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Editor-in-Chief: **Prof. Dr. Mangesh Tiwaskar**

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EDITORIAL

Guillain–Barré Syndrome: Investigating the Link between Rapid Urbanization and Rare Disease Outbreaks

Subhal B Dixit[1], Anand M Tiwari[2*], Kapil G Zirpe[3]

Introduction

Guillain–Barré syndrome (GBS) is a rare but common cause of acute flaccid paralysis globally.[1] This syndrome, first described in 1916 by Georges Guillain, Jean Alexandre Barré, and André Strohl, has captured the interest of clinicians, researchers, and patients all over the world.[2]

GBS is acknowledged as a neurological emergency of concern, where despite treatment, 20% of patients are left with persistent and significant disability.[3] GBS frequency and clinical features fluctuate significantly between various populations and geographical areas, with an estimated yearly incidence ranging from 0.89 to 1.89 cases per 1,00,000 people. Male predominance is reported, with the male-to-female ratio of the syndrome being 1.78.[4] Nonetheless, outbreaks of GBS are extremely rare.

During the second week of February 2025, Pune Municipal Corporation hinted at an epidemiological alert with the hospitalization of 180 cases of a GBS cluster. This GBS outbreak was notable due to the unusually high number of cases.

The above-reported Pune outbreak was surpassed only by the 2019 Peru epidemic of GBS, which affected several regions of the country, with almost 700 reported cases (incidence: 1.2 per 1,00,000 inhabitants).[5]

Geographical mapping of GBS cases in Pune depicted the origin of clusters from newly developed regions of Pune Municipal Corporation. The large number of cases and rapid increase pointed toward point-source exposure. A general water source to these newly merged areas of Pune Municipal Corporation, through a common pipeline from a well, was primarily identified to be contaminated.

Clusters of GBS have been reported with outbreaks of diarrheal illness caused by contaminated water.[6] A comprehensive systematic review of approximately 2,500 GBS cases identified *Campylobacter jejuni* as the most frequently associated preceding infection, accounting for 30% of GBS cases.[7]

Past GBS outbreaks linked to *Campylobacter* have primarily been observed during large outbreaks of cases with symptomatic bacterial enteritis.[8] The demographics of the GBS cases are depicted in Figure 1.

In the Pune GBS outbreak, the highest number of cases were in the 20–29-year age-group. Most of the cases were reported to have had diarrheal illness weeks prior to the development of flaccid paralysis. These findings are contrary to evidence in the literature reporting greater incidence with increasing age. The clinical significance of this observation is unclear.

Based on the clinical-epidemiological characteristics and the study of the identified agents in water samples conducted by the National Institute of Virology in Pune, it was concluded that the outbreak was associated with the presence of *C. jejuni*.

Campylobacteriosis is a major public health issue worldwide, ranking among the top causes of infectious diarrhea and foodborne disease. Sequelae such as GBS and reactive arthritis are widely recognized. Eating undercooked poultry and the cross-contamination of other food and untreated water sources are additional major risk factors for human infection.[9]

Urban planning pitfalls could be an environmental factor playing a key role in such outbreaks. Multiple studies have highlighted challenges of rapid urbanization, which include maintaining sanitation and waste management, ensuring access to clean drinking water, providing secure housing, and ensuring adequate nutrition.[10]

Insights from past Epidemic

The H1N1 influenza pandemic of 2009 caused widespread alarm in India. Pune, a city in southwest India, was the worst hit and was mapped as the epicenter of the pandemic. Of the 93 documented influenza deaths in Pune, 65 were from urban areas and 28 from rural areas.[11]

Epidemic models rely on the disease reproductive rate, which measures how many people the first infected individual transmits the disease to while infectious. Higher population density increases encounters, leading to a higher reproductive rate.[12]

In 2019, the emergence of a novel coronavirus disease was reported in a single city, Wuhan. In a short period, it rapidly escalated into a global pandemic.

A study by Tamrakar et al. analyzed district-level comparisons of COVID-19 data from March to October 2020. Maharashtra was identified as one of the states with the highest infection ratio (101.63), much above the overall national ratio of 42.85 per 1,000 people. The study concluded that the pandemic spread in Indian districts was driven by their characteristics of a larger working-age population, greater population density, a higher proportion of urban residents, and increased testing rates.[13]

Pune was then labeled as a hotspot for COVID-19, positioning urban centers as critical hubs in crisis response. The situation compelled cities across India to confront the challenges posed by unplanned urbanization, where many residents lacked access to essential services and facilities. The preexisting infrastructure deficit significantly hindered the quality of life.[13,14]

To solve these issues, as well as to find solutions to these widely discussed challenges, the impact of urbanization needs to be looked at more critically, especially in the context of outbreaks.

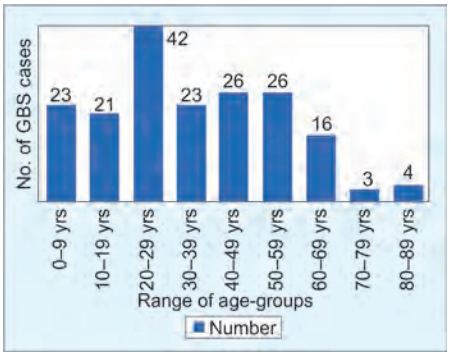

Fig. 1: GBS Patients Distribution categorized by age groups

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Preventive Immunization Link to Guillain–Barré Syndrome

Beyond infectious triggers, vaccinations have attracted attention as possible causes of GBS.

The potential link between the influenza vaccine and GBS has been a concern since 1976, when a U.S. vaccination campaign was abruptly halted due to a rise in GBS cases following the administration of the A/New Jersey/76 "swine flu" vaccine.[15]

The global distribution of various formulations of A/H1N1/2009 vaccines during the pandemic has renewed attention on their potential association with GBS.[16,17]

In response to the COVID-19 pandemic, India launched the "World's Largest Vaccination Drive" on January 16, 2021. However, the rapid development of COVID-19 vaccines led to widespread hesitancy and concerns about their safety and effectiveness.[18]

Jeong et al. studied the global burden of vaccine-associated GBS, finding the highest link with the influenza vaccine and the lowest with the COVID-19 vaccine. Vaccine-associated GBS was more common in older adults, with a mean time of onset at 5.5 days.[19] This highlights the need for vigilance in the 1st week postvaccination, especially during mass immunization events in pandemics.

Rescue Measures Implemented by Local Government (Pune Municipal Corporation)

Ongoing epidemiological surveillance by the local government body, Pune Municipal Corporation (PMC), aims to identify the potential antigenic source of suspected infection through Campylobacter-specific IgM and antiganglioside antibody testing.

Active systematic sample testing and further isolate sequencing for emerging cases are being carried out in collaboration with the National Institute of Virology (NIV) laboratory in Pune.

Strengthening public health initiatives through education, awareness, and surveillance is essential in preventing future epidemics. Reinforcing hygienic practices at the individual level at each link in the food chain—from producer to consumer—is critical in preventing the disease.

Safeguarding Public Health to Avert Future Epidemics

Initiatives ensuring health- and hygiene-related services, such as supplying sufficient clean drinking water, proper sanitation and sewage systems, city cleanliness, and the upkeep of quarantine centers as well as public health care facilities, will help avert future outbreaks.

Conclusion

Urban planning pitfalls may significantly contribute to disease outbreaks.

Effectively managing outbreaks requires collaborative efforts from citizens and strategic coordination between the public and private sectors.

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ORIGINAL ARTICLE

Sample Size Calculation for Paired *t*-test Using *p*-value and Confidence Intervals When Standard Deviation of Difference is Not Given

Shyam Vayyat[1], Nilotpal Chowdhury[2], Manish Goyal[3*]

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Abstract

Sample size calculation is an important step for carrying out any research. Most of the sample size estimating utilities/applications use the standard deviation of differences in their formula for paired design, which usually is not reported in the published articles. Researchers are left to use the pooled standard deviation (SDp) instead of using the standard deviation of differences. The standard deviation of differences gives a more accurate estimate of sample size for a paired design. The standard deviation of differences can be determined from the *p*-value or confidence intervals (CI), which are usually reported in the published articles. In this paper, we have described and illustrated with an example how to determine sample size from the *p*-value or CIs. Readers may follow the given example using scripts for software R.

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Introduction

Sample size calculation is an important step for carrying out any research. The commonly used formula for sample size (per group) calculation for a study design involving two independent groups.[1]

$$n = \frac{2\left[Z_{\left(1-\frac{\alpha}{2}\right)} + Z_{(1-\beta)}\right]^2 \sigma^2}{d^2} + \frac{Z^2_{1-\frac{\alpha}{2}}}{2} \quad (1)$$

Where $Z\alpha$ is determined by permissible alpha error and $Z\beta$ is determined by desired power of the study, d represents the hypothesized difference in the means of two groups, and σ is the pooled standard deviation (SDp). SDp can be determined from Cohen's formula.[2]

$$SDp = \sqrt{\frac{(\sigma_1)^2 + (\sigma_2)^2}{2}} \quad (2)$$

For paired design, the formula is essentially similar, with sigma now representing the standard deviation of the differences (SDd) rather than SDp. As n represents the number of pairs, the constant 2 has been removed.

$$n = \frac{\left[Z_{\left(1-\frac{\alpha}{2}\right)} + Z_{(1-\beta)}\right]^2 (SDd)^2}{d^2} + \frac{Z^2_{1-\frac{\alpha}{2}}}{2} \quad (3)$$

Most of the sample size estimating utilities/applications use SDd in their formula, which most often is not reported in the published articles.[3–7] The researchers are then left with no option other than using SDp (estimated using Cohen's formula), which in general leads to underestimation of actual SDd and sample size. An example demonstrating how Cohen's formula may lead to underestimation of SDp has been given in the R snippets. In this brief paper, we have discussed alternative ways of estimating SDd from the *p*-value, which is better than using SDp.

Estimation of SDd from *p*-value

While authors in their article do not give SDd, they usually report exact *p*-values. Intuitively, the *p*-values can be used to back-calculate the SDd as described in the following steps.

From the information given in the article, find out the *t* value corresponding to the *p*-value and the degree of freedom.

Where *t* is

$$t_{\left(1-\frac{\alpha}{2},df\right)} \quad (4)$$

Calculate the value for SDd from the *t* value, mean difference (*d*), and number of paired observations (*n*) using the following formula.

$$SD_d = \frac{d}{t/\sqrt{n}} \quad (5)$$

When Exact *p*-value Not Given

In case, instead of the exact *p*-value, only the level of significance is indicated by mentioning whether the *p*-value is <0.05, 0.01, or 0.001, in that situation, the sample size may be calculated assuming the upper limit of the *p*-value mentioned. Though it may overestimate the sample size, the estimate will still be better than using pooled SD.

When Confidence Intervals Are Given Instead of *p*-value

In some articles, authors indicate only confidence intervals (CI) rather than *p*-values. In these cases, CIs may be used to determine SDd.[8]

If following a *z*-based CI:

$$SDd = \frac{\sqrt{n}(u-l)}{2 \times Z_{1-\frac{\alpha}{2}}} \quad (6)$$

If following *t*-based CI:

$$SDd = \frac{\sqrt{n}(u-l)}{2 \times t_{\left(1-\frac{\alpha}{2},df\right)}} \quad (7)$$

In the referred article, the methods section should be checked to determine whether the CIs are based on the *z* distribution or t distribution. In case it is not possible to determine whether the given CIs are based on the *z* distribution or *t* distribution, it is safe to assume it to be based on the *z* distribution.

Sample Size Calculations with SDd

Now, using this SDd instead of the SDp in the sample size calculation formula will give an estimate of the sample size for finding the given difference in mean.[1]

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$$n = \frac{\left(Z_{1-\frac{\alpha}{2}} + Z_{1-\beta}\right)^2 2(SDd)^2}{d^2} + \frac{Z^2_{1-\frac{\alpha}{2}}}{2} \quad (8)$$

Illustration for Sample Size Estimation with *p*-value

For example, assume m1 and m2 are 5 and 3, respectively, and the *p*-value is 0.037 (CI: 0.015–3.85), and the number of paired observations is 10 ($n = 10$).

For calculating *t* value,

$$t\left(1-\frac{\alpha}{2}, df\right) = t\left(1-\frac{0.037}{2}, 10-1\right) = 2.45 \quad (9)$$

For calculating SDd from *t* value,

$$SDd = (5 - 3) \times \sqrt{10} / 2.45 = 2.59$$

Alternatively, SDd can also be determined from CIs using equation 7.

Assuming an alpha error of 0.05, $Z_{(1-\alpha/2)} = 1.96$, power of 0.8, $Z_{(1-\beta)} = 0.84$, and substituting $Z_{(1-\alpha/2)} = 1.96$, $Z_{(1-\beta)} = 0.84$, $d = 2$ (hypothesized mean difference), and SDd = 2.59 in equation 8, the sample size turns out to be 16.

$$n = (1.96 + 0.84)^2 \times 2.59^2/(2)^2 + 1.96^2/2$$
$$= 15.08 = 16 \text{ (rounded up)}$$

Conclusion

The method described for sample size determination in this paper, though intuitive, usually misses the attention of statistical tool developers and researchers. It is not in common practice to report the standard deviation of differences. Using the standard deviation of differences instead of SDp gives a more accurate estimate of sample size. We are of the opinion that the standard deviation of differences should be reported in the articles. Readers may follow the given example using scripts for software R.

R Snippets

1. R-snippet (when *p*-value is given)

```
p=0.036     #input p value reported in
            previous study
n=10        #input number of pairs
            studied
m1=5;m2=3   #input reported means of pre
            and post test
pow=0.8     #input desired power
a=0.05      #input permissible alpha
            error (0.05)

# step 1: Determine t value
t=-1*qt(p/2,n-1)
# step 2: Determine standard deviation
of differences (SDd)

SDd=abs((m1-m2)*sqrt(n)/(t))

# Step 3: Determine sample size for
paired t test

ss=power.t.test(power=pow,delta =
(m1-m2),sd=SDd,sig.level = a,type =
"paired") #calculate sample size for
two sided
#paired t test
# Print result
print(round(ss$n))
```

2. R-snippet (when confidence intervals are given)

```
u=0.015;l= 3.85  #input CI values from
                 previous study
n=10             #input number of
                 pairs studied
m1=4.2;m2=2.3    #input reported means
                 of pre and post test
pow=0.8          #input desired power
a=0.05           #input permissible
                 alpha error (0.05)

# step 1: Determine t value

t=-1*qt(a/2,n-1)

# step 2: Determine standard deviation
of differences (SDd)

SDd=abs(sqrt(n)*(u-l)/(2*t))

# Step 3: Determine sample size for
paired t test

ss=power.t.test(power=pow,delta =
(m1-m2),sd=SDd,sig.level = a,type =
"paired") #calculate sample size for
two sided
#paired t test
# Print result
print(round(ss$n))
```

3. R-snippet (demonstrating how Cohen's formula may lead to underestimation of standard deviation of differences)

```
SDp <- length(1000)     # initialize
                        variable for SDp
SDd <- length(1000)     # initialize
                        variables for SDd
x1 <- rnorm(1000,150,30) #simulate data
                        (n=1000, m=150,
                        SD=30)

# step: Resample x1, determine SDp
and SDd for 1000 iterations
for (i in 1:1000){
x2 <- sample(x1) #resample data
SDd[i] <- sd(x1 - x2) #Actual SDd
SDp[i]<- sqrt((sd(x1)^2 + sd(x2)^2)/2)
#Cohen's estimate
}
d=mean(SDp)-mean(SDd) #Difference of
SDp and SDd
print (d) #Print result
hist(SDp) #Display SDp distribution
```

Conflict of Interest

Authors disclose that there are no conflict of interests..

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ORIGINAL ARTICLE

Spectrum of Clinical Manifestations in Patients of Scleroderma and Correlation between Cutaneous and Pulmonary Involvement

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Abstract

Purpose: Our research aimed at characterizing the range of signs and symptoms observed in scleroderma patients at a tertiary care hospital and investigating potential correlations between pulmonary and cutaneous involvement.

Materials and methods: We obtained informed consent from scleroderma patients for conducting a comprehensive clinical assessment, including detailed medical histories and physical examinations. Standard diagnostic investigations like complete blood counts, erythrocyte sedimentation rate, renal function, liver function, electrocardiograms (ECG), high-resolution computed tomography (HRCT) scans, and pulmonary function tests were performed. The modified Rodnan skin score (mRSS) was used to assess skin involvement.

Results: About 74 (71.2%) patients had diffuse cutaneous systemic scleroderma (dcSSc), while 30 (28.8%) patients had limited cutaneous scleroderma (lcSSc). 96 (92.3%) patients had Raynaud's phenomenon.

About 68 (65.4%) patients had mild mRSS, while 26 (25%) and 10 (9.6%) patients had moderate and severe mRSS, respectively. Skin tightening (88.4%) and sclerodactyly (88.4%) were the most common cutaneous manifestations, followed by digital ulcers and pits (57.7%), diffuse edema of hands and feet (38.4%), salt-and-pepper skin (38.4%), calcinosis (30.8%), telangiectasia (25%), and contractures (19.2%).

Pulmonary manifestations showed interstitial lung disease (ILD) in 62 (59.6%) patients and pulmonary hypertension (PH) in 14 (13.5%) patients. 8 (7.7%) patients had ILD with PH. 48 (46.2%) and 18 (17.3%) patients with dcSSc had mild and moderate mRSS, respectively, while 8 (7.7%) patients had severe mRSS. About 20 (19.2%) and 8 (7.7%) patients with lcSSc had mild and moderate mRSS, respectively, while 2 (1.9%) patients had severe mRSS. There was no significant correlation of mRSS and subtypes of scleroderma patients. The mean mRSS score in ILD was low in comparison to the mRSS score in patients with PH (25.7 ± 8.90 vs 28.9 ± 7.62). There was a significant correlation of mRSS and pulmonary involvement as indicated by the Student's *t*-test ($p < 0.05$).

Conclusion: In systemic sclerosis (SSc) patients, the emergence of severe systemic complications such as pulmonary arterial hypertension and ILD can manifest regardless of disease duration or subtype. Symptoms might not consistently align with disease advancement. Therefore, a thorough evaluation that incorporates symptoms and specialized diagnostic tests, such as pulmonary function tests, echocardiography (ECHO), and HRCT, is crucial for early identification, timely treatment, and better prognosis. The mRSS serves as a valuable clinical instrument for monitoring scleroderma progression.

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Introduction

Systemic sclerosis (SSc), also known as scleroderma, is an autoimmune disorder characterized by excessive production of extracellular matrix due to small vessel vasculopathy. Autoantibodies lead to fibroblast dysfunction, resulting in skin and internal organ fibrosis.[1,2] SSc is broadly categorized into limited and diffuse cutaneous disease. Skin thickening, a hallmark symptom, is used for patient classification into subgroups like limited cutaneous SSc (lcSSc) and diffuse cutaneous systemic scleroderma (dcSSc).[3] Progression of skin thickening predicts organ involvement, including cardiac disease, and is used to assess current severity and future prognosis.[4,5] The modified Rodnan skin score (mRSS) is a key measure in clinical trials, correlating with histological skin thickness.[6] The scale is semiquantitative, ranging from 0 (normal) to 3 (severe), and is used to assess the skin thickness of 17 different sites (total score from 0–51). It is correlated with histological skin thickness.[7]

Pulmonary involvement is common in SSc, leading to interstitial lung disease (ILD) and pulmonary hypertension (PH). Within 3 years of diagnosis, significant pulmonary involvement can be detected in >25% of patients using pulmonary function tests.

Lung involvement is the most common cause of morbidity and mortality in scleroderma (33%).[8,9] ILD is associated with the diffuse cutaneous form of SSc and in those with positive anti-topoisomerase antibodies.[10] ILD presents with dyspnea, cough, and a nonspecific interstitial pneumonia pattern on CT scan.

Fewer data are available on SSc-induced ILD in the western part of India. It is important to evaluate the pattern of SSc-induced ILD and PH in this population, and also to see whether there is any correlation between the severity of skin involvement, assessed by mRSS, and the severity of lung involvement.

Materials and Methods

This is a prospective hospital-based observational study conducted with 104 patients to study the spectrum of SSc-related ILD and PH and their correlation to mRSS.

Patients of SSc of either sex, above 18 years, attending the rheumatology center of our hospital were involved. The study duration was from December 2016 to 2021.

Sample Size

For our sample size, considering the expected frequency of cutaneous manifestation was 96.5% in SSc, and with 5% variation allowed, the sample size at 95% confidence level is a minimum of 52 patients.

$$N = Z^2 \times p \times (1 - p)/d^2$$

Where Z = table of alpha error from standard normal distribution table = 1.96^2, Power (p) = 0.05, $(1 - p) = 0.95$, and precision error of estimation (d) = 5%.

Patients of 18 years and above, of either sex and fulfilling 2013 American College of Rheumatology and European League Against Rheumatism (ACR/EULAR) criteria for

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diagnosis of SSc were included. Patients not satisfying 2013 ACR/EULAR criteria,[11] pregnant patients, and those with other connective tissue diseases or overlap syndrome were excluded. Clinical features were recorded at the time of evaluation, and patients were classified into two clinical subgroups based on the extent of skin involvement: lcSSc and dcSSc.[12]

Information on history and complete clinical examination was recorded after obtaining informed consent from the patients.

Assessment of skin involvement was done by the mRSS.

Measurement of skin thickness was done by palpation of 17 areas of the body, and calculation was done by mRSS. Clinical examination of the presence of crackles on auscultation was noted.

Standard investigations like complete blood count, erythrocyte sedimentation rate, liver function tests, renal function tests, electrocardiograms (ECG), chest X-ray, and two-dimensional (2D) echocardiography (ECHO) were done. high-resolution computed tomography (HRCT) was done in all patients to see the changes of ILD, like patchy areas of ground glass opacities, reticular shadows, septal thickening, pleural involvement, honeycombing, etc.

Pulmonary function tests were done to assess and grade the severity of ILD. A restrictive pattern is commonly seen in SSc, wherein both forced vital capacity (FVC) and forced expiratory volume (FEV1) are reduced.

Based on the reduction in FEV1 or FVC, grading of pulmonary involvement was noted as:

- Mild: 70–80% of predicted value.
- Moderate: 60–69% of predicted value.
- Severe: <59% of predicted value.

Two-dimensional ECHO was done to measure the pulmonary artery pressure and the tricuspid regurgitation jet to assess the severity of PH.

Assessment of cardiovascular system: Record of cardiac arrhythmia, pericardial effusion, congestion, and cardiac failure was noted.

Assessment of renal system: Scleroderma renal crisis defined by accelerated hypertension and microangiopathic hemolytic anemia, new onset hypertension recorded of systolic >180 mm Hg and diastolic >110 mm Hg.

Assessment of musculoskeletal system: Objective muscle weakness (score <4 on five-point scale) and creatine kinase four times the upper limit of normal.

In order to explore the potential relationship between mRSS and internal organs involved, we calculated the mRSS in all these patients. It was graded into mild (20 ± 6), moderate (35 ± 7), and severe (42 ± 8).

Observation and Results

The majority of patients (32.5%) were in the age-group of 41–50 years, followed by 23.2% in the 31–40 years age-group. The mean age of the patients was 39.8 ± 13.45 years. A female preponderance was noted (94.2%), while male patients constituted 5.8% of the group.

About 74 patients had dcSSc, while 30 patients had lcSSc.

Raynaud's phenomenon was observed in 96 patients (92.3%). The most common cutaneous involvement was skin tightening (88.4%) and sclerodactyly (88.4%), followed by digital ulcers and pits (57.7%). Other manifestations were diffuse edema of hands and feet (38.4%), salt and pepper skin (38.4%), calcinosis cutis (30.8%), telangiectasia (25%), and contractures (19.2%) of fingers.

mRSS: 68 patients (65.4%) had mild mRSS, while 26 (25%) and 10 (9.6%) had moderate and severe mRSS, respectively. The mean score was 26.3 ± 8.76.

Distribution of patients according to clinical presentation: 100% of the patients (104) had cutaneous manifestations, and the next majority being pulmonary manifestations with 73.1% (76). Table 1 shows the frequency of clinical manifestations in our patients.

