Retained foreign body in the airway leads to local mechanical effects, chemical reactions and inflammation. An animal study has demonstrated that initial reaction to the presence of foreign body in the airway is polymorphonuclear leukocyte infiltration and edema, which is followed by mononuclear macrophage infiltration. These findings have been interpreted as initiation of acute inflammation as early as three days after aspiration and progression to chronic inflammation as early as ten days. Moreover, bronchiectatic changes were observed when a month has passed after aspiration.[7]

Presenting symptoms of foreign body aspiration may vary from vague to specific and include cough, wheeze, dyspnea and fever. Physical examination may reveal focal wheezing or decreased air entry but the findings may also reveal generalized wheezing or the findings may be completely normal.[8] Similarly plain radiographs of chest may reveal unilateral hyperinflation, atelectasis, consolidation or mediastinal shift if there is complete obstruction of airflow by the foreign body or they may be normal especially if there is no obstruction to airflow.[5],[8] Therefore, it is impossible to exclude diagnosis of foreign body aspiration with a normal radiograph.[9]

Diagnosis of foreign body aspiration is usually suggested with clinical history and radiological findings.[3] Foreign body is encountered only in 5% of cases that undergo flexible bronchoscopy without a prior suspicion of aspiration.[3],[5] Considering that early removal of aspirated foreign bodies is necessary to avoid the pathological progress from inflammation that initiates at third day to development of bronchiectasis after 30 days, high suspicion even in cases with vague clinical or radiological findings is required.[7],[8] Therefore, high clinical suspicion and use of flexible bronchoscopy as the initial technique...
of evaluation in patients with suspected foreign body aspiration are prompted. Moreover, flexible bronchoscopy provides detailed information about the nature and localisation of the foreign body as well as the characteristics of airway mucosa.[3]

Detection of a foreign body aspirated into the airway should be followed by removal as soon as possible to prevent the inflammatory reaction and development of granulation tissue.[4] Although flexible bronchoscopy is very often used for evaluation of airway in suspected cases of foreign body aspiration, rigid bronchoscopy remains the method of choice for removal due to the wide working channel. There is a limited number of reports of foreign body removal by flexible bronchoscopy.[3]

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Case Report
Chronic Necrotising Aspergillosis: a less known entity
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ABSTRACT:
Chronic necrotising aspergillosis (CNA), as opposed to aspergilloma, is a rare condition associated with a semi-invasive, subacute destructive process of the lung parenchyma, the mainstay of its treatment being anti-fungal therapy. We describe a patient who was initially diagnosed as a case of aspergilloma of right lung and who underwent a partial resection of the cavity only to present four months later with an increasing cavity size and soft tissue mass suggestive of chronic necrotising aspergillosis. He died due to sepsis and respiratory failure complicating CNA five days after admission.

KEY WORDS: Chronic necrotizing aspergillosis; COPD; Pulmonary tuberculosis

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INTRODUCTION:
Chronic necrotising aspergillosis (CNA) is an indolent, cavitary and destructive process of the lung parenchyma due to invasion by Aspergillus species, usually Aspergillus fumigatus. This entity differs from aspergilloma in that there is local invasion of lung tissue and a preexisting cavity is not essential. In contrast to invasive pulmonary aspergillosis, CNA runs a more chronic and protracted course and there is no vascular invasion or dissemination to other organs. This syndrome is rare, existing literature being mainly based on case reports [1].

We report here a case of CNA in a 71-year-old male patient who presented with fever, cough, expectoration and hemoptysis and had a cavity with fungal mass.

CASE REPORT:
A 71-year-old male, presenting with a five-day exacerbation of shortness of breath, fever with chills, cough with purulence of sputum and hemoptysis, was urgently admitted for evaluation.

He had a history of winter cough and sputum for 12 years, with exertional dyspnea for two years but his health had deteriorated over the past 9 months with repeated episodes of cough, purulent sputum and hemoptysis. He required a hospitalisation for hemoptysis about 7 months back, and a chest roentgenogram [Figure 1a] taken then. CECT scan of the chest taken later suggested a cavity with an intracavitary soft tissue density in the apical segment of the right lower lobe [Figure 1b].

Figure 1: Chest x-ray PA view showing right mid zone thick walled cavity and CT scan thorax showing cavity with an intracavitary soft tissue density in the apical segment of the right lower lobe.

A CT-guided FNAC from his lung lesion was non-contributory. Aspergillus antibody (lg G) was raised (49.22 U/ml, N< 8.00). Sputum was repeatedly negative for AFBs. The patient was diagnosed as having COPD, old PTB with aspergilloma right lung; treated with antibiotics, bronchodilators and referred to cardiothoracic surgery unit. However surgery was deferred and the patient was discharged.
Subsequently he was admitted to another facility four months back and underwent right thoracotomy, and the cavity in his right lung was scraped with the intention of removing the fungal mass [Figure 2].

**Figure 2:** Post thoracotomy chest x-ray PA view showing scraped cavity of right lung.

Lobectomy/segmentectomy was not done probably due to poor lung function or perioperative deterioration of the patient. The patient was apparently well for 2 months after operation; thereafter he developed recurrence of symptoms and took repeated courses of antibiotics failing which he was admitted to our institute.

The patient had a history of PTB 20 years ago; it was treated adequately with antituberculous drugs. He was a normotensive, nondiabetic farmer and had a 30-pack-year smoking history.

On physical examination, the patient was ill, toxic and in respiratory failure with SpO2 < 86% with 3 l/min of supplementary oxygen. The pulse rate was 120/min; respiratory rate was 30/min, and BP-110/60 mm of Hg and temp-101° F. On auscultation there was bilateral diminished VBS with prolonged expiration, bilateral rhonchi and coarse crepitation over right basal areas.