Correlation of subtypes of scleroderma and pulmonary involvement (n = 76): Lung involvement was more commonly seen in patients with dcSSc as compared to lcSSc, as depicted in Table 2.

No significant correlation was found between the subtypes of scleroderma and lung manifestations ($p > 0.05$).

Correlation of mRSS and pulmonary manifestations of patients: The mean mRSS score of patients with ILD was significantly lower as compared to the mRSS score of patients with PH (25.7 ± 8.90 vs 28.9 ± 7.62), as shown in Table 3.

There was a significant correlation between the mRSS and pulmonary manifestations of patients, as determined by the Student's t-test ($p < 0.05$) Table 4.

Correlation of subtypes of scleroderma and mRSS of patients: Out of dcSSc patients, 48 (46.2%) had mild mRSS, 18 (17.3%) had moderate mRSS, and 8 patients had severe mRSS; whereas in lcSSc, 20 (19.2%) had mild, 8 (7.7%) had moderate, and 2 patients had severe mRSS (1.9%). There was no significant correlation of mRSS and subtypes of scleroderma as per Student's *t-test* ($p > 0.05$) Table 5.

Correlation of mRSS with other parameters: There was a significant correlation of mRSS and ILD ($r = 0.224$; $p < 0.05$) and PH ($r = -0.285$; $p < 0.05$).

Table 1: Frequency of clinical manifestation in patients of SSc

Clinical presentation	*N*	*%*
Cutaneous manifestations	104	100
Pulmonary manifestations	76	73.1
Gastroesophageal manifestations	42	40.4
Musculoskeletal manifestations	28	26.9
Renal manifestations	10	9.6
Cardiac manifestations	4	3.8

Table 2: Correlation of SSc and pulmonary manifestations of patients (n = 76)

Pulmonary manifestations	*Diffuse scleroderma*		*Limited cutaneous scleroderma*		*Total*		*p-value*
	N	*%*	*N*	*%*	*N*	*%*	
Interstitial lung disease	52	68	10	13	62	59.6	>0.05
Pulmonary hypertension	8	11	6	8	14	13.5	
Total	60	83	16	22	76	73.1	

Table 3: Correlation of mRSS and pulmonary manifestations

mRSS	*Interstitial lung disease*		*Pulmonary hypertension*		*Total*		*p-value*
	N	*%*	*N*	*%*	*N*	*%*	
Mild	44	42.3	8	7.7	52	50	<0.05
Moderate	10	9.6	4	3.9	14	13.5	
Severe	8	7.7	2	1.9	10	9.6	
Total	62	59.6	14	13.5	76	73.1	
eMean	25.7 ± 8.90		28.9 ± 7.62		26.3 ± 8.76		

Table 4: Correlation of mRSS with other parameters

Parameter	*Pearson correlation coefficient "r"*	*95% CI*	*p-value*
Age	0.224	0.116–0.912	>0.05
Sex	0.276	0.154–0.659	>0.05
Raynaud's phenomenon	0.025	–0.273–1.126	>0.05
ILD	0.362	–1.512–0.497	<0.05
Pulmonary hypertension	-0.285	–0.196–0.074	<0.0

Table 5: Correlation of sub-type of scleroderma and mRSS

mRSS	*Diffuse scleroderma*		*Limited cutaneous scleroderma*		*Total*		*p-value*
	N	*%*	*N*	*%*	*N*	*%*	
Mild	48	46.2	20	19.2	68	65.4	>0.05
Moderate	18	17.3	8	7.7	26	25	
Severe	8	7.7	2	1.9	10	9.6	
Total	74	71.2	30	28.8	104	100	
Mean	26.4 ± 9.21		26.1 ± 7.80		26.3 ± 8.76		

Discussion

In our study, which was conducted at a tertiary care hospital and involved 104 patients diagnosed with scleroderma, our aim was to explore the spectrum of clinical symptoms, with a particular focus on pulmonary complications such as ILD and PH.[8,9] Previous research indicates mortality rates of 33% from ILD to 28% from PH in scleroderma patients.[9]

According to the European Scleroderma Trials and Research Group (EUSTAR), ILD is prevalent in 53 and 35% of dcSSc and lcSSc, respectively.[13] Early autopsy studies have shown parenchymal involvement in nearly all dcSSc patients, with 90% exhibiting interstitial abnormalities on HRCT.[14,15] Timely diagnosis and treatment of pulmonary complications are crucial.

In our study, the age of majority (32.5%) was 41–50 years, with a mean of 39.8 years. Females comprised 94.2% of the cohort. This demographic distribution aligns with findings from previous studies by Hafez et al.,[16] Shand et al.,[17] Pradhan et al.,[18] Deepa et al.,[19] and Arakkal et al.[20]

About 74 patients (71.2%) were diagnosed with dcSSc, while 30 (28.8%) had lcSSc, consistent with the aforementioned studies.

Raynaud's phenomenon was observed in 92.3% of our patients, a finding corroborated by Deepa et al.[19] and Arakkal et al.[20] Deepa et al. additionally reported that all subjects with pulmonary involvement exhibited skin thickening and Raynaud's phenomenon.[19]

Arakkal et al., in their research, noted that the most prevalent cutaneous features observed included skin tightening (100%), Raynaud's phenomenon (85.7%), and pigmentary changes (82%).[20]

In our study, 65.4% of patients had mild mRSS, with a mean mRSS score of 26.3 units. Moderate and severe mRSS were observed in 25 and 9.6% of patients, respectively.

In a comprehensive study conducted by Shand et al., involving a sizable single-center cohort, baseline mRSS data were collected for 210 patients, constituting 93% of the total cohort. The study found that the median mRSS was 30, with a mean ± standard deviation (SD) of 30 ± 11.[17]

In our current investigation, the clinical presentation showcased that all 104 patients (100%) exhibited cutaneous manifestations, while pulmonary manifestations were observed in 76 patients (73.1%). Additionally, 42 (40.4%) patients displayed gastroesophageal involvement, 28 (26.9%) had musculoskeletal involvement, 10 (9.6%) showed renal involvement, and 4 (3.8%) presented with cardiac involvement. These findings are consistent with the observations reported in the studies conducted by Shand et al.[17] and Pradhan et al.[18]

In our study, the prevalent cutaneous manifestations included skin tightening (88.4%) and sclerodactyly (88.4%), followed by digital ulcers and pits (57.7%), diffuse edema of hands and feet (38.4%), salt and pepper skin appearance (38.4%), calcinosis (30.8%), telangiectasia (25%), and contractures (19.2%). These findings align with those reported in the studies conducted by Pradhan et al.[18] and Deepa et al.[19]

In our study, pulmonary manifestations were prevalent, with 62 patients (59.6%) diagnosed with ILD and 14 patients (13.5%) with PH. Additionally, 8 patients (7.7%) presented with ILD accompanied by PH.

Among patients with dcSSc, 52 (50%) had ILD, and 8 (7.7%) had PH. In contrast, among those with lcSSc, 10 patients (9.6%) had ILD, and 6 patients (5.8%) had PH. Statistical analysis using the Chi-squared test indicated no significant correlation between subtypes of scleroderma (SSc) and pulmonary manifestations ($p > 0.05$). These findings are consistent with observations reported in studies conducted by Hafez et al.,[16] Deepa et al.,[19] and Arakkal et al.[20]

In our current investigation, we found that the mean mRSS among patients with ILD was notably lower compared to those with PH (25.7 ± 8.90 vs 28.9 ± 7.62). Further analysis using the student *t*-test revealed a significant correlation between mRSS and pulmonary manifestations among patients ($p < 0.05$).

In our study, we observed a significant correlation between mRSS and both ILD ($r = 0.224$; $p < 0.05$) and PH ($r = –0.285$; $p < 0.05$). This finding is consistent with the observations reported by Hafez et al.,[16] Shand et al.,[17] and Pradhan et al.[18] in their respective studies.

Hafez et al. found that patients with ILD and PH had significantly higher mRSS scores. Additionally, they noted that mRSS was elevated among patients with calcinosis and lower esophageal dysphagia compared to those without these complications (p = 0.024 and 0.03, respectively). Moreover, they observed a significant increase in mRSS among males compared to females ($p = 0.01$).[16]

Shand et al. reported a higher frequency of major internal organ-based complications in patients with a high initial skin score that subsequently improved.[17]

Conclusion

The majority of our patient cohort fell within the age range of 41–50 years, with a predominance of females (94.2%), and 71.2% diagnosed with dcSSc. Furthermore, 65.4% of patients exhibited mild scores on the mRSS, with a mean mRSS of 26.3. In our analysis, we observed a significant difference in mRSS scores between patients with ILD and those with PH. Additionally, there was a notable correlation between mRSS and ILD ($r = 0.224$; $p < 0.05$).

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Book Review

Deshpande's Mechanical Ventilation–Clinical Application

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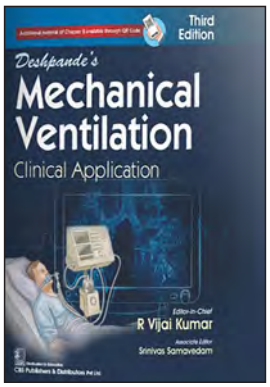

The 3rd edition of *Deshpande's Mechanical Ventilation–Clinical Application* is a welcome addition to the armamentarium of all those who need to take care of critically ill patients admitted in the Intensive Care Units (ICUs). Mechanical ventilation remains the defining criterion between life and death for most such patients. It is also one of the most difficult and complex modalities of treatment to execute for the doctors, nurses and technicians handling these patients in the intensive care units. This book makes it relatively easy for them to understand various aspects of mechanical ventilation and execute them leading to successful outcomes.

The text written in a simple and lucid language which includes a comprehensive description of different aspects of mechanical ventilation. It also includes numerous easy-to-understand graphs, figures and tables which make it even more interesting and readable. Starting from the basic indications, definitions, the content covers different modes, monitoring, supporting care, weaning and extubation. The book includes sections on mechanical ventilation in different clinical scenarios, such as chest trauma, neonatal ventilation, and many pulmonary diseases. It also covers other aspects such as noninvasive ventilation (NIV), extracorporal membrane oxygenation (ECMO) and novel modes of ventilation. All other important issues related to the care of such patients are equally well handled with dexterity and expertise. Nutritional care, transport, special investigations and talking to care-givers are some of the welcome topics which are part of the ten new additional chapters over the previous edition.

Overall, this book is not just a text on mechanical ventilation but provides readable, understandable, and executable information for the holistic care of patients on mechanical ventilation. The quality of the printing is on par with international standards, and yet reasonably priced. I strongly recommend the book to the students of medicine and intensive care, particularly those of pulmonary medicine, critical care medicine, anaesthesia, respiratory therapists, and other related specialties.

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ORIGINAL ARTICLE

Survival and Clinical Outcomes After Single-vessel Percutaneous Coronary Intervention Using Drug-eluting Stent: An Observational and Follow-up Study in a Tertiary Care Center in the Gangetic Plains of North India

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Abstract

Introduction: Percutaneous coronary intervention (PCI) with drug-eluting stents (DES) has transformed the management of coronary artery disease (CAD), particularly for single-vessel disease (SVD), by reducing restenosis rates. However, long-term survival data following PCI in North Indian populations are limited. This study aimed to evaluate survival and clinical outcomes after PCI with DES and identify factors associated with mortality and adverse events, such as chest pain, dyspnea, and bleeding.

Materials and methods: This observational cohort study at Sir Sunder Lal Hospital, Banaras Hindu University, included 1,112 adult patients undergoing single-vessel PCI with DES. Patients were followed for 18 months *via* outpatient assessments and telephonic interviews to assess survival, chest pain, dyspnea, and bleeding. Data were analyzed using IBM SPSS Statistics (Version 25.0). Continuous variables were reported as mean ± SD, and categorical data as frequencies and percentages. Chi-square and independent *t*-tests were used, with a 5% significance level.

Results: Of the 782 patients who were successfully followed up after 18 months, 740 (94.62%) were alive, and 42 (5.38%) had died. Significant factors associated with mortality included older age ($p = 0.013$), history of hospitalization ($p < 0.001$), chest pain ($p < 0.001$), dyspnea ($p < 0.001$), and bleeding ($p < 0.001$). Acute coronary syndrome (ACS) was the leading cause of death (52.3%), followed by post-PCI complications.

Conclusion: PCI with DES demonstrated a high survival rate in North Indian patients with SVD. Key predictors of mortality were age, history of hospitalization, and post-PCI symptoms, emphasizing the need for long-term follow-up and aggressive management of symptoms to improve outcomes.

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Introduction

Percutaneous coronary intervention (PCI) has revolutionized the treatment of coronary artery disease (CAD), particularly with the advent of drug-eluting stents (DES), which significantly reduce restenosis rates. Single-vessel disease (SVD), when treated with DES, typically shows better outcomes than multivessel disease (MVD). However, long-term follow-up data on survival outcomes post-PCI, particularly in the North Indian population, are limited.

This study aimed to fill the gap by evaluating survival and clinical outcomes post-PCI with DES in a tertiary care center in the Gangetic plains. The objective was to identify factors affecting mortality and other adverse clinical outcomes, such as chest pain, dyspnea, and bleeding, after single-vessel PCI using DES.

Materials and Methods

This was a prospective observational cohort study, conducted in the cardiology department of Sir Sunder Lal Hospital, Institute of Medical Sciences, Banaras Hindu University, Varanasi, from 1st January to 31st December 2022. The follow-up period extended from 30th June 2022 to 30th June 2024. The primary aim of the study was to assess survival outcomes in patients undergoing single-vessel PCI with DES and to evaluate postprocedural mortality and symptoms of angina, dyspnea, and bleeding as indicators of morbidity in the follow-up period.

Major inclusion criteria were:

- Patients aged ≥18 years who underwent de novo single-vessel PCI.
- Use of DES during the procedure.
- Consent for participation and follow-up.

Major exclusion criteria were:

- Patients with MVD, revascularization (PCI), or prior coronary artery bypass graft surgery (CABG).
- Contraindications to DES or inability to follow up.

Baseline data (age, sex, etc.) and procedural data were collected from 1,112 participants using validated questionnaires. Follow-up was done through outpatient assessment and telephonic interviews, clinical assessments at 6, 12, and 18 months post-PCI. Symptoms like chest pain, dyspnea, and bleeding were assessed along with survival status. Post-PCI complications in our study included vascular bleed, acute kidney injury, sepsis, left ventricular failure, and cardiogenic shock.

The study was conducted with the approval of the Institutional Ethics Committee of the Institute of Medical Sciences, Banaras Hindu University, Varanasi, and written informed consent was obtained from all the study participants prior to enrolling them in our study.

Statistical analyses were performed using IBM SPSS Statistics for Windows, Version 25.0 (Armonk, NY: IBM Corp.). Continuous measurements were expressed as mean ± SD, and categorical variables as frequencies and percentages. Inferential statistics, such as Chi-square and independent *t*-tests, were applied to test associations. A significance level of 5% was adopted for all analyses.

Results

Baseline Demographical Data and Survival Outcome

The study involved 1,112 participants, comprising 810 men and 302 women, with a mean age of 54 years. The largest age-group

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was between 60 and 65 years, accounting for 214 participants. At the 18-month follow-up, 782 participants (70.32%) were successfully traced and completed the follow-up, while 330 (29.68%) were lost to follow-up. Among those 782 participants, 740 (94.62%) were alive, and 42 (5.38%) did not survive (Table 1).

Association of Gender, History of Hospitalization, and Age with Survival Outcome

Table 2 demonstrates that there is no significant association between gender and survival outcome (alive or dead). A statistically significant association exists between the hospitalization history post-PCI and survival outcome ($p < 0.001$). The majority of those who were dead had a history of hospitalization (61.9%), while none of the alive patients had been hospitalized. The comparison of age between patients who were alive and those who died reveals a statistically significant difference ($p = 0.013$). The mean age of deceased patients (60.80 years) is higher compared to those alive (56.65 years).

Association of Chest Pain, Dyspnea, and Bleeding with Survival Outcome

There is a statistically significant association between chest pain and survival outcome ($p < 0.001$). Patients who experienced chest pain had a much higher proportion of deaths (66.7%) compared to those without chest pain (33.3%). Dyspnea shows a significant association with survival outcome ($p < 0.001$). A higher proportion of those who died experienced dyspnea (47.6%) compared to those alive (25.4%). A significant association was found between bleeding and survival outcome ($p < 0.001$). Patients who experienced bleeding had a higher rate of death (19%) (Table 3 and Fig. 1).

Details of the Deceased Patients

Among the patients who died, 22 individuals (52.3%) succumbed to a documented repeat acute coronary syndrome (ACS), while eight patients (19.04%) died because of complications following PCI, postdischarge. Additionally, eight patients (19.04%) experienced death attributed to acute decompensated heart failure (ADHF), and four patients (9.5%) died from documented intracranial hemorrhage. A significant portion of these patients, totaling 26 (61.90%), died within the hospital setting, whereas 16 patients (38.10%) expired at home. Notably, 19.04% (8 patients) of the deceased lost their lives within 1 month of undergoing PCI, while the majority, comprising 16 patients (38.10%), died between 6 and 12 months post-PCI. Furthermore, 14 patients (33.33%) and 4 patients (9.5%) died between 1 and 6 months and beyond 12 months, respectively, after the PCI procedure (Table 4 and Fig. 2).

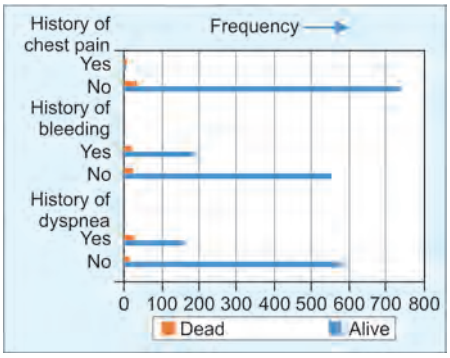

Fig. 1: History of chest pain, bleeding, and dyspnea among patients who were alive and dead

Table 1: Baseline data and status after 18 months of follow-up

	Parameter	*Frequency (n)*	*Percentage*
Gender at study enrollment	Male	810	72.84%
	Female	302	27.16%
Age-group at study enrollment	25–34	14	1.25%
	35–44	102	10.07%
	45–54	314	28.23%
	55–64	388	34.89%
	65–74	240	21.58%
	75–84	50	4.49%
	>85	4	0.35%
Status after 18 months post-PCI	Alive	740	66.54%
	Lost to follow-up	330	29.67%
	Dead	42	3.77%

PCI, percutaneous coronary intervention

Table 2: Association of gender, history of hospitalization, and age with survival outcome

Parameter		*Alive N (%)*	*Dead N (%)*	*Total N (%)*	*Chi-square*	*p-value*
Gender	Female	206 (27.8)	14 (33.3)	220 (28.1)	0.594	0.481
	Male	534 (72.2)	28 (66.7)	562 (71.9)		
	Total	740 (100)	42 (100)	782 (100)		
History of hospitalization	No	740 (100)	16 (38.1)	756 (96.7)	473.85	0.001*
	Yes	0	26 (61.9)	26 (3.3)		
	Total	740 (100)	42 (100)	782 (100)		
Age		Alive	Dead	*t*-value	*p*-value	
	Mean ± SD	56.65 ± 10.19	60.80 ± 12.28	–2.478	0.013*	

*Statistically significant ($p < 0.05$); N, frequency

Table 3: Association of chest pain, dyspnea, and bleeding with survival outcome

	Alive N (%)	*Dead N (%)*	*Total N (%)*	*Chi-square*	*p-value*
History of chest pain					
No	580 (78.4)	14 (33.3)	594 (76)	44.16	0.001*
Yes	160 (21.6)	28 (66.7)	188 (24)		
Total	740 (100)	42 (100)	782 (100)		
History of dyspnea					
No	552 (74.6)	22 (52.4)	574 (73.4)	10.04	0.001*
Yes	188 (25.4)	20 (47.6)	208 (26.6)		
Total	740 (100)	42 (100)	782 (100)		
History of bleeding					
No	736 (99.5)	34 (81)	770 (98.5)	90.09	0.001*
Yes	4 (0.5)	8 (19)	12 (1.5)		
Total	740 (100)	42 (100)	782 (100)		

*Statistically significant ($p < 0.05$); N, frequency

Table 4: Details of the deceased patients

	Frequency (n)	*Percentage*
Cause of death		
Documented ACS	22	52.38%
Post-PCI complication	8	19.04%
ADHF	8	19.04%
Intracranial hemorrhage	4	9.52%
Place of death		
Hospital	26	61.90%
Home	16	38.09%
Time of death since PCI		
<1 month	8	19.04%
1–6 months	14	33.33%
6–12 months	16	38.09%
>12 months	4	9.52%

ACS, acute coronary syndrome; ADHF, acute decompensated heart failure; PCI, percutaneous coronary intervention

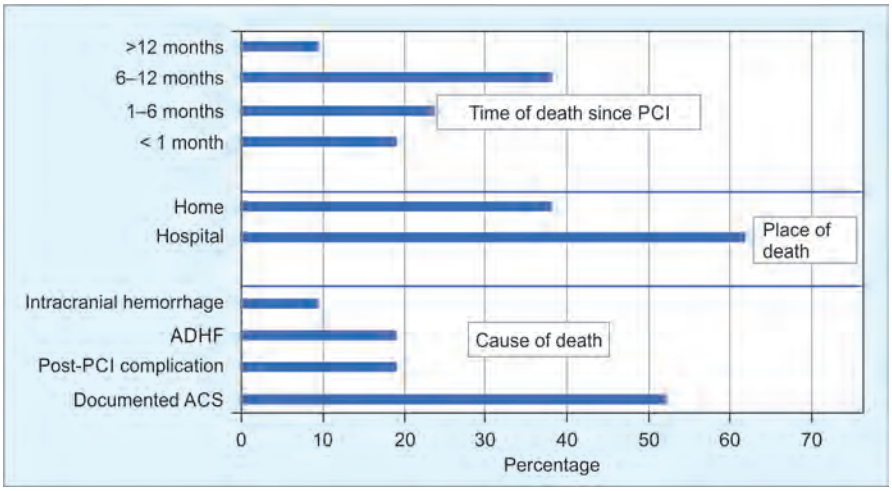

Fig. 2: Details of the deceased patients

Discussion

The introduction of PCI with DES has markedly revolutionized the treatment of CAD. This research aimed to assess the long-term survival rates and associated clinical outcomes following single-vessel PCI with DES in a North Indian cohort and offers valuable contributions to the current literature.

The results from this study on survival and clinical outcomes following single-vessel PCI using DES provide crucial information on the long-term efficacy of DES in treating CAD in a North Indian population. This discussion will evaluate these findings in the context of existing research, offering comparisons, potential explanations, and areas for further exploration.

Survival Outcomes Post-PCI with Drug-eluting Stents

The study reported a survival rate of 94.62% after 18 months of follow-up for patients treated with DES for SVD. This outcome is in line with global PCI data, where DES have consistently shown high survival rates. For instance, a meta-analysis by Bangalore et al. found a 95% survival rate 1 year after PCI with DES, further confirming its effectiveness in reducing restenosis and improving patient outcomes.[1] Similarly, the EXAMINATION trial, which compared DES with bare-metal stents (BMS), demonstrated a significant reduction in all-cause mortality over a 5-year period in patients treated with DES.[2]

The strong survival outcomes observed in this study may be attributed to several factors. DES is well-documented for its ability to suppress neointimal hyperplasia, thereby decreasing restenosis rates, and has consistently performed better than BMS in both SVD and MVD.[3,4] Furthermore, second-generation DES, which have improved design and reduced risks of late stent thrombosis, are likely to have contributed to the observed outcomes.[5] These benefits have been confirmed across various demographics, including Asian populations, as demonstrated by the ABSORB-EXTEND study, which reported comparable survival outcomes in Japanese patients treated with DES.[6]

Influence of Age and Gender on Survival

Age played a significant role in survival outcomes, with the mean age of deceased patients (60.80 years) being higher than that of survivors (56.65 years). Previous research consistently shows that older patients experience worse outcomes following PCI. For example, Harjai et al. identified a strong correlation between increasing age and higher mortality and complications, particularly with every additional decade of life.[7] The higher prevalence of comorbidities such as hypertension and diabetes in older patients can negatively impact recovery and increase the risk of adverse events like stent thrombosis or restenosis.[8]

Interestingly, the current study found no significant difference in survival based on gender, a finding that contrasts with earlier research suggesting that women tend to have worse short-term outcomes post-PCI. However, long-term outcomes between men and women appear to be similar. A study for the analysis of sex-related outcomes post-PCI showed no significant difference in 5-year mortality rates between men and women treated with DES, indicating that gender disparities might be more pronounced in the short term rather than in long-term survival.[9]

Hospitalization and Symptom Associations with Mortality

A notable observation from this study was the strong association between prior hospitalization and mortality. Of the patients who died, 61.9% had been rehospitalized due to cardiovascular events prior to death, while none of the surviving patients had required rehospitalization. This finding is consistent with existing research that links rehospitalization post-PCI with increased risk of mortality. Eccleston et al. showed that patients rehospitalized within the 1st year of PCI had significantly higher mortality and adverse cardiac event rates.[10] Hospitalization often reflects underlying complications, such as heart failure, stent thrombosis, or recurrent angina, all of which can significantly increase the risk of death.[11]

Additionally, symptoms like chest pain, dyspnea, and bleeding were significantly linked to mortality in this study. Among deceased patients, 66.7% reported chest pain, while 47.6% experienced dyspnea. These findings align with those from the study done

by Collison et al., which also identified these symptoms as predictors of adverse outcomes post-PCI.[12] Persistent angina or dyspnea following PCI often suggests incomplete revascularization or the progression of CAD, increasing the likelihood of mortality.[13]

The association between bleeding and higher mortality risk is well-supported by previous studies. Major bleeding events following PCI have been shown to double the risk of death within 1 year, as reported in the ACUITY trial.[14] The interruption of essential antiplatelet therapy, which is critical in preventing stent thrombosis, or the deterioration of a patient's overall condition due to bleeding, may contribute to this elevated mortality risk.[15]

Causes and Timing of Death

In this study, the most frequent cause of death was ACS, accounting for 52.3% of the deaths, followed by PCI complications (19.04%) and heart failure (19.04%). These findings are consistent with other studies identifying ACS as a leading cause of death after PCI. For example, the study done by Wu et al., similarly noted a high rate of ACS-related deaths in PCI patients, particularly among those with incomplete revascularization or poor adherence to medical therapy.[16]

The timing of death post-PCI is another key finding. Most deaths occurred between 7 and 12 months after the procedure, underlining the importance of long-term monitoring in PCI patients. Previous research has shown that the risk of adverse events such as stent thrombosis and recurrent ACS remains elevated for at least 1 year following PCI.[17] This highlights the necessity for proactive secondary prevention strategies, including extended dual antiplatelet therapy and lifestyle modifications, to improve long-term survival.[18]

Study Limitations and Future Research

While the study provides significant insights, it has certain limitations. The relatively high loss to follow-up rate of 29.68% may introduce bias into the survival analysis. Furthermore, as an observational study, it cannot definitively establish causality between variables. Another limitation is the population focus; while this study centers on a North Indian demographic, the results may not be universally applicable due to differences in genetic predisposition, comorbidities, and healthcare access.

Future research should aim to address these limitations by conducting larger, multicentric trials with extended follow-up periods and more rigorous methods of patient tracking. Additionally, further studies are necessary to explore phylogeographic and epigenetic factors that influence PCI outcomes, particularly in South Asian populations where data remains scarce.

Conclusion

This study provides valuable insights into the survival and clinical outcomes following single-vessel PCI using DES in a North Indian population. The survival rate of 94.62% after 18 months reflects the efficacy of DES in managing single-vessel CAD (SVD) and is consistent with global outcomes reported in other studies. Age and prior hospitalization emerged as significant predictors of mortality, with older patients and those with a history of rehospitalization demonstrating higher mortality rates. Symptoms such as chest pain, dyspnea, and major bleeding were also strongly associated with adverse outcomes, highlighting the need for vigilant post-PCI monitoring.

While the study underscores the effectiveness of DES in improving survival, it also points to the importance of addressing patient-specific risk factors such as age, comorbidities, and hospitalization history. The findings emphasize the need for long-term follow-up and preventive strategies, including aggressive management of symptoms and adherence to secondary prevention protocols, to enhance patient outcomes. However, limitations such as the loss to follow-up and the study's observational design warrant caution in generalizing the results.

Ethical Approval

The study was conducted with the approval of the Institutional Ethics Committee of Institute of Medical Sciences, Banaras Hindu University, Varanasi, and written informed consent was obtained from all the study participants prior to enrolling them in our study.

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ORIGINAL ARTICLE

A Clinicoradiological and Bacteriological Profile of Community-acquired Pneumonia in a Tertiary Care Center in Eastern India

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Abstract

Introduction: The world of microbes as a causative agent of community-acquired pneumonia (CAP) has been ever-changing with the emergence of new species, introduction of newer diagnostic techniques, availability of newer antibiotics and vaccines, and changing demographic profiles of patients as reported from different parts of the globe over time.

Objective: The aim of the present study is to evaluate the clinicoradiological and bacteriological profile of CAP among patients admitted to a tertiary care hospital with special reference to the CURB-65 score and acute inflammatory markers.

Materials and methods: It was a descriptive, observational, cross-sectional study conducted over a period of 18 months in the Department of Respiratory Medicine in a tertiary care hospital in the Indian subcontinent. Patients with features of lower respiratory tract infection of all age-groups and sexes were included in the study; immunocompromised patients, pregnant patients, patients with malignancy, active tuberculosis, and those who received antibiotics in the previous 90 days or were admitted to any other healthcare facility were excluded from the study. The study was conducted after obtaining Institutional Ethics Committee clearance and informed consent from study participants. The data obtained were analyzed by Statistical Package for the Social Sciences (SPSS) software and appropriate statistical tests.

Results: A total of 100 patients with male predominance (63%), an average age of 47.61 ± 1.78 years, 33% current smokers, and with diabetes (27%) and hypertension (19%) as comorbid conditions were included in the study. *Klebsiella* and *Pseudomonas* sp. were among the most common isolates, closely followed by *Streptococcus pneumoniae* among the elderly population; whereas *S. pneumoniae* was the most common organism overall, and 48% showed no culture isolate.

Conclusion: It is an absolute necessity to conduct several similar studies in the future among different patient demographics, localities, and practice settings, keeping in consideration the constantly changing microbiological profile over time and the introduction of new diagnostic and management modalities.

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Introduction

The history of pneumonia traces back to the era of the great Greek physician Hippocrates, who described the various presentations of lower respiratory tract infections and proposed a herbal tonic and rest as medical management of the condition, along with some surgical techniques for draining the chest cavity with a metal catheter in case empyema developed as a dreaded complication.[1] However, it was Laennec in 1834, an Italian physician, who demonstrated the art of clinical examination of the chest in describing different stages of developing pneumonia.[2] Since then, several hundreds of organisms, including bacteria, viruses, fungi, etc., have been identified as the causative agents of pneumonia. The annual incidence of community-acquired pneumonia (CAP) varies between 5 and 11 per 1,000 population, of which 20% require hospitalization.[3] CAP still continues to have a huge impact on the global healthcare burden in terms of morbidity and mortality, and India contributes about 23% of the global pneumonia burden with a high case fatality rate.[4] *Streptococcus pneumoniae* was found to be the most common organism causing CAP, usually among young persons, whereas gram-negative organisms like *Pseudomonas* and *Klebsiella* were more common among elderly persons.[5] The C-reactive protein (CRP) is an acute-phase reactant of hepatic origin that increases following interleukin-6 release by macrophages and T cells and activates the complement system *via* C1q. CRP is synthesized by the liver in response to factors released by dead and dying macrophages and fat cells. In healthy adults, the normal concentration of CRP varies between 0.8 and 3.0 mg/L and may increase to >500 mg/L in response to acute-phase stimuli. However, CRP may be falsely elevated with age, possibly due to subclinical conditions.[6]

The microbiological pattern responsible for CAP reported so far in the literature has been changing over time, depending on the geographic and demographic variation, clinical settings of the study, local antibiotic policy, access to newer antibiotics, adult vaccination policy in the community, and availability of over-the-counter (OTC) medication, including antibiotics.

The aim of the study is to evaluate the clinico-radiological and bacteriological profile of CAP and the utility of the CURB-65 scoring system and the role of inflammatory markers (CRP and procalcitonin levels) in the assessment of disease severity in such cases.

Materials and Methods

This was a descriptive, observational, cross-sectional study conducted over a period of 18 months (March 2018 to August 2019) in a pulmonary care unit in a tertiary care hospital in Eastern India.

Sample Size

The sample size was calculated using the following formula, $n = (Z_{1-\alpha/2} / \delta)^2\, p\,(1-p)$, where $Z_{1-\alpha/2} = 1.96$ is the standard normal variate for 5% error, p is the expected proportion in the study population based on a review of literature on the prevalence of *S. pneumoniae* as the most common isolate among patients with CAP in the Indian population (7%), and δ is the precision level within 5%. Hence, the sample size was calculated to be 100.

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Study Population

The patients who were admitted to the Department of Pulmonary Medicine of a tertiary care hospital with clinical and radiological features of CAP over a period of 1.5 years, from March 2018 to August 2019, were the study population of the present study.

Inclusion Criteria

Patients of either sex, older than 18 years of age, presenting with symptoms of an acute lower respiratory tract illness (cough and at least one other lower respiratory tract symptom), new focal chest signs on examination, and at least one systemic feature (either a symptom complex of sweating, shivering, aches and pains, and/or a temperature of 38°C or more) were included in the study.

Exclusion Criteria

Those who did not consent to the study, pregnant and immunocompromised patients, those suffering from malignancy, active tuberculosis, hospital-acquired pneumonia, or aspiration pneumonia, were excluded from the study. Also, those who received antibiotics within the previous 90 days or were admitted to any other healthcare facility were excluded from the study.

The patients were examined clinically, and basic investigations like complete blood count, blood sugar, liver and renal function tests, arterial blood gas (ABG) analysis, inflammatory markers like CRP and procalcitonin, and chest radiographs were done.

The Institutional Ethics Committee approval was obtained, and data were collected in a predesigned proforma.

Statistical Analysis

The data obtained were compiled and tabulated using Microsoft Excel 2013. Descriptive statistics, including the mean and standard deviation of the parameters, were calculated using Microsoft Excel. Inferential statistical analysis was done by the *t*-test and Fisher's exact test with the help of Statistical Package for the Social Sciences (SPSS) 22.0 software.

Results

The present study included a total of 100 patients (63 males and 37 females). Most of the patients were either over 60 years of age (27 males and 8 females, 30%) or younger than 30 years (12 males and 13 females, 26%). The mean age of the present study population was 47.61 ± 1.78 years. The most common presenting complaints were cough with expectoration (93%) and fever (91%), followed by shortness of breath (64%) and chest pain (47%). Among the study population, 33% were current smokers, and 10% were addicted to alcohol. Diabetes and hypertension were among the most common comorbid conditions (27 and 19%, respectively). Both diabetes and hypertension were significantly more common among patients older than 50 years of age compared to those younger than 50 years (hypertension 10.4 vs 42.3%, $p = 0.001$; diabetes 3.2 vs 30.7%, $p = 0.0002$). The CURB-65 score at the time of initial presentation was 0–1 among 44 out of 100, whereas 37 presented with a score of 2, and 19 presented with a score ≥3. The clinical and radiological profile of the patients with respect to the CURB-65 score is presented in Table 1. Overall, 58 out of 100 patients had CRP ≤10 mg/dL, and 42 had CRP >10 mg/dL, out of which 13 had CRP >40

Table 1: Clinical, radiological, and bacteriological profile of patients with respect to CURB 65 score

CURB65	*0–1*	*2*	*≥3*
Female	17	14	6
Male	27	23	13
Age, mean ± SD (years)	43.159 ± 16.6	43.405 ± 16.94	66.105 ± 7.46
Smoker	15	13	5
Alcohol	5	3	2
Hypertension	11	7	9
Diabetes	9	4	6
Clinical features			
Respiratory rate (breaths/minute)	28.6 ± 4.56	32.21 ± 2.89	31.78 ± 3.18
SpO_2	93.27 ± 0.03	92.93 ± 0.03	91.63 ± 0.04
TLC, range	4000–26000	3830–24000	6870–25400
Average neutrophil count per cumm	8400.73 ± 5175.74	8467.65 ± 4470.72	8317.68 ± 4718.95
Biomarkers			
CRP, mg/L	12.74 ± 16.03	27.25 ± 39.52	10.19 ± 17.55
Procalcitonin, ng/mL	14.05 ± 16.66	20.64 ± 17.78	21.04 ± 21.68
CXR findings			
UL ML	32	25	9
BL ML	2	5	5
ML PE	8	7	5
NAD	2		
Sputum culture			
No organism isolated	27	16	5
S. pneumoniae	11	11	4
K. pneumoniae	4	5	3
S. aureus		3	2
Others	2	2	5

BL ML, bilateral multilobar; ML PE, multilobar with pleural effusion; NAD, no abnormality detected; UL ML, unilateral multilobar

mg/dL (reference normal value <0.6 mg/dL). Procalcitonin levels were >2 ng/mL in 69 out of 100 patients, <0.15 ng/mL in 2, and the rest were in between. However, there was no significant correlation between the CURB-65 score and CRP or procalcitonin level ($r = 0.03266$ and 0.18211, respectively).

The organisms isolated on aerobic culture with respect to radiological involvement are given in Table 2. *S. pneumoniae* (26%) was the most commonly isolated organism, followed by *Klebsiella pneumoniae* (12%) in the study population, most of whom presented with unilateral involvement of the lung. Whereas all four patients with *Staphylococcus aureus* infection presented with bilateral multilobar infiltrates. Out of 48 patients who were microbiologically negative, most of them (34 out of 48, 70.8%, $p = 0.0418$) presented with unilateral multilobar infiltrates on chest X-ray. gram-negative organisms were the most commonly isolated organisms in the elderly population over 60 years of age (6 with *Klebsiella* sp. and 5 with *Pseudomonas aeruginosa*, 31.4%), closely followed by gram-positive organisms (*S. pneumoniae* 9 and *S. aureus* 1), and no organism was isolated in 14 of the elderly population. Cough and expectoration among those with *P. aeruginosa* isolate and shortness of breath among those with *S. aureus* isolate were the predominant symptoms, and the finding was statistically significant with *p*-values of 0.0097 and 0.0202, respectively, as given by Fisher's exact test. The mean CRP level among those with sputum and/or bronchoalveolar lavage (BAL) fluid culture-positive isolates was significantly greater than those among microbiologically negative patients (26.05 ± 35.29 vs 8.49 ± 12.28, $p < 0.0001$) by unpaired *t*-test. Similarly, procalcitonin levels were significantly higher among microbiologically positive patients (25.07 ± 19.14 vs 9.44 ± 12.63, $p < 0.0001$) by unpaired *t*-test.

The distribution of sputum and/or BAL fluid culture with respect to blood culture is shown in Table 3. The average CRP values were 12.74 ± 16.02, 27.25 ± 39.5, and 10.19 ± 17.5 in patients with CURB-65 scores of 0–1, 2, and >3, respectively. CRP value and CURB-65 score were weakly correlated in the present study ($r = 0.0327$, $p = 0.746$). The CRP value was relatively lower in those with a CURB-65 score greater than 3, which may be due to the fact that most of the elderly population presented with less severe disease.

Out of 100 patients, those who had chest X-ray findings of bilateral multi-lobar infiltrates had a mean CRP level of 30.63 (SD 27.29) and a mean procalcitonin (PCT) level of 37.84 [standard deviation (SD) 20.58], respectively.

The CRP and PCT values were significantly increased in patients with multilobar infiltrates by unpaired *t*-test ($p = 0.0030$ and 0.0006, respectively). *Staphylococcal* infection most commonly presented with bilateral multilobar infiltrates (66.66%), whereas *P. aeruginosa* presented with both bilateral multilobar infiltrates (37.5%) and unilateral multilobar infiltrates (25%). Increased CRP values were statistically significant in cases of unilateral multilobar infiltrates as well, with a *p*-value < 0.00001. In microbiologically negative patients, most had unilateral multilobar infiltrates (75%).

Discussion

The mean age of the present study population was 47.61 ± 1.78 years, with a slight male predominance, which is very similar to other studies from this part of the subcontinent.[3,7] Studies have shown that age and gender have a significant influence on the occurrence of CAP, with more prevalence among the elderly population and male gender.[3,8] Cough and fever were among the most common presenting symptoms in the present study as well as in several previous studies.[6,9,10] Shortness of breath, chest pain, and expectoration were among the other common symptoms. Diabetes (27%) and hypertension (19%) were among the most common comorbid conditions in the present study. Chronic obstructive pulmonary disease (COPD) and obesity, in addition to hypertension and diabetes, were among the most common comorbidities, as found in several previous studies.[3,9] The risk factors for severe CAP are elderly population, obesity, regular alcohol intake, and previous history of respiratory tract infection within the last year.[3]

The choice of empiric antibiotic is crucial in the management of CAP, which may later be modified depending on the culture report and response to the initial antibiotic administered. In the present study, no microorganism could be identified in 48% of cases, very similar to several previous studies that failed to identify the causative organism in around 50% of cases.[4,11] Microorganisms, including viruses and *Candida* sp., could be isolated in only 34% of cases in a study from southern India.[3] Though *S. pneumoniae* has been claimed as a less common causative organism in several western studies,[11] the organism is still one of the most common bacterial isolates, at least in some geographic locations (Table 4). Lim et al. concluded that *S. pneumoniae* is still the

Table 2: Distribution of sputum culture isolates with respect to radiological involvement

	No growth	*S. pneumoniae*	*S. aureus*	*K. pneumoniae*	*P. pneumoniae*	*H. influenzae and Escherichia coli*
UL ML	34	21	1	7	2	1
BL ML	2	1	4	1	3	1
ML PE	10	4		4	1	1
NAD	2					

BL ML, bilateral multilobar; ML PE, multilobar with pleural effusion; NAD, no abnormality detected; UL ML, unilateral multilobar

Table 3: Distribution of sputum and/or BALF culture isolate with respect to blood culture

		S. pneumoniae	*S. aureus*	*P. auroginosa*	*K. pneumoniae*	*H. influenzae and E. coli*	*No growth*	*Total*
Blood culture	*S. pneumoniae*	2						2
	S. aureus						1	1
	P. auroginosa			2			2	4
	K. pneumoniae				2			2
	H. influenzae and *E. coli*							
	No growth	24	5	4	10	3	45	91
Total		26	5	6	12	3	48	100

Table 4: Comparative study of culture isolates in different geographical location

Author, place, reference	*Period of study*	*Study population, mean age*	*Comorbidities*	*Positive culture*	*Organism isolated*
Lim et al., UK 2001[11]	October 1998–September 1999	267, 65.4 (19.6) years	Chronic lung disease, cardiac ailments, diabetes, cerebrovascular diseases, mental illness		*S. pneumoniae* (48%), influenza A virus (19%), *Chlamydia pneumoniae* (13%), *H. influenzae* (7%), *Mycoplasma pneumoniae* (3%), *Legionella pneumophilia* (3%), other *Chlamydia* spp. (2%), *Moraxella catarrhalis* (2%), *Coxiella burnetii* (0.7%), others (3%)
Tsai et al., Central Australia[12]	2011–2014	185, retrospective study		63.2%	*S. pneumoniae* (28.2%), *H. influenzae* (19.7%), influenza A/B (16.2%) and *S. aureus* (14.5%)
Mahendra et al., KA, India[3]	March–July 2015	100, 54.03 years	Hypertension, obesity, diabetes, COPD	34%	H1N1 (8), *Klebsiella* sp. (8), *Psudomonas (5), Streptococcus* (4)
Shah et al., Kashmir, India[10]	December 1998–December 2000	100, 53.68 years	Smoking, COPD and other structural lung disease, diabetes	29%	*Pseudomonas* (10), *S. aureus* (7), *E. coli* (6), *Klebsiella* sp. (3), *S. pneumoniae* (1)
Menon et al.[13]	January–December 2009	145, 18–90 years	–	76%	*S. pneumoniae*, *K. pneumoniae*, *P. aeruginosa*, Alpha hemolytic streptococci, *E. coli*, Beta hemolytic streptococci and atypical coli
Present study	March 2018–August 2019	100, 47.61 (1.78) years	Smoking, diabetes, hypertension,	52%	*S. pneumoniae* (26), *K. pneumoniae* (12), *Pseudomonas* (6), *S. aureus* (5), *H. influenzae* and *E. coli* (3)

most common pathogen to be addressed in empirical therapy considering all age-groups, with atypical pathogens being more common among younger populations with less severe disease.[11] *S. pneumoniae*, *Haemophilus influenzae*, *S. aureus*, and Gram-negative bacilli were identified as the most common causative organisms in decreasing order of frequency in a systematic review article by Shoar and Musher.[14] In contrast, viral pneumonia caused by H1N1 and *Klebsiella* sp. were the most common isolates in another study from South India.[3] *P. aeruginosa* was the second most common bacterial isolate, only after *Klebsiella* sp.[3] In contrast, *S. pneumoniae*, followed by *Klebsiella* sp., was the most common isolate from sputum and/or blood in the present study. The predominance of pneumococcus in the present study may be due to the relatively younger population who were not vaccinated against pneumococcus as per standard recommendations. Moreover, those who were admitted with a CURB-65 score >3 were mostly elderly individuals with less severe illness in terms of respiratory rate, leukocyte count, oxygenation status, and radiological involvement. In other words, this study is limited by a small number of severe CAP cases among the elderly population. The overall diagnostic yield of cultures from different relevant specimens, including expectorated sputum, induced sputum, protected brush specimens, tracheal aspirates, varies widely, ranging from 25 to 72%.[3,4,10] The reason for such wide variation in microorganism isolation rates, as reported in different studies conducted over the last few decades, may be multifactorial: namely patient demographics, comorbid conditions of the study population, infrastructure facilities, and diagnostic modalities applied, including viral polymerase chain reaction (PCR) techniques, antigen detection, or methods used to obtain respiratory specimens such as expectorated sputum, induced sputum, bronchoalveolar lavage fluid, or transthoracic needle aspiration. The introduction of newer antibiotics in the pharmaceutical market and the intake of antibiotics prior to admission in outpatient settings also contribute to this variability. Eshwara et al. have reviewed several original articles from different corners of the Indian subcontinent conducted over a wide time period and have shown variation in microbiological isolates in different studies, including the emergence of a new pathogen, *Burkholderia pseudomallei*.[4] The authors emphasized the need for a comprehensive diagnostic approach and the development of local evidence on sensitivity patterns to improve the outcomes of CAP management.[4]

According to the REACH multinational study, negative sputum and/or blood culture reports were more common among early responders, defined as those who clinically improved in ≤4 days.[15] Musher et al. have pointed out the changing trends in the microbiological pattern of CAP over time.[16] However, *S. pneumoniae* continues to be the most prevalent causative organism, especially among critically ill patients. The vaccination policies in different geographical areas also contribute to the variations in microbiological patterns, as reported in studies from various parts of the globe. Menon et al. analyzed data from 145 patients with CAP admitted to a hospital and found that the relative incidence of the etiological organism varied with the age of the patient.[13] In the present study, the CRP and procalcitonin levels were significantly elevated among those with positive culture isolates ($p = 0.00156$ and <0.001, respectively), as demonstrated by unpaired *t*-tests. This finding is consistent with those of Boussekey et al., where serum procalcitonin levels were significantly elevated in CAP patients with positive culture isolates (4.9 vs 1.5 ng/dL, $p = 0.0001$), and in the presence of bacteremia and/or septic shock (4.9 vs 1.5 ng/dL, $p = 0.0003$).[17] However, higher procalcitonin levels were not specific to any particular pathogen. Despite this, there was a small negative correlation between the CURB-65 score at presentation and CRP levels (Pearson correlation coefficient, $r = -0.091$). Conversely, raised procalcitonin levels showed a significant medium positive relationship with the CURB-65 score (Pearson correlation coefficient, $r = 0.337$). This suggests that procalcitonin at admission may serve as a better predictor of disease severity compared to the CURB-65 score. In a randomized interventional trial involving >300 patients with suspected CAP, Christ-Crain et al. concluded that procalcitonin-guided

management reduced the total antibiotic prescription ($p < 0.001$) and the mean duration of antibiotic therapy ($p < 0.001$) compared to conventional guideline-based treatment. This approach ensured early de-escalation of antibiotics and a reduction in antibiotic costs, although the clinical outcomes were similar in both groups.[18]

Limitations

However, the present study is limited by the small size of the study population, and only aerobic culture was considered for organism isolation. The present study considered only the CURB-65 score to define severe CAP infection.