On admission he was put on oxygen (facemask, 5 L/min), IV antibiotics with pseudomonal and anaerobic coverage and nebulised bronchodilators. A CECT scan done on the 2nd day of his present admission showed a large low-density soft tissue mass lesion in a cavity in the lower lobe of the right lung (inflammatory pseudo mass formation) [Figure 3].

**Figure 3:** CT scan thorax showing a large low-density soft tissue mass lesion in a cavity in the lower lobe of the right lung (inflammatory pseudo mass formation).

His blood sugar, serum urea, creatinine, electrolytes on admission were normal. Sputum for AFB was negative, HIV serology was negative, USG whole abdomen was normal. Owing to significant cough with expectoration and streaky hemoptysis, the patient could not be put on NIPPV. The patient refused invasive ventilation. Systemic antifungal treatment (itraconazole) was added on the 3rd post-admission day. Despite all efforts his condition deteriorated and he died of sepsis and respiratory failure five days after admission.

Tissue removed from the wall of abscess cavity during surgery done 4 months back showed necrotic tissue containing branching fungal hyphae [Figure 4].

and culture had grown A. *fumigatus*.

**Figure 4:** Branching fungal hyphae morphologically compatible with aspergillus.
DISCUSSION:
CNA also termed as semi-invasive or subacute invasive aspergillosis, was first described by Binder et al, and Gefter et al, in 1981. [2],[3] It usually occurs in middle-aged and elderly patients with H/O underlying lung disease like COPD, old tubercular cavity, silicosis, previous lung resection etc.[4] Patients with mild immunosuppression like diabetes, those on steroid therapy or those suffering from connective tissue diseases are also susceptible to developing CNA.[1]

Imaging studies usually show cavitory pulmonary lesion with evidence of paracavitory infiltrate, new cavity formation or expansion of size of cavity over time.[5] The diagnosis is confirmed by histopathological demonstration of tissue invasion by the fungus and its subsequent growth on culture.[1] The yield from TBBL or from percutaneous aspires is relatively poor which may be a contributing factor in the morbidity and mortality associated with CNA.[6]

In our patient, the incomplete removal of the fungal mass and cavity at surgery led to a rapid fungal growth, presenting as an invasive polyploid mass filling and expanding the cavity. Systemic antifungal therapy is the cornerstone of treatment. Although amphotericin B was previously used in a dose of 0.5-1.0 mg/kg/day, now-a-days itraconazole has become a reliable alternative with a lesser side-effect profile.[1] A more recent alternative is voriconazole though it is costly.[7] Surgical resection has high post-operative complication rate and is only reserved for young patients with focal disease not responding to antifungal treatment. [5] Mortality from CNA was 39% in American reports using itraconazole.[1]

A diagnosis of CNA requires a high index of suspicion, as it is quite difficult to differentiate it from aspergillosis. Some authors put them in one group called chronic cavitary pulmonary aspergillosis seen in non immunocompromised patients with chronic lung disease.[8] Often in symptomatic patients of aspergillosi, surgical resection of the cavity cannot be performed. Itraconazole may be useful in management of this subset of patients.

Mitra S: Chronic Necrotising Aspergillosis

To summarise, when dealing with symptomatic cavitory lesions with intracavitary mass, CNA, a ‘semi-invasive’ disease, should be kept in mind together with its more common non-invasive sibling, aspergillosi. The subset of patients of aspergillosi who cannot undergo surgical resection due to chronic lung disease like COPD may be put on systemic antifungals to prevent morbidity / mortality.

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CASE REPORT:
A 32 years male came to our chest outdoor with high-grade fever with chill for 2 weeks. He had associated cough with left sided lateraled stabbing chest pain for 1 week. On chest examination there was restricted movement in left side; dull percussion note along the mid axillary line from 5th intercostal space (ICS) to 7th ICS; decreased vesicular breath sound with decreased vocal fremitus in axillary and infra-axillary areas. Immediate chest x-ray PA view was done (Fig. 1). After seeing the chest x-ray patient was admitted immediately. What is your diagnosis?

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ANSWER: Chest x-ray PA view showing a D shaped homogenous opacity at left mid and lower zone with convexity medially. This is called inverted D or pregnant lady sign. It is a classical sign of loculated empyema. In our patient after admission intravenous antibiotics (piperacillin + tazobactum injection at a dose of 4.5 gm thrice daily) was started and a ultrasonography guided intercostal 24 F chest drain was given. Antibiotics were given for 4 weeks and chest drain drainage became less than 50 ml after 10 days. Chest drain was removed after 14 days after seeing the normal chest x-ray.

An empyema, by definition, is pus in the pleural space i.e. pleural effusions with thick, purulent appearing pleural fluid. The evolution of an empyema can be divided into three stages; exudative stage, fibropurulent stage and organization stage. The usual clinical presentation is either a patient with pneumonia whose chest radiograph suggests pleural fluid or whose clinical progress is unsatisfactory, or a patient in whom radiographic pleural opacity and clinical indices suggest infection (fever, raised inflammatory markers, etc.). Up to 57 percent of pneumonia patients develop pleural fluid at some point in their clinical course. Pleural fluid loculation often results in a ‘D’ shaped subpleural opacity, which can easily be interpreted as a lung mass by an inexperienced observer. Thoracic ultrasound enables the exact localization of any pleural fluid collection and so facilitates image-guided diagnostic aspiration if required. It can detect the presence of as little as 5 ml of pleural fluid and is also highly effective in detecting localizations not seen on CT images. On CT scan thorax with contrast empyemas are usually lenticular in shape with compression of the surrounding lung parenchyma and the ‘split pleura’ sign is often noted, caused by enhancement of both parietal and visceral pleural surfaces which are separated by the pleural fluid collection.
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