Conclusion

The role of empiric antibiotic therapy in the management of CAP is immense, and the ever-changing microbiological pattern often poses a great challenge in its management. Hence, the study of the microbiological pattern of CAP needs to be conducted from time to time, among different patient populations, in different geographic areas, and among different practice settings—community clinics or secondary or tertiary care centers.

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ORIGINAL ARTICLE

Role of Meditation as Adjuvant Therapy on Gastrointestinal Quality of Life among Individuals with Functional Dyspepsia in an Outpatient Setting: A Randomized Pilot Trial

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Abstract

Background: Functional dyspepsia (FD) is one of the most common reasons for medical visits. Patients with FD incur large direct and indirect expenditures and may have significant financial burdens that affect quality of life. Our study aimed to assess the effectiveness of meditation as an adjuvant to the standard treatment in individuals diagnosed with FD. This will explore more cost-effective therapeutic management in diseases like FD, which is believed to be related to the gut-brain axis. Meditation is a nonpharmacological therapy, safer and economical, and its adjuvant use can minimize or avoid the adverse effects of long-term use of proton pump inhibitors (PPI) and tricyclic antidepressants (TCA).

Objectives: We wanted to comprehensively assess the role of meditation as an adjuvant therapy in patients with FD and compare it with the control arm receiving standard treatment alone. The primary objective was the change in gastrointestinal quality of life index (GIQLI) score, and the secondary objective was to assess the changes in the hospital anxiety and depression scale (HADS) score and Pittsburgh sleep quality index (PSQI) score before and after the intervention.

Methods: Patients fulfilling the inclusion criteria were divided equally into two arms (experimental and control groups). The experimental group received standard treatment for dyspepsia (PPI, domperidone, TCAs) and Vaishvanara Agni meditation (VAM), while the control group received standard treatment alone. Both groups were compared at weeks 0, 4, and 8 in terms of change in GIQLI score, HADS (HADS-A and HADS-D score), and PSQI score.

Results: Our study showed that both groups experienced significant changes in GIQLI, HADS-A, HADS-D, and PSQI scores at 4 and 8 weeks when compared with the baseline time point. However, when both groups were directly compared, it was observed that the experimental group exhibited notable variations in the GIQLI score after 8 weeks, the HADS-D score after 8 weeks, and the PSQI score after 4 weeks when contrasted with the control group. These differences were found to be statistically significant.

Conclusion: FD does not have an identified structural or biochemical cause, making it a functional gastrointestinal (GI) disorder that requires a tailored treatment approach. Our pilot randomized controlled trial (RCT) investigated the impact of meditation as adjuvant therapy for FD, revealing improvements in GI health, mental well-being, and sleep quality compared to standard treatment alone. The study recommends incorporating meditation into the management of FD and similar conditions, highlighting its holistic nature that addresses not only specific symptoms but also overall well-being. This study pioneers the examination of meditation as a complementary approach for FD, offering promising results in improving GIQLI, HADS, and PSQI scores and thus adding value to preexisting literature.

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Introduction

Functional dyspepsia (FD), characterized by persistent upper abdominal discomfort, is a common gastrointestinal (GI) disorder with significant medical and financial implications.[1,2] While global prevalence estimates were previously as high as 20%, the introduction of the Rome IV criteria for diagnosis suggests a lower rate, though the burden is believed to be higher in the Indian population.[3] The Rome IV criteria define FD based on symptoms persisting for at least 3 months and occurring at least once a week for 6 months. These symptoms include bothersome postprandial fullness, bothersome early satiation, bothersome epigastric pain, or bothersome epigastric burning. Subtypes include postprandial distress syndrome (PDS), epigastric pain syndrome (EPS), or having overlap symptoms.[4] Recent research highlights the intricate and heterogeneous nature of FD, involving factors like compromised vagal signaling, increased sensitivity of vagal afferents, and abnormalities in response to gastric and duodenal distension.

Individuals with FD exhibit deficiencies in their vagovagal reflexes, affecting responses to distension and potentially contributing to symptoms.[5] Dysbiosis, alterations in microbial density, and small intestinal bacterial overgrowth (SIBO) are reported in FD, impacting the gut-brain axis and contributing to psychological conditions.

Stress is implicated in changing intestinal mucus composition, influencing motility, and affecting the gut microbiota.[6] The bidirectional influences between the gut and the brain involve alterations in neurotransmission, behavior, and neurogenesis.[7] Cyclic meditations (CM) have been shown to improve cognitive abilities and vagal tone in numerous studies by alleviating stress-induced gut microbiota dysbiosis.[8,9] In summary, FD presents a complex clinical picture influenced by various physiological and psychological factors.

The standard medical treatment of FD involves proton pump inhibitors (PPI), prokinetics, and antidepressants. Our study aimed to assess the cost-effective therapeutic potential of GI-related meditation in managing FD, considering the implications of the gut-brain axis in its causation. With our study, we tried to explore the role of meditation as an adjuvant therapy that holds promise for a safer, economical alternative to standard pharmacotherapy, providing valuable insights into the holistic management of this challenging GI condition.

Methodology

The study was a pilot randomized trial conducted at AIIMS, Rishikesh, Uttarakhand. About 60 patients were recruited from March

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to September 2023 from the outpatient departments (OPDs) of Gastroenterology, General Medicine, and the Lifestyle Clinic. These patients were allocated equally to the experimental and control arms (i.e., 30 patients in each arm).

In our study, we included patients between the age-group of 18 and 60 years who met the ROME IV criteria for FD with a normal upper GI endoscopy and a negative *Helicobacter pylori* urea breath test. Patients with dyspepsia with alarm signs, secondary dyspepsia due to chronic conditions, malignancies, and those who had undergone major GI surgeries were excluded.

The experimental arm received Vaishvanara Agni meditation (VAM), which was taught in person by a qualified yoga instructor on the day of recruitment, followed by a daily virtual session of 22 minutes for a total duration of 8 weeks.[10] Both the control and experimental arms were given standard medical care during this time.

Baseline data were entered into the data collection sheet, and the outcomes were assessed at three-time intervals, that is, day 0, 4, and 8 weeks. All outcomes were assessed at pre- and postintervention intervals by a principal investigator who was blinded to the participants in each arm.

The following tools were used for assessment:

- Gastrointestinal quality of life index (GIQLI)
- Hospital anxiety and depression scale (HADS-A and HADS-D)
- Pittsburgh sleep quality index (PSQI)

These parameters were compared between two arms and checked for statistical significance.

Informed consent was obtained before enrolling the patients in the study, and the questionnaire was filled out. The study was conducted after obtaining ethical clearance from the Institutional Ethics Committee and the Clinical Trials Registry—India [CTRI/2023/02/049643].

Statistical Analysis

The data were entered into the Windows Excel sheet. Statistical Package for Social Sciences (SPSS, version 29.0) for Windows was used for data analysis.

For descriptive statistics, the normality of the data was assessed by the Shapiro–Wilk test. The data were then represented as mean and standard deviation, followed by the application of parametric and nonparametric tests based on the normality results.

For inferential statistics, an independent *t*-test was used to compare the two arms at baseline and follow-up; a paired *t*-test was used to compare the same arm before and after 4 and 8 weeks. The Wilcoxon–Mann–Whitney test was used to compare the two arms, and the Wilcoxon signed-rank test was used to compare within an arm at different time points for not normally distributed data. Intention to treat (ITT) was followed for data analysis. Missing data were managed using the last observation carried forward (LOCF) method.

Results

We invited 86 patients to participate in our study after they met the inclusion criteria, of which 60 patients volunteered to participate. These participants were randomized equally to experimental and control arms. The baseline parameters were comparable between both arms, with no significant difference in age and gender.

Discussion

Functional dyspepsia constitutes a significant portion of OPD visits, highlighting its prevalence and the substantial number of individuals seeking medical attention for this GI condition.[10] We adopted the treatment approach recommended by the American College of Gastroenterology (ACG)/Canadian Association of Gastroenterology (CAG) for FD as the standardized therapeutic method in both study groups. The drug burden associated with FD can vary depending on the severity of symptoms, the specific subtype of FD, and individual responses to treatment. With this study, we aimed to identify a more cost-effective and readily accessible substitute for the existing treatment. To the best of our understanding, this study is the first randomized controlled trial (RCT) examining the impact of meditation as an adjuvant intervention in the management of FD.

A multicentral nationwide study by Kim and Kim showed that FD is more common in females.[11] However, in Indian populations, most patients of dyspepsia were males, according to a pan-India, multi-centric observational study by Sud et al.[12] There were more male patients (61.7%) in our study, and it was more prevalent in the age-group 31–40 years (35%), as shown in Table 1. Kapoor et al., in their studies, observed a disparity in outpatient visits to tertiary centers in India, noting that women tend to seek medical attention less frequently than men, indicating a comparatively lower inclination among females in India to prioritize their health.[13] Consequently, the lower enrollment of female participants in our study may be due to the limited engagement of women in India with

Table 1: Baseline characteristics

Demographic parameters	*Experimental (n = 30)*	*Control (n = 30)*	*p-value*
Age (years)	36.37 ± 11.80	36.97 ± 11.21	0.841[1]
Age			
18–30 years	11 (36.7%)	8 (26.7%)	0.806[2]
31–40 years	9 (30.0%)	12 (40.0%)	
41–50 years	6 (20.0%)	6 (20.0%)	
51–60 years	4 (13.3%)	4 (13.3%)	
Gender			
Male	16 (53.3%)	21 (70.0%)	0.184[3]
Female	14 (46.7%)	9 (30.0%)	
Height (cm)	158.73 ± 9.13	162.93 ± 7.78	0.060[1]
Weight (kg)	60.60 ± 11.71	63.02 ± 10.90	0.211[4]
BMI (kg/m^2)	23.99 ± 3.68	23.67 ± 3.25	0.620[4]
BMI			
<18.5 kg/m^2	1 (3.3%)	1 (3.3%)	0.894[2]
18.5–22.9 kg/m^2	10 (33.3%)	14 (46.7%)	
23.0–24.9 kg/m^2	10 (33.3%)	8 (26.7%)	
25.0–29.9 kg/m^2	6 (20.0%)	5 (16.7%)	
30.0–34.9 kg/m^2	3 (10.0%)	2 (6.7%)	
FD types			
PDS	17 (56.7%)	15 (50.0%)	0.378[3]
EPS	10 (33.3%)	8 (26.7%)	
Overlap	3 (10.0%)	7 (23.3%)	

***Significant at $p < 0.05$; 1: *t*-test; 2: Fisher's exact test; 3: Chi-squared test; 4: Wilcoxon–Mann–Whitney *U* test

healthcare services, resulting in reduced hospital visits.[14]

Yamamoto et al., in their study, found an inverse relationship between BMI and FD among young Japanese.[15] However, the study by Sud et al. in the Indian population found that 56.1% were obese (BMI >25 kg/m^2), and obesity was considered a risk factor for dyspepsia.[12] In our study, the mean BMI of participants was 23.83 ± 3.45 (females 23.54 ± 3.47 and males 24.00 ± 3.46), which corresponded to overweight for the Asian/Indian population, as shown in Table 1.

A cross-sectional population-based study conducted by Aziz et al. showed that the FD subtype distribution was 61% PDS, 18% EPS, and 21% overlapping variant with both syndromes.[16] In our study, 53.3% (32) participants had PDS, 30% (18) had EPS, and 16.7% (10) had overlap syndromes (Table 1).

Control Arm

Participants assigned to the control group maintained their standard treatment regimen. After 8 weeks, they showed improvement in GIQLI, HADS, and PSQI scores with standard treatment alone. However, these changes were less when compared to the experimental arm.

Experimental Arm

These patients were given standard treatment along with meditation as adjuvant therapy. A special form of meditation—VAM—was provided to the participants. VAM is a 22-minute practice focusing on the navel and gut areas to activate the digestive system. It is an open monitoring meditation that begins by minimizing distractions and gradually shifts attention from the navel toward broader meta-awareness, stimulating heightened awareness of the present moment. Daily VAM meditation sessions were given for 8 weeks. Predefined questionnaires were used to follow up at 4 and 8 weeks to see changes in GIQLI, HADS, and PSQI scores, which showed significant improvement, as shown in Table 2.

The autonomic nervous system (ANS) and hypothalamic-pituitary-adrenal axis (HPA) axis collaboratively regulate intestinal functions, influencing GI disorders.[17] GI neural signals conveyed through the enteric nervous system and the vagus nerve interact with biochemical messengers like cytokines, chemokines, neurotransmitters, and SCFAs produced by gut microbiota. Sudo et al. highlighted the vital role of gut microbiota in stress hormone regulation, suggesting that restoring the intestinal ecosystem could reverse abnormal stress responses, as supported by recent research experiments demonstrating reduced stress mediators and receptor expressions in pathogen-free animals.[18,19]

The bidirectional gut-brain axis may be the connection for the frequent presence of GI and psychiatric disorders occurring together.[20] These coexisting conditions suggest a shared physiological basis, highlighting the major role of this network in managing emotional, cognitive, and gut functions. This interaction is highlighted by the common use of antidepressants to address GI issues, suggesting that medications influencing the CNS also affect the gut, emphasizing the close link between mental health and GI well-being. The enteric nervous system, neurotransmitters, hormones, the microbiota-gut-brain axis, and immunological factors collectively contribute to this complex network, impacting both mental states and gut functionality.[21] This two-way communication offers opportunities for comprehensive therapeutic approaches such as meditation that consider the interconnected nature of emotional, cognitive, and gut health.

Meditation may help to maintain a healthy balance in the gut flora by lowering inflammation and regulating stress hormones.[22,23] The body's reaction to stress can be moderated, and inflammatory indicators can be reduced by practicing meditation. This could foster a more favorable environment for gut microbiota and improve GI health in general.

Kanchibhotla et al. studied the effect of VAM meditation on healthy volunteers with GI quality of life.[24] In their study, the mean GIQLI score saw a rise from 84 to 94 following the VAM intervention when assessed at day 50. Their study suggested that engaging in meditation techniques specifically designed to alleviate dyspepsia symptoms can serve as a valuable strategy for promoting and optimizing gut health. In our study, we employed the VAM meditation consistently every day for 8 weeks and then evaluated the outcomes, as shown in Table 3. Our result showed that the GIQLI score increased from 88.47 to 113.63 at week 8 in the experimental arm, which was significantly more compared to the control arm where GIQLI increased from 90.83 to 106.23, as shown in Figure 1.

A meta-analysis conducted by Esterita et al. which included 13 studies involving 14,076 subjects showed a significant association of FD with anxiety and depression.[25] In our study, the mean HADS-A scores in the experimental and control arms were 6.67 ± 2 and 6.83 ± 2.91, respectively, at day 0. About 10 participants in the experimental arm and 12 in the control arm had HADS-A scores of ≥8 at baseline, indicating the association of anxiety with FD, as shown in Table 2. However, both groups reported a significant decrease in HADS-A score at 4 weeks (p-value: 0.374) and 8 weeks timepoint (p-value: 0.280), as shown in Table 4 and represented in Figure 2. Similarly, the mean HADS-D scores for our

Table 2: Summary table for association between group and parameters

Parameters	*Experimental (n = 30)*	*Control (n = 30)*	*p-value*
GIQLI score (day 0)	88.47 ± 13.00	90.83 ± 14.03	0.501[1]
GIQLI score (4 weeks)	106.60 ± 11.35	101.63 ± 12.59	0.114[1]
GIQLI score (8 weeks) ***	113.63 ± 10.38	106.23 ± 12.44	0.015[1]
HADS-A score (day 0)	6.67 ± 2.34	6.83 ± 2.91	0.808[1]
HADS-A score (4 weeks)	4.77 ± 1.81	5.43 ± 2.42	0.374[4]
HADS-A score (8 weeks)	3.93 ± 1.28	4.47 ± 1.63	0.280[4]
HADS-D score (day 0)	5.87 ± 1.76	5.33 ± 2.07	0.258[4]
HADS-D score (4 weeks)	3.70 ± 1.42	4.07 ± 1.34	0.288[4]
HADS-D score (8 weeks) ***	2.73 ± 1.08	3.47 ± 1.14	0.007[4]
PSQI score (Day 0)	5.27 ± 3.27	5.10 ± 3.25	0.844[1]
PSQI score (4 weeks) ***	2.47 ± 2.03	3.80 ± 2.47	0.033[4]
PSQI score (8 weeks)	1.97 ± 1.54	2.73 ± 2.10	0.173[4]
Days of pantoprazole	24.73 ± 11.75	29.63 ± 13.85	0.138[4]
Days of domperidone	10.13 ± 9.84	10.63 ± 8.08	0.351[4]
Days of amitriptyline	3.73 ± 7.57	5.53 ± 9.12	0.381[4]
Requirement of PPI (yes)	30 (100.0%)	30 (100.0%)	1.000[3]
Requirement of domperidone (yes)	21 (70.0%)	21 (70.0%)	1.000[3]
Requirement of amitriptyline (yes)	7 (23.3%)	10 (33.3%)	0.390[3]

***Significant at $p < 0.05$, 1: t-test, 2: Fisher's exact test, 3: Chi-squared test, 4: Wilcoxon–Mann–Whitney U test; the GIQLI score at 8 weeks, HADS-D score at 8 weeks, and PSQI score at 4 weeks were significantly associated ($p < 0.05$)

experimental and control arms were 5.87 ± 1.76 and 5.33 ± 2.07, respectively, at day 0. 5 subjects in the experimental arm and 5 in the control arm had a HADS-D score of ≥8 at baseline, indicating the association of depression with FD, as shown in Table 2. However, both groups reported a significant decrease in HADS-D score at 4 weeks (*p*-value: 0.288) and 8-week time points (*p*-value: 0.007), as shown in Table 5 and represented in Figure 3. The decrease in the experimental arm was more significant than the control arm at week 8.

Lacy et al. found that sleep-related disorders are more common in FD patients than in healthy controls.[26] The mean PSQI in the experimental and control arms was higher, that is, 5.27 ± 3.27 and 5.10 ± 3.25, respectively, in our study. A PSQI score >5 in both arms was suggestive of poor sleep quality at 0 weeks. Both the experimental and control arms had significant changes in PSQI score from baseline when assessed at 4 and 8 weeks, as shown in Table 6. However, there was a marked increase in the quality of sleep observed in the group that underwent the intervention compared to the control at 4 weeks (*p*-value < 0.033). At the 8-week time point, the two groups were comparable in terms of PSQI score (*p*-value: 0.173), as shown in Figure 4. In our study, there was no significant difference in the mean duration of medications between the experimental and control arms. Larger studies in the future may correlate with the investigation.

Our RCT demonstrated the efficacy of meditation as an adjuvant therapy. The experimental group exhibited a significant improvement compared to the

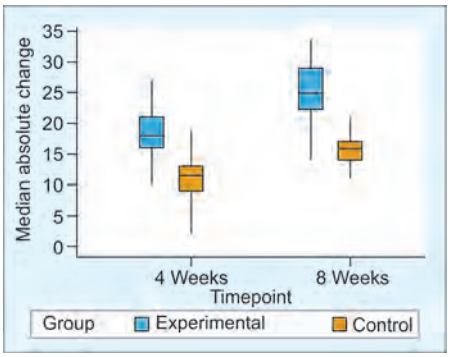

Fig. 1: A boxplot diagram depicting the absolute difference of GIQLI score between the day 0 timepoint and 4 and 8 weeks in the two groups

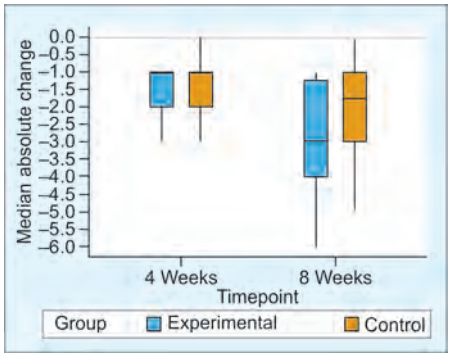

Fig. 2: A boxplot diagram depicting the absolute difference of HADS-A score between the day 0 timepoint and 4 and 8 weeks in the two groups

Table 3: Analysis of absolute change in GIQLI score over time

Timepoint comparison	*Change in GIQLI score from day 0 to follow-up timepoints*				*p-value for comparison of the two groups in terms of difference of GIQLI score from day 0 to follow-up timepoints*
	Group: experimental		*Group: control*		
	Mean (SD) of absolute change	*p-value of change within group*	*Mean (SD) of absolute change*	*p-value of change within group*	
4 weeks to day 0	18.13 (4.38)	<0.001	10.80 (3.20)	<0.001	<0.001
8 weeks to day 0	25.17 (4.73)	<0.001	15.40 (3.57)	<0.001	<0.001

Note: *Post hoc* pairwise tests, conducted *via* the Tukey method following repeated measures ANOVA, assessed the statistical significance of GIQLI score changes from day 0 to subsequent follow-up time points. Group comparisons for GIQLI score changes were conducted using the *t*-test.

Table 4: Analysis of absolute change in HADS-A score over time

Timepoint comparison	*Change in HADS-A score from day 0 to follow-up timepoints*				*p-value for comparison of the two groups in terms of difference of HADS-A score from day 0 to follow-up timepoints*
	Group: experimental		*Group: control*		
	Mean (SD) of absolute change	*p-value of change within group*	*Mean (SD) of absolute change*	*p-value of change within group*	
4 weeks to day 0	−1.90 (0.96)	<0.001	−1.40 (0.86)	<0.001	0.035
8 weeks to day 0	−2.73 (1.39)	<0.001	−2.37 (1.56)	<0.001	0.311

Note: *Post hoc* pairwise tests, employing the Nemenyi test after the Friedman test, explored the statistical significance of HADS-A score changes from day 0 to subsequent follow-up time points. Group comparisons for HADS-A score changes utilized the Wilcoxon–Mann–Whitney test.

Table 5: Analysis of absolute change in HADS-D score over time

Timepoint comparison	*Change in HADS-D score from day 0 to follow-up timepoints*				*p-value for comparison of the two groups in terms of difference of HADS-D score from day 0 to follow-up timepoints*
	Group: experimental		*Group: control*		
	Mean (SD) of absolute change	*p-value of change within group*	*Mean (SD) of absolute change*	*p-value of change within group*	
4 weeks to day 0	−2.17 (1.18)	<0.001	−1.27 (1.01)	0.004	0.002
8 weeks to day 0	−3.13 (1.17)	<0.001	−1.87 (1.25)	<0.001	<0.001

Note: *Post hoc* pairwise tests, employing the Nemenyi test following the Friedman test, assessed the statistical significance of HADS-D score changes from day 0 to subsequent follow-up time points. Group comparisons for HADS-D score changes utilized the Wilcoxon–Mann–Whitney test.

Table 6: Analysis of absolute change in PSQI score over time

Timepoint comparison	*Change in PSQI score from day 0 to follow-up timepoints*				*p-value for comparison of the two groups in terms of difference of PSQI score from day 0 to follow-up timepoints*
	Group: experimental		*Group: control*		
	Mean (SD) of absolute change	*p-value of change within group*	*Mean (SD) of absolute change*	*p-value of change within group*	
4 weeks to day 0	−2.80 (1.65)	<0.001	−1.30 (1.09)	0.003	<0.001
8 weeks to day 0	−3.30 (2.05)	<0.001	−2.37 (1.73)	<0.001	0.035

Note: *Post hoc* pairwise tests, employing the Nemenyi test following the Friedman test, assessed the statistical significance of PSQI score changes from day 0 to subsequent follow-up time points. Group comparisons for PSQI score changes utilized the Wilcoxon–Mann–Whitney test.

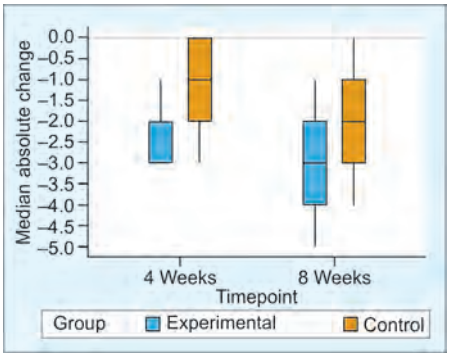

Fig. 3: A boxplot diagram depicting the absolute difference of HADS-D score between the day 0 timepoint and 4 and 8 weeks in the two groups

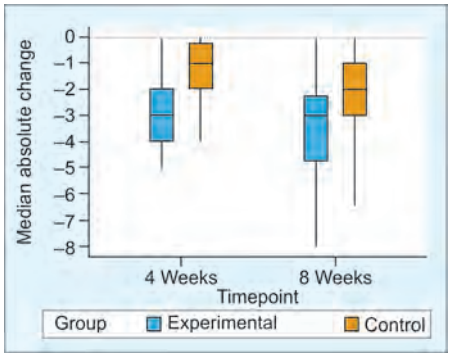

Fig. 4: A boxplot diagram depicting the absolute difference of PSQI score between the day 0 timepoint and 4 and 8 weeks in the two groups

control group, as evidenced by a notable improvement in GI parameters, that is, GIQLI score (*p*-value: 0.015) at 8 weeks, a decrease in HADS-D score after 8 weeks (*p*-value: 0.007), and a lower PSQI score at 4 weeks (*P*-value < 0.033). Based on these findings, we highly recommend incorporating GI-related meditation as an adjuvant therapy for patients with FD.

Conclusion

Functional dyspepsia is a complex disorder with problems in many aspects of patients' health. The disease itself can be a financial burden to the patient, and many psychosocial factors play a role. Our study showed that meditation as adjuvant therapy improves GI health, mental health, and sleep quality compared to standard treatment alone. Prolonged use of PPI, prokinetics, and antidepressants comes with several adverse effects and potential drawbacks. Meditation is a holistic practice that addresses not only specific symptoms but also the overall well-being of an individual, including mental, emotional, and spiritual aspects. It is a non-invasive and cost-effective practice that emphasizes the mind-body connection, promoting awareness and mindfulness.

Meditation, used as a complementary therapy alongside conventional medical treatment, enhances the effectiveness of medications or other therapeutic interventions.

Limitations of the Study

A larger, multicenter study with a prospective study design and extended follow-up would provide a more comprehensive and impactful understanding.

Key Points

- Functional dyspepsia impairs various aspects of a person's health, including GI health, mental health, and sleep quality.
- Treatment of FD involves relieving symptoms and improving the patient's quality of life with the use of medications like PPIs, prokinetics, and antidepressants.
- Gut-related meditation, used along with standard treatment, may have better outcomes.

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ORIGINAL ARTICLE

Clinical Phenotypes and Disease-specific Health-related Quality of Life in Patients of Chronic Obstructive Pulmonary Disease

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Abstract

Background: Chronic Obstructive Pulmonary Disease (COPD) is a common health issue globally and is expected to increase in the future. The latest Global Initiative for COPD (GOLD) guidelines describe the various phenotypes of COPD. This study assessed the different clinical phenotypes and disease-specific health-related quality of life (HRQoL) in patients with COPD.

Materials and methods: A hospital-based cohort study was conducted among COPD patients of various phenotypes. All patients were evaluated through detailed history, clinical examination, complete blood count, and electrocardiogram (ECG) to fulfill the inclusion and exclusion criteria and categorized into different phenotypes: nonsmoker, nonexacerbator phenotype (NEP), exacerbator phenotype (EP), and asthma-COPD overlap (ACO). Following this, the participants were evaluated based on the modified Medical Research Council (mMRC) dyspnea scale and COPD assessment test (CAT) score to assess HRQoL at the beginning and after 3 months of standard treatment.

Results: Among the 100 participants, the average age of the participants was 57.85 ± 6.78 years, with male predominance (62%). There was a significant difference in the CAT score and mMRC among the study groups. The CAT score was worst in the ACO group (22.68), with partial improvement (14.26) after 3 months of treatment, still being relatively lower than in other groups.

Conclusion: Patients with ACO had significantly poorer HRQoL compared to those with NEP, EP, and nonsmokers. Hence, patients with ACO, NEP, and EP should be offered a different treatment approach, focusing on the components that exacerbated the symptoms.

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Introduction

Chronic obstructive pulmonary disease (COPD) is a chronic respiratory disease caused by exposure to noxious particles or gases, which usually affects middle-aged and older individuals. It is also expected to become the third leading cause of death by 2020.[1,2] COPD is a growing global health concern, affecting over 300 million people worldwide and contributing to approximately 3 million deaths every year.[3]

According to Jindal et al.,[4] 2–22% of men and 1.2–19% of women in India had COPD. COPD patients of Global Initiative for COPD (GOLD) class III and IV usually suffer from respiratory symptoms such as chronic cough, phlegm, shortness of breath, and exercise intolerance.[5,6]

There are different clinical phenotypes of COPD, for example, nonsmoker COPD, nonexacerbator COPD, exacerbator COPD, and asthma-COPD overlap (ACO).

Many studies have been done in the past on this topic in other countries, but most of them were conducted in European or American populations. This study was conducted in the Indian population and includes follow-up responses in different COPD phenotypes.

Materials and Methods

Approval was taken from the Institutional Ethics Committee. Study was conducted for 18 months at a tertiary care center in Delhi NCR from January 2020 to June 2021 on COPD patients. To complete the study, we had to approach 160 patients due to the rarity of the ACOS group of patients. Finally, 100 participants completed the study. Informed written consent was obtained from all participants. On the basis of history and physical examination, patients were divided into 4 phenotypes.

Study Design

Analytical cohort study.

Sample size was calculated using the study by Chai et al.[7] using the following formula:

$$n = \frac{\left(\sigma_1^2 + \sigma_2^2\right) \cdot \left[Z_{1-\frac{\alpha}{2}} + Z_{1-\beta}\right]^2}{\left(M_1 - M_2\right)^2}$$

Where, Zα/2 is the critical value of the normal distribution at α/2, Zβ is the critical value of the normal distribution at β, σ1, and σ2 are the standard deviations of the two groups, and M1 and M2 are the means of the two groups. After putting in the relevant values, the sample size came out to be 100.

Study Population

The study was conducted on different phenotypes of COPD patients, age >40 years, irrespective of their gender, educational, and economic status. Pregnant females, diabetic, and cardiac patients were excluded from the study.

Study Variable

Body mass index (BMI) was interpreted as per World Health Organization (WHO) guidelines.[8] Patients having no history of smoking at all or smoked <100 cigarettes in a lifetime were labeled as nonsmoker COPD. Patients having 0–1 exacerbation history but no hospitalization in the past 1 year were labeled as nonexacerbator COPD. Patients having ≥2 exacerbations with no hospitalization or one history

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of hospitalization in the past 1 year were labeled as exacerbator COPD. Patients having features of both asthma and COPD together were labeled as asthma COPD overlap.[3] Health-related quality of life (HRQoL) was assessed using COPD assessment test (CAT) questionnaires,[9] and modified Medical Research Council (mMRC)[10] dyspnea scale.

Statistical Analysis

Statistical analysis was done using SPSS version 17.0 (Statistical Package for the Social Sciences). Mean ± SD or median (IQR) was calculated for continuous variables to present the distribution. ANOVA was used to compare the various groups. The Chi-squared test or Fisher's exact test was used for the analysis of categorical data. A *p*-value <0.05 was considered significant.

Results

The overall mean age of the patients was found to be 57.85 ± 6.78 years, with 58.56 ± 5.72 years in the nonsmoker group, 59.28 ± 6.12 years in the COPD nonexacerbator phenotype (NEP) group, 62.84 ± 4.55 years in the COPD exacerbator phenotype (EP) group, and 51.12 ± 4.82 years in the ACO group. There is a male preponderance in the present study, with 62% of the patients being male and 38% female, resulting in a male-to-female ratio of approximately 2:1.

On comparing the CAT score and spirometry changes among different groups, it was observed that the CAT score was highest in the ACO group and lowest in the NEP group, with obstruction also being highest in the ACO group (Table 1).

Among nonsmokers, there was an improvement in the spirometry values and a statistically significant improvement in the CAT score after 3 months of standard treatment (Table 2).

On comparing the CAT score and spirometry values among the nonexacerbator group, improvement was observed in the CAT score, but almost the same spirometry values were seen after 3 months of treatment (Fig. 1).

Using the paired *t*-test among the COPD NEP group, significant improvement was observed in the CAT score, but almost similar values were observed in the spirometry values after 3 months of treatment (Table 3).

Table 2: Comparison of the mean level of CAT score and spirometry parameters with follow-up 3rd month among nonsmokers using paired *t*-test

Nonsmoker	*0 month*		*3rd month*		*Paired t-test (p-value)*
	Mean	*SD*	*Mean*	*SD*	
CAT score	21.80	7.47	14.92	6.95	0.001
FEV1	49.52	17.21	49.52	17.21	0.99
FVC	86.80	3.08	87.24	3.09	0.61
FEV1/FVC	60.52	3.25	60.80	3.28	0.76
Reversibility					
FEV1	54.76	17.21	55.48	17.49	0.88
FVC	87.36	3.15	86.44	5.92	0.49
FEV1/FVC	63.32	2.95	64.36	2.94	0.21

Table 1: Comparison of the CAT score and spirometric changes between the different groups using unpaired *t*-test

	Nonsmoker (n = 25)		*COPD NEP (n = 25)*		*COPD EP (n = 25)*		*ACO (n = 25)*		*p-value*
	Mean	*SD*	*Mean*	*SD*	*Mean*	*SD*	*Mean*	*SD*	
CAT score	21.80	7.47	19.44	5.44	22.16	5.37	25.68	5.29	0.235
FEV1	57.52	17.21	49.00	12.65	48.00	10.89	42.76	9.27	0.055
FVC	86.80	3.08	87.96	3.34	89.20	4.17	90.00	5.89	0.049
FEV1/FVC	60.52	3.25	53.96	4.82	55.04	3.02	49.72	3.37	0.005
FEV1 reversibility	54.76	17.21	62.36	12.40	53.20	11.14	51.12	9.50	0.052
FVC reversibility	87.36	3.15	88.08	3.38	89.20	4.17	90.00	5.89	0.140
FEV1/FVC reversibility	63.32	2.95	61.12	4.55	60.88	3.00	56.56	3.34	0.001

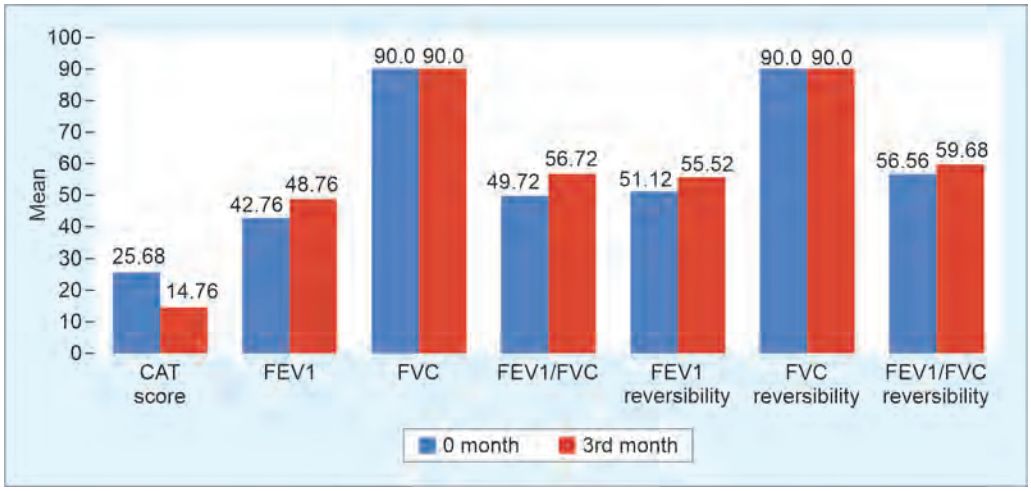

Fig. 1: Comparison of the mean level of CAT score and spirometry parameters with follow-up 3rd month among ACO group

Table 3: Comparison of the mean level of CAT score and spirometry parameters with follow-up 3rd month among COPD NEP group using paired *t*-test

COPD NEP	*0 month*		*3rd month*		*Paired t-test (p-value)*
	Mean	*SD*	*Mean*	*SD*	
CAT score	19.44	5.44	12.76	4.83	0.001
FEV1	57.00	12.65	57.00	12.65	0.99
FVC	87.96	3.34	87.96	3.34	0.99
FEV1/FVC	58.96	4.82	58.92	4.80	0.99
Reversibility					
FEV1	62.36	12.40	63.88	12.53	0.66
FVC	88.08	3.38	88.04	3.41	0.98
FEV1/FVC	61.12	4.55	62.12	4.30	0.63

Table 4: Comparison of the mean level of CAT score and spirometric parameters with follow-up 3rd month among COPD EP group using paired *t*-test

COPD EP	*0 month*		*3rd month*		*Paired t-test (p-value)*
	Mean	*SD*	*Mean*	*SD*	
CAT score	22.16	5.37	14.44	5.72	0.001
FEV1	48.00	10.89	48.00	10.89	0.99
FVC	89.20	4.17	89.20	4.17	0.99
FEV1/FVC	59.04	3.02	59.04	3.02	0.99
Reversibility					
FEV1	53.20	11.14	54.24	10.95	0.74
FVC	89.20	4.17	89.00	3.85	0.67
FEV1/FVC	60.88	3.00	61.84	2.88	0.25

Table 5: Comparison of the mean level of CAT score and spirometric parameters with follow-up 3rd month among ACO group using paired *t*-test

ACO	*0 month*		*3rd month*		*Paired t-test (p-value)*
	Mean	*SD*	*Mean*	*SD*	
CAT score	25.68	5.29	14.76	5.25	0.001
FEV1	42.76	9.29	48.76	9.27	0.99
FVC	90.00	5.89	90.00	5.89	0.99
FEV1/FVC	49.72	3.37	56.72	3.37	0.99
Reversibility					
FEV1	51.12	9.50	55.52	9.43	0.60
FVC	90.00	5.89	90.00	5.89	0.99
FEV1/FVC	56.56	3.34	59.68	3.12	0.69

Using the paired *t*-test, significant improvement in the CAT score and slight improvement in spirometry values were seen in the exacerbator group after 3 months of treatment (Table 4).

Significant improvements were seen in the CAT score and spirometric values in the ACO group after 3 months of treatment (Table 5).

Discussion

In the present study, we had taken four phenotypes of COPD—nonsmokers, COPD NEP, COPD EP, and ACOS according to GOLD guidelines. Out of 100 participants in the present study, the overall mean age of the patients was found to be 57.85 ± 6.78 years with male predominance, whereas in a similar study by Chai et al.,[7] they documented a mean age ranging between 70 and 74.1 years. The difference in the mean age of the patients could be due to the different population being studied.

In this study, the mean CAT score was highest (25) among the patients of the COPD-ACO group as compared to other groups, while in a multicenter observational study in Spain, Miravitlles et al.[11] found the CAT score to be higher in patients with the COPD EP group ($p < 0.001$). Also, in another study with different phenotypes by Corlateanu et al.,[12] the CAT score was higher in the frequent exacerbators and nonexacerbators groups. In this study, ACO was not used as a separate phenotype.

On spirometry analysis, FEV1 and FEV1/FVC ratio were lower (51.12 and 56.56, respectively) in the ACOS group compared to others. Kurashima et al.[13] conducted a study with three groups, that is, Asthma, COPD, and ACO, and showed lower FEV1 and FEV1/FVC in the ACO group.

Among all the four groups, spirometry changes were analyzed at the 0 and 3rd month, in which we found a difference in the spirometry readings and a reduction in the CAT score at the 3rd month of follow-up compared to the 0 month result. There was also a significant improvement in the dyspnea score after 3 months of follow-up.

This study was conducted on different phenotypes of COPD to assess the severity of airflow limitation, HRQoL, and improvement in various variables after 3 months of standard treatment. Most of the previous studies were conducted on white populations, whereas our study was conducted on an Asian (Indian) population.

The time for follow-up was only 3 months, which could have been extended further. The ACOS group was the worst group among the four groups, so special attention must be given to this group with respect to assessment, treatment, and response. Further studies with a larger sample size and prolonged follow-up can be conducted on the Asian population.

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ORIGINAL ARTICLE

Clinical Spectrum and Therapeutic Outcome of Myasthenia Gravis in a Tertiary Care Hospital: A Retrospective Study

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Abstract

Introduction: Myasthenia gravis (MG) is characterized by defective transmission of electric impulses across the neuromuscular junction. To date, there is a lack of real-world data to understand its management, specifically in the Indian context. To bridge this gap in clinical knowledge, the current study was designed to understand the clinical management of MG in the Indian population.

Materials and methods: This retrospective study included clinical data of MG patients at Madras Medical College, Chennai (2021–2023). Patients were assessed for demographics, clinical characteristics, therapeutic interventions, and clinical outcome. Statistical analysis was performed using GraphPad Prism v.8.0.1.

Results: A total of 49 MG cases were observed, and 14 patients presented with myasthenic crisis (MC). Young onset was observed in 26 cases. Clinical features included ptosis (90%), diplopia (90%), bulbar symptoms (60%), and respiratory illness (19.2%). Bedside tests depicted a decremental response to repetitive nerve stimulation (RNS) (93.8%), acetylcholine receptor (AChR) antibody positivity (45%), and MUSK Ab positivity (3.8%). Treatment comprised intravenous immunoglobulin (IVIG) (10.79%), plasmapheresis (PLEX) for impending crisis or thymoma (3.5%), and combination therapy using acetylcholine esterase inhibitors with immunomodulators (63.26%). Mortality was observed in 4 cases (8.1%), while the remaining 45 MG patients (91.84%) exhibited stable vitals with a median hospital stay of 14 days. Thymectomy had potentially reduced the risk of crisis.

Discussion and conclusion: Early detection of MG can prevent the onset of crisis. Electrophysiological studies were crucial in the diagnosis of atypical cases. Rituximab successfully normalized bulbar and respiratory functions in PLEX/IVIG-resistant patients, enhancing crisis response. Combining AChE inhibitors with immunomodulators ensured good drug compliance and, thereby, reduced the risk of crisis and enabled effective management of MG. Centric studies like this may serve as reference points for designing more extensive studies on MG involving multiple centers nationwide.

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Introduction

Myasthenia gravis (MG) is a rare prototypic autoimmune disorder that affects the neuromuscular junction (NMJ) of the skeletal muscles.[1] It is characterized by the formation of autoantibodies against the postsynaptic membrane proteins, which results in the reduction of electric impulse transmission across the NMJ.[2] The current mainstay treatment for MG involves the use of acetylcholinesterase (AChE) inhibitors such as pyridostigmine bromide, immunosuppressive agents, and thymectomy, while plasmapheresis (PLEX)/intravenous immunoglobulins (IVIG) have been reserved for patients exhibiting symptoms such as crisis or muscle weakness.[3]

Based on factors such as age of onset, antibody status, gender, ocular or generalized movement, and thymus condition, MG can be categorized into several subgroups.[4] In Western countries, MG is prevalent in 50–125 persons per million, with a male predominance in patients who are above 50 years of age and a female predominance in those <40 years.[5] With reference to its prevalence in the Indian population, being a rare disorder, to date, there exists only limited data on its epidemiology and management. For instance, in a large hospital-based study, Singhal et al. reported that MG was more common in males (2.7:1), with a single peak of age at onset (females—3rd decade, males—5th–6th decade).[6] They also reported that MG patients in India tend to have more ocular symptoms, a high prevalence of thymoma, and very low response to immunosuppressive agents when compared with other countries.[6] While our current understanding of the clinical presentation and outcome of MG patients is mainly based on previous reports in other countries, to date, there exists very little literature reporting the precipitating factors of MG during hospital stay and the clinical outcome of MG patients in India.[7,8] This puts forth a pressing need to elucidate the clinical factors pertaining to MG and their outcomes in a patient setting. Hence, this retrospective study was conducted to clarify the clinical profile and final outcomes of all the MG cases that were seen at our hospital from 2021 to 2023.

Materials and Methods

In this retrospective study, the records on clinical information of all the patients diagnosed with MG at the Madras Institute of Neurology, Madras Medical College (MMC), Chennai, between 2021 and 2023 were included. The inclusion criteria comprised all the patients diagnosed with MG based on clinical history and their response to cholinesterase inhibitors. Patients admitted for conditions such as Lambert-Eaton syndrome, lower motor neuron syndromes, or congenital myopathies, which may mimic MG, were excluded. All the MG patients were evaluated based on clinical information and demographic factors such as age of onset, sex, and clinical presentation of MG. Clinical features of MG, including the factors associated with functional outcome, possible precipitating factors, and mortality, were assessed.

Statistical Analysis

Statistical analysis was carried out using GraphPad Prism v.8.0.1 (GraphPad Software, San Diego, California). The quantitative variables were estimated by mean ± standard deviation. The qualitative data were represented as proportions and frequencies. The Chi-squared test was done to compare the proportions. $p < 0.05$ was considered to be statistically significant.

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Results

Demographic Profile

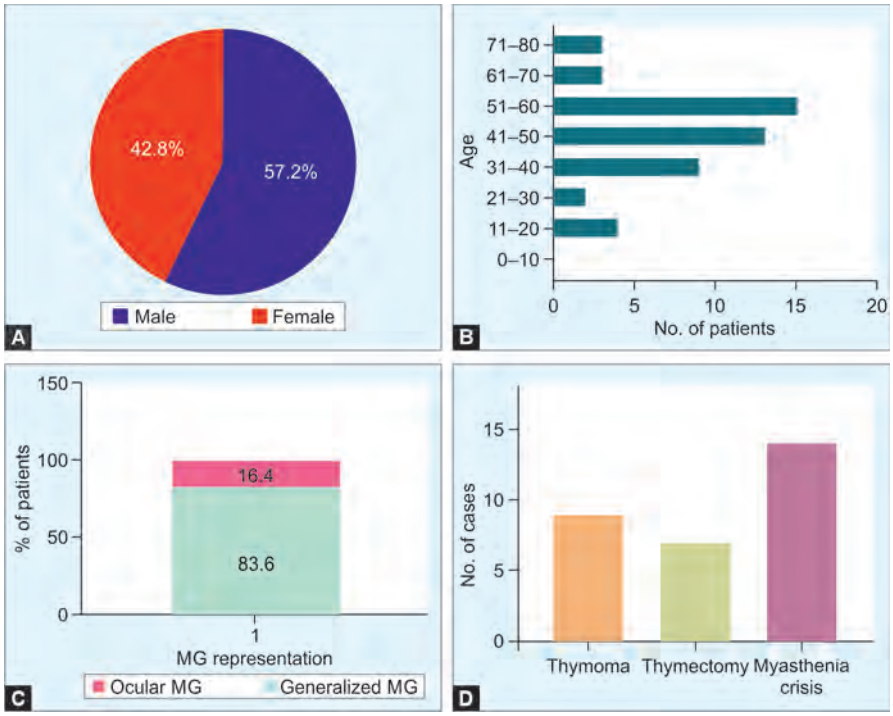
This retrospective study was carried out using the case sheets of 49 patients admitted with MG at MMC during the study period from 2021 to 2023. The baseline characteristics observed in the patients are tabulated in Table 1. It was observed that among the 49 MG cases, 28 were males (57.1%) and 21 were females (42.8%) (Fig. 1A). The age-wise distribution of patients with MG was plotted in Figure 1B, wherein it was observed that the majority of the patients were distributed between 51 and 60 years. The mean age of the patients diagnosed was 43.6 years, with a range of 13–78 years. The male-to-female ratio was found to be 1.33:1. There were no patients below 10 years or above 80 years of age. Young onset of MG was observed in 26 patients (<50 years). In young onset MG cases, the median age was 38.5 years, comprising 53.8% males and 46.1% females (14 males and 12 females). With reference to the presentation of MG, it was observed that about 83.6% of the patients demonstrated the clinical representation of generalized MG, with the involvement of muscles such as pharyngeal, palatal, facial, and proximal limbs. Ocular MG, on the other hand, characterized by the weakness of ocular muscles, eye closure, ptosis, blurring of vision, and diplopia, was observed in 16.3% of MG patients (Fig. 1C). Also, among the studied cases, 14 MG patients represented myasthenic crisis (MC). Alongside, in the current study, thymoma was ruled out in 9 MG patients, 7 of whom underwent thymectomy (Fig. 1D). Interestingly, it was found that the presence of thymoma did not increase the risk of MC, and the risk of MC was reduced in some of the MG patients who underwent thymectomy.

Clinical Characteristics

Following assessment of the demographic profile, the clinical characteristics of the patients were assessed. About 83% of the patients depicted generalized MG, while 16% portrayed ocular symptoms. Factors such as diurnal variation of symptoms, ocular diplopia/ptosis, bulbar symptoms, respiratory illness, and generalized weakness were enumerated to gain insights into the clinical manifestation of MG (Table 2). Interestingly, it was observed that about 44 MG patients (89.8%) had diplopia in addition to ptosis (either unilateral or bilateral). Bulbar symptoms such as difficulty in swallowing and speech were reflected in 31 patients (63.3%). Alongside, diurnal variation of symptoms and generalized weakness were observed in 21 patients (42.86%), while breathing difficulty and respiratory illness were manifested in 10 patients (19.2%) (Fig. 2A).

Table 1: Demographic profile

S. no.	*Age*	*Sex*	*Year*	*Presentation of MG*	*Myasthenia crisis*	*Thymoma*	*Thymectomy*
1.	47	F	2022	Ocular	No	No	No
2.	45	F	2021	Generalized	No	No	No
3.	70	F	2023	Generalized	Yes	No	No
4.	57	M	2021	Ocular	No	No	No
5.	14	F	2022	Generalized	No	No	No
6.	56	M	2021	Generalized	Yes	No	No
7.	43	M	2022	Generalized	Yes	No	No
8.	45	M	2023	Generalized	No	Yes	Yes
9.	73	M	2022	Generalized	No	No	No
10.	42	M	2021	Generalized	No	No	No
11.	34	M	2021	Generalized	No	Yes	No
12.	43	F	2022	Generalized	No	No	No
13.	78	M	2022	Generalized	No	No	No
14.	45	M	2021	Generalized	Yes	No	No
15.	53	M	2021	Generalized	No	No	No
16.	57	F	2021	Generalized	No	No	No
17.	60	F	2021	Generalized	Yes	No	No
18.	50	M	2020	Generalized	Yes	No	No
19.	37	F	2021	Generalized	Yes	No	Yes
20.	40	M	2021	Generalized	No	Yes	No
21.	53	M	2022	Generalized	No	No	No
22.	50	F	2022	Generalized	No	No	No
23.	48	F	2021	Generalized	No	No	No
24.	37	F	2022	Generalized	No	No	No
25.	37	M	2021	Generalized	Yes	No	No
26.	28	M	2021	Ocular	No	No	No
27.	40	M	2021	Ocular	No	No	No
28.	58	F	2021	Generalized	No	No	No
29.	25	F	2022	Generalized	No	Yes	Yes
30.	33	F	2023	Generalized	No	Yes	Yes
31.	55	F	2023	Generalized	No	No	No
32.	42	M	2022	Ocular	No	No	No
33.	60	F	2022	Generalized	Yes	No	No
34.	36	M	2021	Generalized	No	Yes	Yes
35.	14	M	2022	Ocular	No	No	No
36.	46	M	2021	Ocular	Yes	No	No
37.	45	F	2021	Generalized	No	No	No
38.	72	M	2023	Generalized	Yes	No	No
39.	55	M	2023	Generalized	No	No	No
40.	65	M	2021	Generalized	No	No	No
41.	13	M	2022	Generalized	No	No	No
42.	53	F	2022	Generalized	Yes	Yes	Yes
43.	54	M	2021	Generalized	No	No	No
44.	35	F	2023	Generalized	Yes	Yes	Yes
45.	69	M	2021	Generalized	Yes	No	No
46.	18	F	2021	Ocular	No	No	No
47.	55	M	2021	Generalized	No	No	No
48.	54	M	2023	Generalized	No	Yes	No
49.	56	F	2023	Generalized	No	No	No



Figs 1A to D: Demographic profile of MG patients

Comorbidity and Complications

With reference to the comorbidities, it was observed that about 10 MG patients had a past history of diabetes mellitus (DM) (20.4%), while systemic hypertension (SHTN) and a known history of MG were observed in 11 MG patients (22.4%). Cases of hypothyroidism were reported in 5 of the 49 patients (10.2%), while an old cerebrovascular accident (CVA) was reported in 2 patients (4.08%). A known history of ovarian carcinoma, chronic kidney disease (CKD), psoriasis vulgaris, cholecystectomy, limb stiffness, and atrial septal defect (ASD) patch closure was reported as a past history in 2.04% of the MG patients included in the present study (Fig. 2B). Alongside, assessment of the complications of MG revealed that aspiration pneumonitis was associated as a risk factor in 3 of the 52 MG patients studied, while sepsis developed in 2 patients. However, complications pertaining to CO2 inhalation were observed in only one of the MG patients employed for the current study (Table 3).

Lab Tests

Following assessment of the clinical implications, the positivity of bedside test reports was evaluated for all the chosen MG patients. Specifically, positivity for the levels of acetylcholine receptor antibody (AChR Ab), muscle-specific kinase antibody (MUSK Ab), ice pack test, and repetitive nerve stimulation (RNS) was performed. Firstly, the RNS analysis depicted a >10% decremental response in the majority of the MG patients included in the present study (93.8%). The AChR Ab test was done in 41 patients, out of which 22 were positive and 14 were negative; the AChR Ab test reports were pending for 5 patients and were not diagnosed in 8 patients (Table 4). Also, 2 patients who were negative for AChR Ab depicted positivity for MUSK Ab, and 9 patients were seronegative for both the antibodies tested. For those patients who depicted a decremental response in RNS but were either negative, pending, or not diagnosed due to logistic issues for the AChR Ab test, the ice pack test was done, which depicted positivity in 7 MG patients (Fig. 2C). Overall, from the bedside tests, it was observed that the majority of the patients had presented a decremental response to RNS and were seropositive for AChR Ab, representing a positive diagnosis of MG.

Treatment Received

Following assessment of the demographic profile, clinical manifestations, and bedside test reports, the treatment provided for each of these patients was evaluated. Briefly, the treatment history on IVIG, PLEX, AChE inhibitors/steroids, and immunomodulators was examined, wherein we found that, to modify the immune system with normal antibodies, IVIG therapy was provided to 10.79% of the MG patients. About 3.59% of the MG patients who developed impending crisis/thymoma received 6 cycles of PLEX. Following this, AChE inhibitors (pyridostigmine and neostigmine) and steroids (prednisolone) treatment were administered to alleviate AChE activity and reduce symptoms. About 48 patients received AChE inhibitors/steroid treatment, while 40 MG patients were on AChE inhibitors alone. Additionally, among the 49 patients, 31 of them received AChE inhibitors/steroid treatment combined with immunomodulators (mycophenolate mofetil and azathioprine) (Fig. 2D and Table 5).

Outcome

Following the assessment of treatment provided, the outcome was assessed for all the 49 admitted patients (Table 5). With reference to the hospital stay, the overall median days of stay were 14 days, with a minimal stay period of 6 days and a maximal stay period of 61 days. The majority of the MG patients were discharged within 10 days of admission (34.7%) (Fig. 2E). Interestingly, it was observed that all the 14 MG patients who developed a crisis had also improved clinically with stable vitals and were requested for follow-up after 2 weeks. Out of the 49 patients diagnosed with MG, mortality was observed in 4 cases, accounting for 8.1% of the total. Conversely, the remaining 45 MG patients, comprising 91.84% of the cohort, exhibited stable vitals throughout their hospitalization (Fig. 2F).

Discussion

MG is a potentially life-threatening neuromuscular disorder characterized by fatigue and chronic muscle weakness with classical diurnal variation of the underlying weakness.[4] Pathologically, MG is manifested by the accumulation of IgG autoantibodies, which bind to various proteins and receptors to inhibit the NMJ signal transmission.[9] Being a rare and debilitating disorder, there is very little literature reporting the clinical presentation and outcome of MG, which makes it difficult to understand the pathophysiology of the disease. More specifically, in the Indian context, there is a dire need to decipher the clinical characteristics of MG patients and evaluate the outcome of the current treatment modality being practiced. Hence, the current study was conducted to bring limelight to the demographic profile of MG patients, their clinical characteristics, current state-of-the-art treatment, and the outcome of all the MG cases that were reported in our hospital between 2021 and 2023. The study comprised 49 patients, with a gender distribution of 57.1% males and 42.8% females, denoting trivial male preponderance in alignment with other reports depicting a similar trend of gender distribution among MG patients.[10]

Table 2: Clinical characteristics

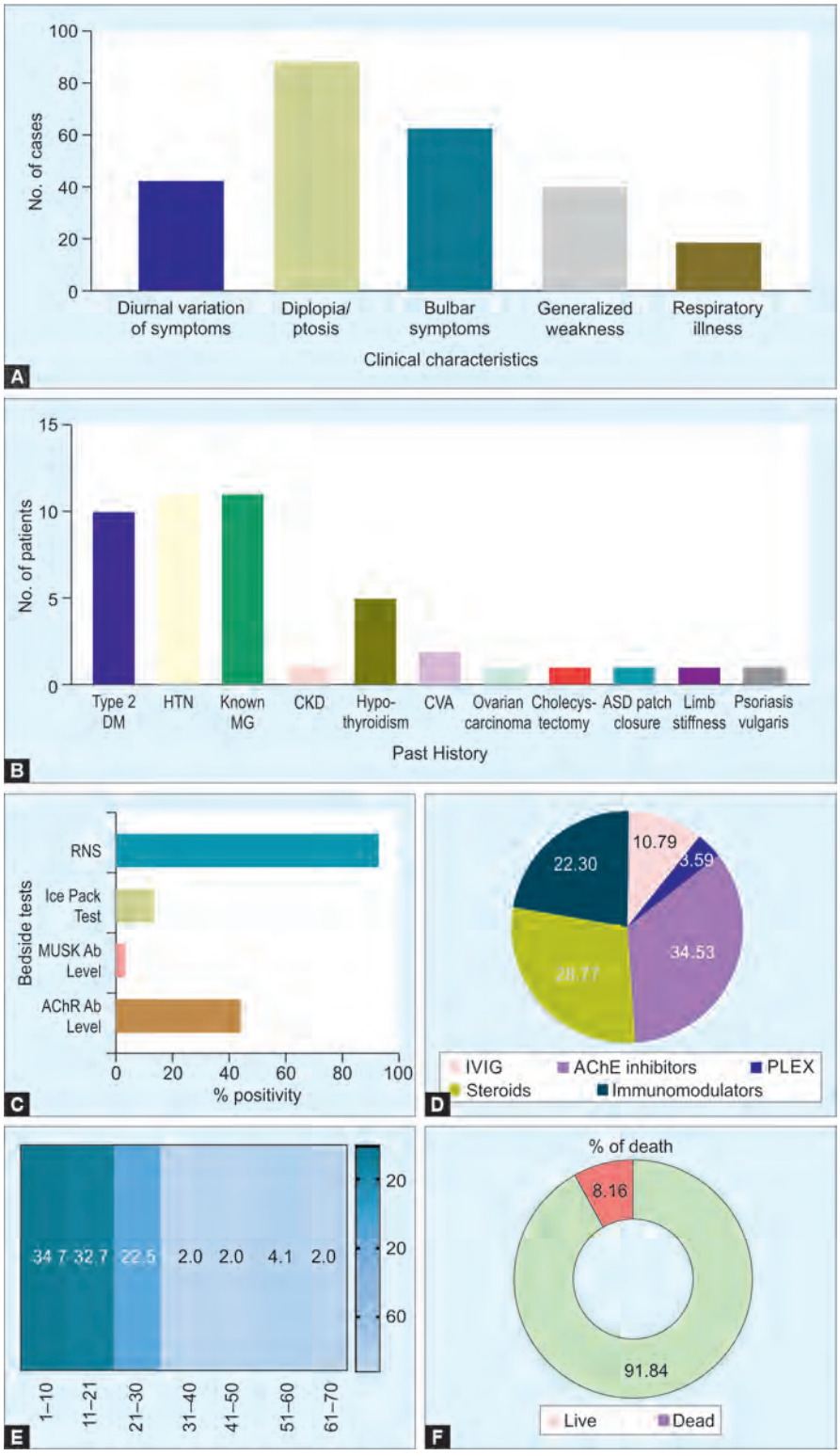
S. no.	*Age*	*Diurnal variation of symptoms*	*Ocular diplopia/ ptosis*	*Bulbar symptoms*	*Generalized weakness*	*Respiratory illness*
1.	47	No	Yes	No	No	No
2.	45	Yes	No	Yes	No	No
3.	70	Yes	Yes	Yes	No	Yes
4.	57	No	Yes	No	No	No
5.	14	No	Yes	Yes	Yes	No
6.	56	Yes	Yes	Yes	Yes	No
7.	43	Yes	Yes	Yes	Yes	Yes
8.	45	Yes	Yes	Yes	Yes	No
9.	73	Yes	Yes	Yes	Yes	No
10.	42	Yes	Yes	Yes	No	No
11.	34	No	Yes	Yes	Yes	Yes
12.	43	No	No	Yes	No	No
13.	78	Yes	Yes	No	No	No
14.	45	Yes	Yes	Yes	Yes	No
15.	53	No	Yes	No	No	No
16.	57	No	Yes	Yes	Yes	Yes
17.	60	No	Yes	Yes	Yes	Yes
18.	50	No	Yes	Yes	No	Yes
19.	37	No	Yes	Yes	Yes	No
20.	40	No	Yes	Yes	No	No
21.	53	Yes	Yes	Yes	No	No
22.	50	No	No	Yes	Yes	No
23.	48	No	Yes	Yes	No	No
24.	37	No	Yes	Yes	No	No
25.	37	No	Yes	No	No	Yes
26.	28	Yes	Yes	No	No	No
27.	40	Yes	Yes	No	No	No
28.	58	No	Yes	Yes	No	No
29.	25	Yes	Yes	No	Yes	No
30.	33	No	Yes	No	No	No
31.	55	Yes	Yes	Yes	No	No
32.	42	No	Yes	Yes	Yes	No
33.	60	Yes	Yes	Yes	No	No
34.	36	No	Yes	No	No	No
35.	14	Yes	Yes	No	No	No
36.	46	No	Yes	No	Yes	Yes
37.	45	Yes	Yes	No	Yes	No
38.	72	Yes	Yes	Yes	Yes	Yes
39.	55	No	No	Yes	No	No
40.	65	No	Yes	Yes	No	No
41.	13	No	Yes	No	No	No
42.	53	Yes	Yes	Yes	Yes	No
43.	54	No	Yes	No	No	Yes
44.	35	Yes	No	Yes	Yes	No
45.	69	No	Yes	Yes	No	No
46.	18	Yes	Yes	No	No	No
47.	55	No	Yes	No	Yes	No
48.	54	No	Yes	No	No	No
49.	56	No	Yes	Yes	Yes	No

Age-wise distribution assessment unveiled that a significant proportion of MG cases was concentrated between 51 and 60 years of age, with a broad range spanning from 13 to 78 years and a median of 38.5 years, indicating that MG mostly manifests in individuals at a specific age range.

While MG was traditionally coined as a "disorder of younger women and older men," from the age distribution, we found that a young incidence was observed in a substantial portion of the cases (26 MG patients). Also, the distribution of young onset was balanced between males and females (53.8% and 46.1%), thereby challenging the conventional statement that MG mostly affects females at a younger age. One plausible reason may be that the majority of the patients enrolled in this study were admitted to the hospital for the first time, and a relatively small sample size was employed for this retrospective study.

Regarding the clinical presentation of MG, about 83% of generalized MG cases were enumerated, while only 16% of ocular MG cases were reported. This is in line with the typical manifestation of MG, wherein generalized muscle weakness is the major symptom.[11,12] Another noteworthy finding in the present study was the development of MC in 14 MG patients (28.5%), who required intensive medical intervention. Additionally, thymoma was ruled out in 9 MG cases, among which 7 of them underwent thymectomy. Our findings indicate that the incidence of thymoma did not elevate the risk of MC, and that thymectomy plays a pivotal role in reducing the risk of MC in MG patients, which warrants further investigation.

Following the demographic profile, the clinical factors such as ptosis, diurnal variation of symptoms, bulbar symptoms, and respiratory illness were enumerated to gain a comprehensive overview of the clinical manifestations of MG. While painting a detailed picture of the challenges faced by MG patients, these factors provide a nuanced approach for disease diagnosis. One striking observation in our study was the high incidence of ptosis and diplopia in about 90% of MG patients, which underscores the significance of assessing the ocular symptoms during MG evaluation, as it appears to be a prominent feature in the majority of the cases included. Bulbar symptoms involving swallowing and speech difficulty were also prevalent in these cases (60%), highlighting the need for multidisciplinary care and tailored medical interventions. Additionally, diurnal variation of symptoms and generalized weakness was observed in



Figs 2A to F: Clinical characteristics, past history, bedside tests, treatment strategy, and outcome of MG patients

a substantial portion of patients (42.86%), portraying the dynamic picture of MG, with symptoms fluctuating during the course of the day. Respiratory illness was experienced in 19.2% of MG patients, underscoring the severity of MG and emphasizing the vigilant monitoring of respiratory functions during clinical evaluation.

In terms of comorbidities, the prevalence of DM in this study (20.4%) was in alignment with an earlier report which had depicted a similar range (15–25%) in MG patients.[13] SHTN cases were slightly higher (22.4%) than the studies reported previously about SHTN cases in MG patients (10–20%),[14] which might be due to variations in the demographics or sample size across studies. Parallelly, the prevalence of hypothyroidism (10.2%) and CVA (4.08%) in MG patients was found to be consistent with earlier studies that reported ranges between 5–15% and 3–6%.[15,16] The low prevalence of other comorbidities such as ovarian carcinoma, psoriasis vulgaris, CKD, limb stiffness, and ASD patch closure (2.04%) was in line with previous literature.[15] Regarding the complications of MG, the incidence of sepsis (3.8%), aspiration pneumonitis (5.8%), and CO_2 inhalation (1.9%) was also in accordance with the low incidence rates.[17–19]

Following the clinical implications of bedside tests, it was assessed that a significant proportion of MG patients (93.8%) depicted a decremental response to RNS,[20] while the levels of AChR Ab varied considerably, which might be due to the heterogeneity of MG and the differences in the patient population. In consensus with the reported literature, it was observed that 2 patients who were negative for AChR Ab were positive for MUSK Ab, highlighting the importance of assessing MUSK Ab levels in cases where AChR Ab is negative. The Ice pack test conducted in those patients for whom AChR Ab results were either negative or unavailable resulted in positivity in 7 MG patients, signifying its utility as a complementary diagnostic tool.[21] Regarding the seronegative cases, nine patients were negative for both AChR and MUSK Abs, which reinforces the importance of considering other diagnostic tests and clinical symptoms in tandem with antibody assays.

With reference to the treatment strategies, one of the notable findings was the utilization of IVIG therapy in MG patients (10.79%), which underscores the significance of immunomodulatory interventions in MG. Further, a subset of MG patients (3.59%) who were at risk of MC associated with thymoma underwent 6 cycles of PLEX, to mitigate the exacerbations with severe MG presentation. Besides, a combination therapy of AChE inhibitors, Pyridostigmine and Neostigmine, along with prednisolone, alleviated the activity of AChE and symptom relief, thereby reflecting a tailored approach for MG management. Apart from this, about 31 MG patients received AChE along with immunomodulators, which signifies an integrative approach to target multiple pathways implicated in the pathogenesis of MG.

To gain insights into the effectiveness of the treatment interventions administered, the clinical outcome was assessed. Four mortality cases (8.16%) were observed, while about

Table 3: Comorbidity and clinical implications

S. no.	*Age*	*Past history*	*Aspiration pneumonitis*	*Sepsis*	*CO_2 inhalation*
1.	47	Nil	No	No	No
2.	45	Ovarian carcinoma—stage 4, type 2 DM	No	No	No
3.	70	CKD-stage 4, SHTN	Yes	No	No
4.	57	Type 2 DM, SHTN	No	No	No
5.	14	Congenital myasthenic syndrome	No	No	No
6.	56	Type 2 DM, SHTN	No	Yes	No
7.	43	Nil	Yes	No	No
8.	45	Nil	No	No	No
9.	73	Systemic HTN	No	No	No
10.	42	Nil	No	No	No
11.	34	Nil	No	No	No
12.	43	Nil	No	No	No
13.	78	Type 2 DM	No	No	No
14.	45	Nil	No	No	No
15.	53	Nil	No	No	No
16.	57	Type 2 DM, SHTN	No	No	No
17.	60	Hypothyroidism, systemic HTN	No	No	No
18.	50	Nil	No	No	No
19.	37	Myasthenia since 2018.AchR positive. s/p thymectomy done in 2019	No	No	No
20.	40	MG diagnosed in 2017	No	No	No
21.	53	MG for 7 years, DM	No	No	No
22.	50	Hypothyroidism & Bronchial asthma	No	No	No
23.	48	MG diagnosed on 2018	No	No	No
24.	37	Cholecystectomy	No	No	No
25.	37	ASD patch closure	No	No	No
26.	28	Nil	No	No	No
27.	40	Stiffness of both lower limbs on exposure to inhalational pesticides	No	No	No
28.	58	Type 2 DM, SHTN	No	No	No
29.	25	Generalized MG/S/P Thymectomy type 2 DM	No	No	No
30.	33	Nil	No	No	No
31.	55	Nil	No	No	No
32.	42	Nil	No	No	No
33.	60	Hypothyroidism, DM, HTN	No	No	No
34.	36	MG, thymoma	No	No	No
35.	14	Nil	No	No	No
36.	46	Ocular MG, hypothyroidism, DM, HTN			
37.	45	Nil	No	No	No
38.	72	Psoriasis vulgaris	No	Yes	No
39.	55	Old CVA	No	No	No
40.	65	Nil	No	No	No
41.	13	Nil	No	No	No
42.	53	Nil	No	No	Yes
43.	54	MG, SHTN, old CVA, seizure disorder, hypothyroidism	No	No	No
44.	35	MG/thymoma s/p thymectomy	No	No	No
45.	69	MG diagnosed on 2014	No	No	No
46.	18	Nil	No	No	No
47.	55	Nil	No	No	No
48.	54	Nil	No	No	No
49.	56	Systemic HTN	Yes	No	No

91.84% of the patients were stable, denoting that MG is manageable and potentially curable provided early preventive measures are implemented and current treatment protocols are successfully followed. Another important outcome was the stable vitals observed in the majority of patients, highlighting that the treatment was able to maintain the patient's overall health and stability throughout their

Table 4: Bedside tests

S. no.	*Age*	*AChR Ab level*	*MUSK Ab level*	*Ice pack test*	*RNS*
1.	47	Could not be done (logistic issues)	–	–	Positive
2.	45	Positive	Negative	–	Positive
3.	70	Negative	Negative	–	Positive
4.	57	Positive	–	–	Positive
5.	14	Deficiency	–	–	Positive
6.	56	Positive	–	–	Positive
7.	43	Positive	–	–	Positive
8.	45	Positive	–	–	Positive
9.	73	Positive	–	–	–
10.	42	Pending	–	–	Positive
11.	34	Positive	–	–	Positive
12.	43	Pending	–	–	Positive
13.	78	Pending	–	Positive	Positive
14.	45	Positive	–	–	Positive
15.	53	Positive	–	–	Positive
16.	57	Not mentioned	–	–	Positive
17.	60	Negative	Negative	–	Positive
18.	50	Positive	–	–	Positive
19.	37	Positive	–	–	Positive
20.	40	Positive	–	–	Positive
21.	53	Negative	Positive	–	Positive
22.	50	Negative	Negative	–	Positive
23.	48	Not mentioned	–	–	Positive
24.	37	Logistic issue	–	–	Positive
25.	37	Positive	–	–	Positive
26.	28	Negative	Negative	–	Positive
27.	40	Negative	Negative	Negative	Negative
28.	58	Positive	–	–	Positive
29.	25	–	–	Positive	Positive
30.	33	Positive	–	–	Positive
31.	55	–	–	–	Positive
32.	42	–	–	Positive	Positive
33.	60	Positive	–	–	Positive
34.	36	Positive	–	–	Positive
35.	14	Negative	–	Positive	Positive
36.	46	Negative	Positive	–	Positive
37.	45	Negative	Negative	Positive	Positive
38.	72	Positive	–	–	Positive
39.	55	Negative	Negative	–	Positive
40.	65	Positive	Negative	Positive	Positive
41.	53	Positive	–	–	Positive
42.	13	Pending	–	Negative	Positive
43.	54	Negative	Negative	–	Negative
44.	35	Positive	–	–	Positive
45.	69	Positive	–	–	Positive
46.	18	Negative	Negative	–	Positive
47.	55	Negative	–	Positive	Positive
48.	54	Pending	–	–	Positive
49.	56	Negative	Pending	–	Positive

hospitalization. Additionally, a noteworthy aspect of the study was the analysis of the hospital stay duration. A median hospital stay of 14 days was reported, which reflects an average benchmark for the duration of hospitalization and serves as a positive indicator of the efficacy of the treatment approach employed. The relatively short length of stay for the majority of patients

Table 5: Treatment received and disease outcome

S. no.	*Age*	*IVIG*	*PLEX*	*Medications (AChE inhibitors and steroids)*	*Immunomodulators*	*Hospital stay (days)*	*Death during hospital stay*
1.	47	No	No	Yes	Yes	9	No
2.	45	Yes	No	Yes	Yes	25	No
3.	70	No	Yes	Yes	No	21	No
4.	57	No	No	Yes	Yes	25	No
5.	14	No	No	Yes (AChE alone)	No	14	No
6.	56	Yes	No	Yes	No	21	No
7.	43	Yes	No	Yes	Yes	17	No
8.	45	Yes	No	Yes	No	21	No
9.	73	No	No	Yes	Yes	12	No
10.	42	No	No	Yes (AChE alone)	Yes	11	No
11.	34	No	Yes	Yes	Yes	18	Yes
12.	43	No	No	Yes (AChE alone)	No	10	No
13.	78	No	No	Yes (AChE alone)	No	7	No
14.	45	No	Yes	Yes	No	61	No
15.	53	No	No	Yes	Yes	10	No
16.	57	No	No	Yes	No	6	No
17.	60	Yes	No	Yes	No	11	No
18.	50	Yes	No	Yes	No	21	No
19.	37	No	Yes	Yes	Yes	10	No
20.	40	No	No	Yes	No	7	No
21.	53	No	No	Yes	No	14	No
22.	50	Yes	No	Yes	Yes	15	Yes
23.	48	No	No	Yes	Yes	6	No
24.	37	No	No	Yes	Yes	13	No
25.	37	Yes	No	Yes	Yes	45	No
26.	28	No	No	Yes	Yes	8	No
27.	40	No	No	No	Yes	16	No
28.	58	No	No	Yes	Yes	12	No
29.	25	No	No	Yes	Yes	8	No
30.	33	No	No	Yes	Yes	9	No
31.	55	No	No	Yes	Yes	28	No
32.	42	No	No	Yes	Yes	12	No
33.	60	Yes	No	Yes	Yes	10	No
34.	36	No	No	Yes	Yes	40	Yes
35.	14	No	No	Yes	Yes	23	No
36.	46	Yes	No	Yes	No	10	No
37.	45	No	No	Yes	Yes	24	No
38.	72	No	No	Yes	No	26	No
39.	55	No	No	Yes	Yes	21	No
40.	65	No	No	Yes	Yes	17	No
41.	13	No	No	Yes (AChE alone)	No	17	No
42.	53	Yes	No	Yes	No	59	No
43.	54	No	No	Yes	Yes	10	No
44.	35	Yes	No	Yes	Yes	58	No
45.	69	Yes	No	Yes (AChE alone)	No	9	No
46.	18	No	No	Yes	Yes	15	No
47.	55	No	No	Yes (AChE alone)	No	8	No
48.	54	No	Yes	Yes (AChE alone)	Yes	7	Yes
49.	56	No	No	Yes	Yes	17	No

further emphasizes the positive outcomes from the management strategies in place.

To summarize, the novel aspects presented in the current study include:

- Early detection of MG can potentially prevent the onset of crisis.
- In the present study, some of the MG patients included did not show typical diurnal variation of symptoms. However, electrophysiological studies aided in the accurate diagnosis of the condition, allowing timely administration of the appropriate treatment.
- Also, while there was no statistical significance between the seronegative and seropositive cases, exploration of the expression levels of antibodies such as Agrin, Col Q, and LRP-4 could provide valuable insights. Unfortunately, these tests were not conducted in this study due to feasibility constraints.
- Notably, no instances of mortality were reported in the current study. The primary aim was to understand the current trends among MG patients and highlight the potential reversibility of the disease through timely therapeutic interventions.
- A noteworthy finding was the minimal to no side effects in patients treated with AChE inhibitors. Combining immunomodulators demonstrated a positive response, showcasing good drug compliance at primary and secondary treatment stages. The drug dosage was adjusted based on the responsiveness of MG patients.
- For those MG patients unresponsive to PLEX/IVIG, Rituximab treatment had effectively normalized their bulbar and respiratory functions, leading to an improved crisis response.
- Centric studies like this would provide a bigger picture and may serve as a reference point to conduct studies from the centers of different states of India.
- Moreover, centric studies like this provide valuable insights into regional variations, clinical practices, and outcomes related to MG management. They may also serve as reference points for designing more extensive studies involving multiple centers across different states of India.

Nevertheless, there are certain limitations in the current study. Firstly, the study was conducted in a relatively small patient population. In addition, the study was performed in a single tertiary care hospital. Large-scale retrospective studies are required to validate these findings. It would have been beneficial to delve into the mortality aspect among MG patients. Alongside, incorporating a follow-up of patients could have provided insights into the effectiveness of AChE inhibitors.

Conclusion

MG is a relatively rare autoimmune disorder with fluctuating muscle weakness and fatigue. Evidence on the clinical management of MG from hospital-based repositories is crucial to advance medical knowledge and improve the therapeutic outcome of MG patients. The current study has shed insights into the demographic profile, clinical characteristics, and outcome of MG patients, specifically in the Indian context. From the clinical data assessed, it is evident that early diagnosis of MG can have a favorable clinical outcome, thereby laying a solid foundation for future research and influencing clinical practices in MG management. Collaborative efforts involving various healthcare institutions can facilitate a deeper understanding of MG management, leading to better patient care and outcomes nationwide. Therefore, expanding such research initiatives to include centers from diverse geographic regions can provide a broader perspective on MG epidemiology, treatment practices, and outcomes in the Indian population.

Clinical Significance

- Early detection of MG can prevent the onset of crisis.
- Electrophysiological studies were crucial in the diagnosis of atypical cases.
- Rituximab successfully normalized bulbar and respiratory functions in PLEX/IVIG-resistant patients, enhancing crisis response.
- Combining AChE inhibitors with immunomodulators ensured good drug compliance, thereby reducing the risk of crisis and enabling effective management of MG.
- Centric studies like this may serve as reference points for designing more extensive studies on MG involving multiple centers nationwide.

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ORIGINAL ARTICLE

To Assess Prevalence of Thyroid Dysfunction in Patients with Heart Failure and Impact on Its Prognosis

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Abstract

Objective: To evaluate the prevalence of thyroid dysfunction in patients with heart failure (HF) and its impact on prognosis, specifically regarding hospital stay duration.

Methods: One hundred eighty-five HF patients aged >18 years were enrolled, and the study was conducted at Swaroop Rani Nehru Hospital between 21st July 2021, and 20th July 2022. All patients diagnosed with HF underwent demographic, clinical, hematological, biochemical, and thyroid function test (TFT) evaluations. Thyroid stimulating hormone (TSH) > 4.94 mIU/L was diagnosed as hypothyroidism, and TSH < 0.5 mIU/L was taken as hyperthyroidism, whereas those with normal TFT were defined as euthyroidism. Patients were monitored until discharge or final outcome. Data analysis was done using Statistical Package for the Social Sciences (SPSS) software 21.

Results: Thyroid disorders were seen in 28.6% of patients, with 6.5% having hyperthyroidism and 22.2% hypothyroidism. Thyroid disorders were significantly associated with higher New York Heart Association (NYHA) class (3/4), serum urea, serum creatinine, and lower hemoglobin levels. However, age, sex, or brain natriuretic peptide (BNP) were not significantly associated with thyroid disorders. There was no significant difference in HF patients' length of hospital stay with or without hypothyroidism. Though 6.5% of HF patients died during the course of the study, this was not statistically significant.

Conclusion: Thyroid disorders are highly prevalent among HF patients and have a significant clinical impact on their prognosis. Patients with thyroid disorders exhibited anemia, higher NYHA class, greater renal dysfunction, and longer hospital stays. Future studies are needed in this field. Clinicians should consider screening HF patients for thyroid dysfunction to improve patient outcomes.

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Introduction

Heart failure (HF) is a clinical condition due to structural or functional derangement in blood ejection or ventricular filling.[1] Among endocrine disorders, thyroid dysfunction is common and plays a critical role in cardiovascular homeostasis, particularly in HF.[2,3] The various molecular pathways involved affect the cardiac parameters in thyroid dysfunction, resulting in cardiac hypertrophy and HF progression.[4] Hence, this study was undertaken to evaluate thyroid dysfunction in the development and prognosis of HF.

A prospective observational study was conducted at Swaroop Rani Nehru Hospital, Prayagraj, for a duration of 1 year from 2022 to 2023. The study included adult patients of both sexes attending medicine and cardiology outpatient department (OPD) and requiring admission with clinical symptomatology of HF. HF was determined through history, physical examination, electrocardiogram (ECG), brain natriuretic peptide (BNP), and 2D echocardiography (2D echo). Proper consent in their local language was taken.

One hundred eighty-five HF patients underwent comprehensive assessments, including demographic, clinical, hematological, biochemical, and thyroid profile evaluations. The severity of HF was graded using the New York Heart Association (NYHA) functional classification. Thyroid status was categorized as hypothyroidism: thyroid stimulating hormone (TSH) > 4.94 mIU/L, hyperthyroidism: TSH < 0.5 mIU/L, and euthyroidism: TSH 0.5–4.94 mIU/L. Subclinical hypothyroidism and hyperthyroidism cases were also included. Patients were followed up until the final outcome.

Ethical committee approval was obtained from the Institutional Ethics Committee, and informed consent was taken from all participants.

Results

In the study, there was a slight male preponderance (n = 106; 57.3%) with a male-to-female ratio of 1.34. Also, the patients with HF had a mean age of 58.39 ± 13.98 years.

Table 1 describes the distribution of cases.

Table 2 shows the thyroid function profile of the study population. The majority of patients had low fT3 levels (58.9%), normal fT4 (81.6%), and normal TSH (71.4%).

Table 3 describes the 2D echo findings of the cases. The majority of them had EF < 50%.

Table 4 depicts the BNP status in the study population.

Table 5 highlights that patients presenting in NYHA class 3 and 4 (61.5%) had higher thyroid dysfunction. Also, there was a significant elevation of serum urea and serum creatinine in the thyroid dysfunction group compared to euthyroid individuals ($p < 0.05$).

Table 5 also emphasizes that the patients with thyroid dysfunction (3.74 ± 0.92 days) had a longer length of hospital stay compared to euthyroid patients (3.45 ± 0.86 days), though there was no significant difference.

Discussion

In this study, the cases had a male preponderance (57.3%) with a younger age span of 58.39 ± 13.98 years compared to other studies.[5,6]

Among the 185 patients, 28.6% of HF patients had thyroid dysfunction, with 6.5% having hyperthyroidism and 22.2% having hypothyroidism, which was similar to studies like Jabbar et al., which reported an overall prevalence of 20.1%, and AlQahtani et al.,[12] which found a 42.2% prevalence with a higher prevalence of hypothyroidism (14.5%). Though Nanchen et al.[5] found a lower prevalence (5.1%), Sato et al.[7] focused on subclinical hypothyroidism, reporting a prevalence of 12.7%, whereas a prevalence of 7.3–38.6% was seen in other studies.[8–13] Zhao et al.[13] focused on low T3 syndrome, reporting a prevalence

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Table 1: Distribution of cases according to their comorbidities

S. no.	*Comorbidity*	*No. of cases*	*Percentage*
1.	No comorbidity	113	61.1
2.	T2DM	52	28.1
3.	COPD	12	6.5
4.	Hypertension	6	3.2
5.	CAD	3	1.6
6.	CVA	2	1.1
7.	Morbid obesity	1	0.5
8.	Tuberculosis	1	0.5
9.	Known case of hypothyroidism	1	0.5
10.	PNC	1	0.5

Most common comorbidity seen is T2DM

Table 2: Cases distribution as per thyroid status

S. no.	*Parameter*	*Range*		*Mean*	*SD*	*Remarks*		
		Min	*Max*			*Below normal*	*Normal*	*Above normal*
1.	fT3 (pg/mL)	1.02	16.93	1.69	1.26	109 (58.9%)	75 (40.5%)	1 (0.5%)
2.	fT4 (ng/mL)	0.39	8.20	1.10	0.66	17 (9.2%)	151 (81.6%)	17 (9.2%)
3.	TSH (µIU/mL)	0.0004	58.4599	4.83	7.51	12 (6.5%)	132 (71.4%)	41 (22.2%)

The majority of patients (71.4%) were euthyroid. Among the remaining, 12 patients (6.5%) were hyperthyroid, and 41 patients (22.2%) had hypothyroidism. In total, 53 patients (28.6%) exhibited thyroid dysfunction

Table 3: 2D echo findings in cases

S. no.	*2D echo findings*	*Cases (N)*	*%*
1.	Disease		
	IHD	59	31.9
	DCMP	39	21.1
	ICMP	35	18.9
	RHD	32	17.3
	Others	20	10.8
2.	Ejection fraction		
	≥50%	51	27.6
	<50%	134	72.4

Majority of patient has rHF (reduced HF)

Table 4: BNP status (pg/mL)

S. no.	*Variable*	*Statistic*
1.	Minimum	249
2.	Maximum	5000
3.	Mean ± SD	979.19 ± 748.81
4.	Median (interquartile range)	765 (560–1200)

of 28.3%. Jabbar et al.[14] categorized thyroid disorders into subclinical hypothyroidism (17.3%), subclinical hyperthyroidism (1.3%), and low T3 syndrome (1.4%).

The duration of hospital stay was a mean of 3.59 ± 0.89 days. There were 12 inhospital deaths (6.5%). Patients with thyroid dysfunction experienced significantly longer hospital stays compared to euthyroid patients. However, no significant association between thyroid dysfunction and mortality was identified, either collectively or for individual thyroid disorders, which could be due to the focus on inhospital mortality, younger age of patients, and fewer comorbidities. Consistent with these findings, Yang et al.[15] and Nanchen et al.[5] also showed similar findings to this study. Similarly, Leite et al.[16] reported no significant link between thyroid dysfunction and inhospital mortality.

Thyroid dysfunction was found to have a significant association with mortality in some studies.[7,17–19] These findings suggest that thyroid dysfunction may negatively influence the clinical course of HF patients.

Limitations

These findings should be considered in the context of the characteristic younger age and low-comorbidity profile of the patients, with the clinical course and outcomes limited to hospitalization only.

Table 5: Demographic and clinical profile—a comparison

S. no.	*Characteristic*	*Thyroid dysfunction (n = 53)*		*No thyroid dysfunction (n = 132)*		*Statistical significance*	
		Mean/No.	*%/SD*	*Mean/No.*	*%/SD*	*"t"/χ^2*	*"p"*
1.	Age (years) (mean ± SD)	59.72 ± 11.81 (27–84)		57.86 ± 14.78 (19–90)		$t = 0.818$; $p = 0.415$	
2.	Sex—male	29	54.7%	77	58.3%	0.202	0.653
3.	NYHA class						
	1 and 2	21	39.6%	77	58.3%	5.314	0.021
	3 and 4	32	60.4%	55	41.7%		
4.	Median BNP (IQR) (ng/mL)	765 (572.5–1200)		712 (516–1120)		$z = 1.394$; $p = 0.163$	
5.	Hematological parameters						
	Hb (gm/dL)	10.69	2.25	11.84	2.05	–3.35	0.001
	TLC (cells/cumm)	12.17	5.38	14.36	13.77	–1.12	0.263
	Platelet count (lakhs cells/cumm)	1.86	0.82	1.70	0.88	1.08	0.283
6.	Kidney functions						
	S. urea (mg/dL)	70.23	47.22	55.96	34.97	2.26	0.025
	S. creatinine (mg/dL)	1.80	1.41	1.37	0.69	2.80	0.006
7.	Preserved EF (>50%)	20	37.7%	31	23.5%	3.846	0.050
8.	Mean duration of hospital stay ± SD (range) in days	3.74 ± 0.92		3.45 ± 0.86		$t = 1.97$; $p = 0.050$	
9.	Outcome						
	Discharged	49	92.5	124	93.9	0.138	0.711
	Expired	4	7.5	8	6.1		

Conclusion

Thyroid dysfunction is highly prevalent among patients presenting with HF and is associated with a higher NYHA class, prolonged hospital stays, greater renal function impairment, and lower hemoglobin levels, all of which may influence the clinical progression and outcomes of the disease, though there was no statistical significance in in-hospital mortality between the two groups. Future studies with larger sample sizes, additional variables, and extended follow-up periods are recommended for further findings.

Clinicians should consider screening HF patients for thyroid dysfunction to improve their disease progression.

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REVIEW ARTICLE

Management of Vasodilatory Shock: A Concise Review

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Abstract

Vasodilatory shock is a severe circulatory disorder characterized by excessive vasodilation, resulting in impaired tissue perfusion and organ dysfunction. The condition arises from dysregulated vasodilation and reduced vascular responsiveness to endogenous vasoconstrictors, disrupting normal vasoregulatory mechanisms. This review delves into the complex pathophysiology, clinical significance, and treatment approaches for vasodilatory shock. It offers a comprehensive summary of established and emerging pharmacological and nonpharmacological therapies. Designed for clinicians and researchers, this article consolidates critical insights to improve the understanding and management of vasodilatory shock.

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Introduction

Shock is a critical medical condition characterized by an inadequate delivery of oxygen and nutrients to tissues and organs, resulting in cellular and metabolic dysfunction. Around one-third of intensive care unit (ICU) patients exhibit harboring shock,[1] which are broadly categorized into four groups (Table 1).

Pathophysiology of Vasodilatory Shock

The hallmark of vasodilatory shock is the impaired vascular response to catecholamine stimulation, as depicted in Figure 1.[2] This condition is marked by reduced sensitivity to catecholamines and uncontrolled pathological vasodilation (vasoplegia), stemming from disruptions in receptor signaling pathways, metabolic imbalances, and depletion of endogenous vasoactive substances. Excessive nitric oxide (NO) production, frequently linked to the activity of inducible nitric oxide synthase (iNOS), is a key factor driving inappropriate vasodilation. Elevated NO levels enhance cyclic adenosine monophosphate and cyclic guanosine monophosphate (cGMP) within the vasculature, triggering vasodilation.[3] Moreover, the activation of adenosine triphosphate-sensitive potassium channels in vascular smooth muscle cells impedes calcium influx, a crucial process for vasoconstriction. This mechanism bridges metabolic disturbances (such as hypoxia and acidosis) and inflammatory responses (including NO overproduction) with the development of vasoplegia.[2] Shock states may also result in absolute or relative deficiencies of endogenous vasoactive hormones like cortisol, vasopressin (VP), and angiotensin II, further reducing the effectiveness of vasopressors.[4–6] Importantly, vasodilation does not affect all vascular beds uniformly in shock. Microcirculatory abnormalities lead to regions of low or absent flow coexisting with areas of extreme vasodilation and rapid flow, compromising tissue oxygen delivery.[7] Additionally, the combined effects of pathological vasodilation and vasoconstriction caused by vasopressor agents lead to heterogeneous impacts across vascular beds, resulting in blood flow maldistribution despite apparently stable systemic hemodynamic metrics.[8,9]

Hemodynamic Changes

In vasodilatory shock, the body initially compensates for reduced oxygen supply by increasing cardiac output, heart rate, and left ventricular contraction, leading to a hyperdynamic state. However, despite increased cardiac activity, vasodilation causes decreased systemic vascular resistance (SVR), blood pooling in the veins, and reduced cardiac output. Counterregulatory systems like the sympathetic nervous system and the renin-angiotensin-aldosterone system are activated, but tissue oxygenation remains compromised due to decreased SVR and preload (refer to Fig. 1).

In septic shock, a type of distributive shock, early signs include a hyperdynamic state with tachycardia, bounding pulses, warm extremities, and rapid capillary refill ("warm shock"). This stage can be reversible with fluids and vasoactive support. If untreated, shock progresses to a hypotensive state ("cold shock") with cool extremities, delayed capillary refill, and thready pulses, leading to multiorgan dysfunction and death if not managed aggressively.

Management

Fluid Resuscitation

In the treatment of sepsis, fluid resuscitation constitutes a crucial aspect. Sepsis induces severe vasoplegia, often linked to glycocalyx shedding and resulting in distributive shock.

Type of Fluids

Crystalloids

These fluids, categorized as chloride-rich solutions and balanced crystalloids, are deemed the preferred choice in sepsis/septic shock cases.[10,11] Balanced crystalloids are particularly favored due to their electrolytic composition closer to plasma, reducing the risk of hyperchloremic acidosis associated with chloride-rich solutions. The volume of fluids to be infused in the early stages of septic patient treatment remains a topic of ongoing debate.[12]

Colloids

Colloids such as hydroxyethyl-starch (HES), gelatins, and dextrans were traditionally preferred due to their perceived advantage in minimizing extravascular fluid leakage.[13–15] However, in septic patients, the disruption of glycocalyx integrity undermines the expected intravascular volume benefits associated with colloids.[15–17] Studies have consistently failed to demonstrate any mortality benefit of colloids over crystalloids in sepsis management,[13] with increased risks of tubular necrosis and acute kidney injury (AKI) reported.[18,19] As a result, the European Medicines Agency (EMA) has advised suspending the use of HES solutions within Europe.

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Table 1: Overview of different types of shock

Pathophysiology	Low CO (+) FR	Low CO (–) FR	Low CO ± FR	High CO ± FR
Type	Hypovolemic shock	Cardiogenic shock	Obstructive shock	Vasodilatory shock
Causes	Hemorrhage excessive diuresis third-spacing	Myocardial dysfunction: ACS, takutsubo	Cardiac tamponade, tension pneumothorax, pulmonary embolism, dynamic hyperinflation	Sepsis Anaphylactic shock Drugs: propofol, vasodilators Metabolic acidosis Hypocalcemia
Evaluation and management	Laboratory evaluation Imaging to localize bleeding sites Check cardiac filling pressure Fluid challenge Blood transfusion, if bleeding	Laboratory evaluation Echo Inotropes NIV/invasive ventilation	Chest radiograph, echo, lung USG Fluid challenge Correction of underlying cause	Laboratory evaluation: blood cultures, procalcitonin, ionized calcium, ABG, lactate Antibiotics Discontinue offending medications Increase vasopressors

ABG, arterial blood gas; ACS, acute coronary syndrome; CO, cardiac output; Echo, echocardiography; NIV, Noninvasive ventilation; USG, ultrasonogram

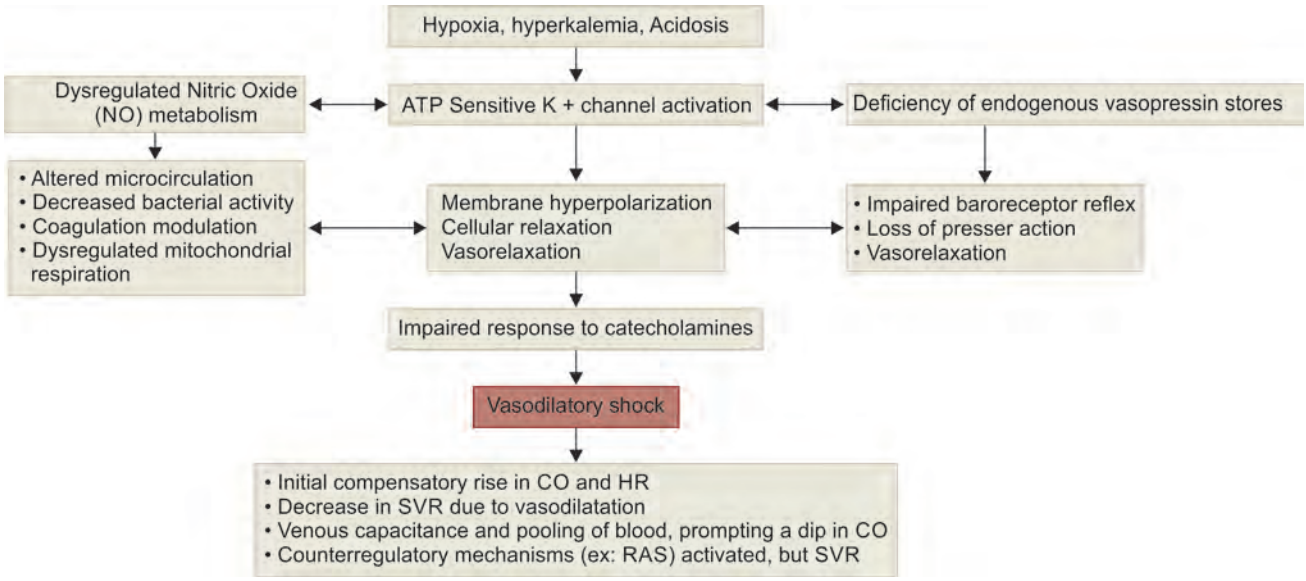

Fig. 1: Pathophysiology of vasodilatory shock

Albumin

Despite theoretical advantages, numerous studies and meta-analyses have failed to demonstrate improved mortality with albumin infusion in sepsis treatment.[20–24]

Amount of Fluids

The ideal fluid volume for resuscitating septic patients remains a topic of ongoing debate. The Surviving Sepsis Campaign previously advocated administering 30 mL/kg of intravenous crystalloids within the first 3 hours. More recently, there has been a shift toward personalized approaches, such as "glycocalyx resuscitation," which consider both fluid tolerance (FT) and fluid responsiveness (FR). FT refers to the capacity to administer fluids without causing organ dysfunction, while FR evaluates the stroke volume increase following a fluid bolus.

Although various techniques are available for assessing FR, no universally accepted standard exists. Dynamic assessment methods are generally favored over static measures to optimize microcirculation. One proposed strategy involves administering repeated boluses of 250–500 mL of intravenous crystalloids with continuous FR monitoring and introducing vasopressors early if required. Nonetheless, research indicates no significant difference in 90-day mortality outcomes between restrictive and liberal fluid management strategies for sepsis-induced hypotension.

Intensivist's Perspective

Balanced crystalloids are the preferred choice for resuscitation, with fluid administration tailored to individual patient factors such as FT and FR, as standardizing fluid volumes for all patients is not feasible. Given that restrictive and liberal fluid strategies yield comparable outcomes, it is recommended to administer small, incremental boluses of 250–500 mL while closely monitoring hemodynamic parameters to minimize the risk of fluid overload.

Catecholamines

Catecholamines, vasopressors, and inotropes are often confused but represent distinct drug categories with some overlap. Catecholamines [e.g., epinephrine, norepinephrine (NE)] are natural neurotransmitters that act as vasopressors or inotropes, though some agents, like phenylephrine, are not catecholamines. Vasopressors constrict blood vessels and include both catecholamines and noncatecholamines (e.g., VP). Inotropes, which increase heart contractility, include drugs like dobutamine and milrinone.

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Newer Agents

Angiotensin

Angiotensin II, an octapeptide generated within the renin-angiotensin system (RAS), is derived from angiotensinogen through the action of renin, a process initiated by the juxtaglomerular apparatus.[25] In the classical RAS pathway, angiotensin I is subsequently converted into angiotensin II by the angiotensin-converting enzyme (ACE), which is predominantly produced and active in the pulmonary vasculature (Fig. 2). Angiotensin II exerts its effects primarily by binding to angiotensin type I receptors in vascular smooth muscle,[26] triggering vasoconstriction *via* an increase in cytosolic calcium levels.[25]

The angiotensin II for the treatment of high-output shock (ATHOS) trial, a preliminary study involving 20 participants, demonstrated the potential of human angiotensin II to raise MAP.[5] Building on this foundation, the larger ATHOS-3 trial was conducted across 75 ICUs and included 344 patients. This study confirmed the effectiveness of angiotensin II in improving blood pressure in cases of vasodilatory shock that were refractory to high-dose conventional vasopressors.[27]

Based on these findings, the U.S. Food and Drug Administration (FDA) approved Giapreza (angiotensin II) in December 2017.[28]

V1a Selective Agonist

Two drugs, VP and selepressin (a selective V1a receptor agonist), are undergoing development and clinical trials. A recent multicenter, double-blind, parallel-group, placebo-controlled study on early septic shock (n = 53) highlighted significant findings with selepressin administered at 2.5 ng/kg/minute. This intervention resulted in a greater proportion of patients maintaining MAP without requiring NE, a lower cumulative NE dose, and a reduced duration of shock. These outcomes were associated with mortality benefits, indicating selepressin's therapeutic potential in early septic shock management.[29]

Methylene Blue

Methylene blue (MB), a thiazine dye commonly used to treat methemoglobinemia, affects vascular function indirectly. It inhibits cGMP-mediated vasodilation by targeting iron heme and soluble guanylate cyclase (sGC) in vascular smooth muscle cells.[30] Additionally, MB inhibits iNOS and scavenges NO.[31]

While initial studies reported hemodynamic improvements in hyperdynamic septic shock, they found no changes in cellular oxygen availability. A reduction in serum lactate concentrations, attributed to MB's direct reductive effects, was observed. Retrospective analyses and a 2022 meta-analysis indicated benefits in refractory vasodilatory shock,[32] especially among septic shock patients receiving continuous MB infusions.

The 2022 meta-analysis, encompassing 15 studies with 832 patients,[33] demonstrated significant mortality reduction in nine studies with low heterogeneity. Benefits were particularly noted in septic shock cases and among patients treated with continuous MB infusion. Two studies also documented a reduced incidence of acute renal failure.

However, variability in MB dosing, timing, administration methods, and concurrent vasopressor usage complicates its evaluation.[34] Using MB as salvage therapy after conventional treatments fail may introduce bias against its effectiveness. Consequently, current evidence is insufficient to support routine MB use for septic shock outside clinical trials.[33]

A forthcoming randomized controlled trial (RCT) will compare standard care with standard care plus early MB administration to further evaluate its role in septic shock management.[35] Nonetheless, caution is warranted in distributive shock, where MB may exacerbate tissue hypoxia and anaerobic metabolism, offering limited benefits in enhancing NE responsiveness.

Hydroxocobalamin

High-dose hydroxocobalamin, known as Cyanokit, is a standard treatment for cyanide toxicity, administered intravenously at a dose of 5 gm over 15–30 minutes.[36] While primarily recognized as an active form of vitamin B12, hydroxocobalamin can also counter cyanide toxicity by binding cyanide molecules for urinary excretion.[37] It's important to note that vasodilatory shock, including vasoplegic shock, involves vasodilation through NO-mediated mechanisms.[38] Hydroxocobalamin is believed to effectively bind or scavenge NO, contributing to its therapeutic efficacy.

Hydroxocobalamin has shown potential in catecholamine-resistant shock scenarios, including cases refractory to vasopressor therapy postcardiopulmonary bypass (CPB).[39,40]

Despite its promising outcomes, the use of hydroxocobalamin is not without adverse effects, including chromaturia, erythema, elevated blood pressure, and injection site reactions.[38] Additionally, it can interfere with laboratory blood analysis[38] and trigger blood leak alarms in some hemodialysis machines.[41–43] Therefore, while hydroxocobalamin holds potential as a treatment for various forms of shock, further research is needed to better understand its clinical utility and ensure patient safety.

Extracorporeal Membrane Oxygenation

In recent years, extracorporeal membrane oxygenation (ECMO) has shown promise in providing respiratory support *via* venovenous (VV) cannulation and cardiac or cardiorespiratory support using a venoarterial (VA) strategy.[44,45] This technique helps

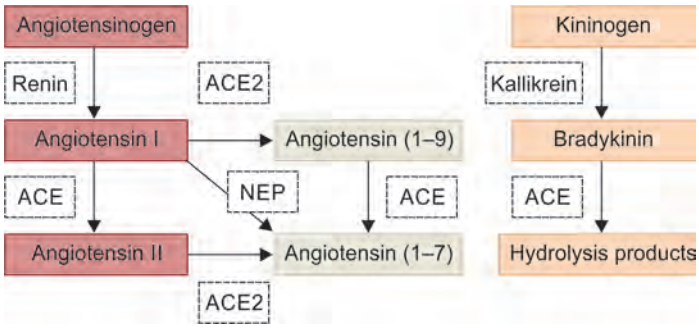

Fig. 2: Angiotensin metabolism: ACE dysfunction disrupts the classicals RAS pathway, leading to a redirection toward the ACE2 NEP pathway. This alteration causes an accumulation of vasodilatory angiotensin (1–9) and (1–7), as well as bradykinin through the kallikrein pathway. Abbreviations: ACE, angiotensin-converting enzyme; NEP, neprilysin; RAS, renin-angiotensin system

optimize tissue perfusion, allowing metabolic rest by reducing the dependence on vasopressor and inotropic drugs and enabling less invasive ventilatory support.[46–48]

Extracorporeal blood purification therapies have also been proposed to improve outcomes in patients with severe sepsis, regardless of the presence of AKI.[49,50] These methods aim to remove excessive inflammatory mediators and bacterial toxins from circulation, helping to modulate the host's inflammatory response.

The primary goal of blood purification is to restore "immune homeostasis" by addressing immune dysregulation during infection.[51] Despite initial promise, multicenter RCTs using high-volume hemofiltration (HVHF) techniques have not demonstrated improved survival outcomes.[52,53] Similarly, meta-analyses evaluating extracorporeal blood purification methods have not consistently shown survival benefits,[54] likely due to differences in cytokine production, receptor clearance, and mediator affinity.[51,55]

A recent RCT with 20 patients receiving CytoSorb hemadsorption therapy within the first 24 hours of septic shock onset showed safety and a significant reduction in NE requirements compared to controls.[55] Although case studies have indicated reduced vasopressor requirements, further research is needed to establish the broader clinical efficacy of blood purification techniques in sepsis. Ongoing studies emphasize the complexity of individual responses and the need for continued evaluation.

Adjunctive Therapies

Corticosteroids

The role of corticosteroids in sepsis treatment remains a subject of discussion. An analysis of 37 RCTs found that corticosteroid use in sepsis led to a modest but statistically significant reduction in 28-day mortality [risk ratio (RR) 0.90, 95% confidence interval (CI) 0.82–0.98].[56] Additional benefits included faster shock reversal, more vasopressor-free days, quicker resolution of shock, and improved organ function assessment.

A Cochrane review further supports these findings, suggesting moderate certainty that corticosteroids reduce both 28-day and hospital mortality in septic shock.[57] A network meta-analysis of data from 22 studies found no strong evidence favoring specific corticosteroid regimens, although hydrocortisone boluses and infusions showed a higher likelihood of shock reversal compared to methylprednisolone boluses or placebos.[58]

Low-dose corticosteroids (LDC), defined as ≤300 mg/day of hydrocortisone or its equivalent, have demonstrated promising results. Patients treated with LDC showed improved 7-day shock reversal without significantly increasing the risk of gastrointestinal bleeding, superinfections, or 28-day mortality. However, variability in the initiation of corticosteroid therapy across trials poses challenges, particularly regarding the NE dose at which treatment began, which ranged from 3.0 to 32.7 µg/minute across different sites.[59]

Vitamin C

Alternative therapies, such as high-dose vitamin C (ascorbic acid), have been explored to supplement standard sepsis management. However, a meta-analysis of 11 RCTs found no significant short-term mortality benefit associated with vitamin C use (RR 0.88, 95% CI 0.73–1.06, $p = 0.18$).[60]

A recent Canadian RCT involving 872 ICU patients with sepsis compared vitamin C infusions (50 mg/kg every 8 hours) to placebo. The study found a higher rate of death or persistent organ failure at day 28 in the vitamin C group (44.5%) compared to the placebo group (38.5%, RR 1.21, 95% CI 1.04–1.40, $p = 0.01$).[61] These findings raise concerns about the potential efficacy of vitamin C in septic shock management.

Conclusion

Septic shock continues to be associated with unacceptably high mortality rates, even when guidelines and recommended best practices are followed. While fluid therapy and vasoactive medications are crucial for supportive care, relying solely on a single drug, such as NE, to address vascular failure has been linked to well-described side effects. To enhance outcomes, a new paradigm has been suggested that emphasizes harnessing all physiological aspects of the host's response to vascular failure. Future RCTs will be crucial to validate this strategy.

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REVIEW ARTICLE

Kidney and Lungs: Do they Cross-talk?

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Abstract

The kidneys and lungs, often studied in isolation, are integral organs in maintaining homeostasis within the human body. However, the lung and kidney have multiple shared physiological and pathological pathways. It is important to understand these complex interactions and the cross-talk to manage patients, especially in critical care. This review delves into the intricate relationship between the kidneys and lungs, shedding light on how dysfunction in one organ can profoundly impact the other. It explores shared mechanisms, molecular mediators, and clinical implications, demonstrating the significance of understanding this cross-talk. By elucidating the nuanced interplay between the kidneys and lungs, we hope to pave the way for more holistic approaches to the diagnosis and treatment of diseases, ultimately enhancing patient care.

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Introduction

The kidneys and lungs are vital organs for maintaining homeostasis. Their functional harmony is necessary to maintain a normal physiological milieu.[1] Kidney and lung interactions start early in fetal age, wherein the kidney remains the main source of growth factors and nutrients, which are secreted in the urine and form the fundamental component of amniotic fluid, helping in lung growth and maturation.[1] In healthy conditions, maintenance of acid-base balance is a key function performed by the kidneys and lungs in conjunction. Kidneys and lungs interact during pathological conditions by releasing certain inflammatory mediators, making it important to study these interactions to understand the diseases better (Fig. 1).

Anatomical and Physiological Overview

The kidneys have a wide variety of functions, the most important of which is maintaining fluid, electrolyte, and acid-base balance. The kidneys filter approximately 180 L of fluid per day, most of which is reabsorbed in the tubules, resulting in excretion of urine that varies in osmolality between 50 and 1200 mosm/kg.[2] During reabsorption, most electrolytes are reabsorbed in the proximal tubule and loop of Henle, whereas some reabsorption occurs at the level of the distal tubule. The electrolyte balance is also maintained by secreting potassium in the distal tubule and collecting duct. The acid-base balance remains the major function of the kidney. Other crucial roles of the kidney are the regulation of blood pressure, which is done by the renin-angiotensin system, and the secretion of hormones, including erythropoietin, renin, and 1,25 dihydroxy-vitamin D.[2]

The lungs are vital organs that maintain life by providing respiration, wherein the blood is oxygenated and distributed to the entire body, and carbon dioxide (CO_2) is removed during expiration. Lungs also function as immune systems by eliminating foreign particles and organisms inhaled from the environment. The pH of the body systems is maintained between 7.35 and 7.45 by active pulmonary and metabolic (renal) interplay. Metabolic acidosis is compensated by hyperventilation, leading to the washing out of CO_2 and restoring the pH to the normal range. Coexistence of chronic obstructive pulmonary disease (COPD) and chronic kidney disease (CKD) can worsen acidemia, as both metabolic and respiratory acidosis can occur simultaneously.[2]

Renal-lung Interactions

The renal-lung interactions should be studied to better understand the disorders and manage them more effectively (Fig. 2).

Renal to Pulmonary Pathways

Lung involvement is not an uncommon finding in patients with kidney disease.[1] Ehrich and McIntosh described bronchiolitis obliterans in patients with Bright's disease, and Doniach described fibrinous alveolitis in patients with "uremic lung."[1] Bass et al. described the pathology of "uremic lung" in detail as early as 1951. The postmortem examination of patients who died with azotemia and had typical findings of pulmonary edema on chest radiology showed the presence of marked alveolar wall thickening and fibrinous alveolitis with various stages of hyalinization of the intraalveolar exudate and hyaline membrane lining the alveoli. The authors proposed that some of these patients may have died of lung involvement rather than renal disease.[1]

The accumulation of fluid in alveoli in a patient with acute kidney injury (AKI) is not only due to an overall positive fluid balance; rather, multiple mechanisms aggravate this. Epithelial sodium channels (ENaC) are present in the walls of the alveoli, which reabsorb fluid from the alveoli into the circulation. The experimental models of ischemia-reperfusion injury[2] showed an inhibition of ENaC channels, aquaporin 5, and Na–K-ATPase in the alveoli and reverse alveolar chloride transport *via* CFTR and NKCC2 channels, leading to an influx of fluid into the alveoli. This explains how loop diuretics dramatically affect patients with pulmonary edema, even in patients without fluid overload. In contrast, amiloride, which causes ENaC inhibition, may worsen cardiogenic pulmonary edema.[3]

Inflammatory pathways also play a key role in the enhanced pulmonary microvascular permeability. The inflammatory cytokines, such as interleukin-6 (IL-6) and 1b and tumor necrosis factor-α, damage the pulmonary parenchyma. Damaged parenchyma releases proteases and reactive oxygen species, leading to a chain reaction. These pathological mechanisms closely involve

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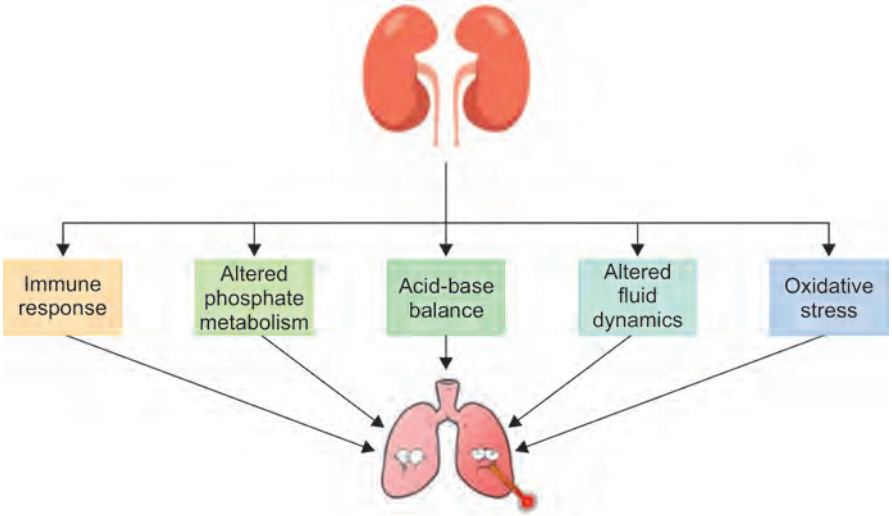

Fig. 1: Mechanisms of kidney-lung cross talk. The lungs and kidneys are interconnected through a variety of mechanistic pathways including immune response, phosphate metabolism, hormonal imbalances, acid-base balance, fluid dynamics, and oxidative stress. Frequently, more than one of these pathways may be contributing to interorgan crosstalk that leads to worse prognosis for patients with CKD and acute or chronic lung

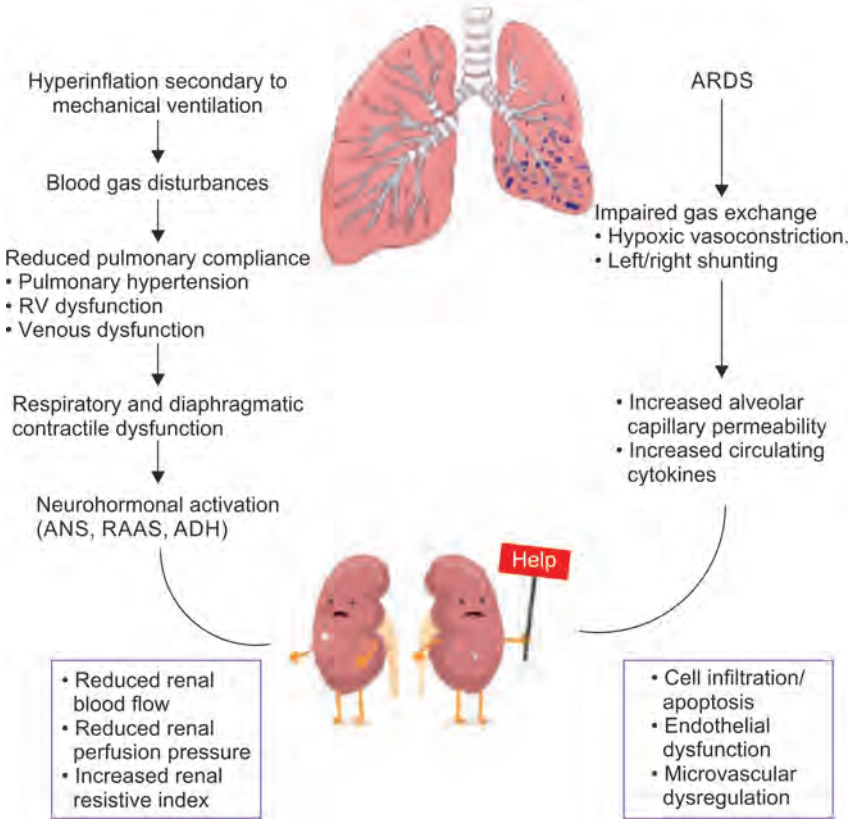

Fig. 2: Shows multiple dependent pathways in the setting of acute pulmonary disorders elevate the risk of AKI. Shown are the possible hemodynamic, neurohormonal, proinflammatory, and proapoptotic consequences of both hyperinflation and lung inflammation on renal function, and their clinical features

the nitric oxide (NO) pathway *via* asymmetric dimethyl-arginine (ADMA), an endothelial NO synthase inhibitor that is increased due to renal injury. This redirects the NO metabolism to the production of reactive oxygen species, leading to systemic damage. Evidence suggests that AKI results in activation of tumor necrosis factor receptor 1 (TNFR1)-mediated programmed cell death in lungs, as well as microvascular barrier dysfunction, resulting in acute lung injury (ALI). TNF receptor antagonists like etanercept may block these pathways in experimental models.[4]

Acute kidney injury can cause lung injury through increased vascular permeability, inflammatory reactions, and oxidative stress. Down-regulation of the pulmonary ENaC, Na–K ATPase, and aquaporin-5 can cause increased vascular permeability. The inflammatory, proapoptotic, and fluid influx pathways lead to surfactant damage, leukocyte migration into the alveoli and interstitium, and alveolar hemorrhage.[5]

Chronic pulmonary fluid accumulation is often found in patients with CKD, leading to myofibroblast proliferation and extracellular matrix deposition, causing the thickening of the alveolar-capillary barrier. Although this process is initially protective and prevents pulmonary edema, it eventually becomes maladaptive, leading to restrictive lung physiology.[6]

The role of the kidney is to balance nitrogenous waste, fluid status, and acid-base balance. In the presence of AKI, these functions are affected, compromising lung functions. Studies have shown poor gas exchange in patients with uremia, reduction in forced vital capacity (FVC), forced expiratory volume in 1 second (FEV1), and maximal breathing capacity (MBC).[7] A decreased diffusion capacity for carbon monoxide is often seen in patients with CKD, more so in those on hemodialysis, and contributes to reduced exercise capacity.[8]

Pulmonary to Renal Pathways

Pulmonary diseases, either acute like ARDS and pneumonia or chronic like COPD, sleep-disordered breathing (SDB), idiopathic pulmonary fibrosis (IPF), scleroderma-associated lung disease, asthma, cystic fibrosis, environmental lung diseases, and pulmonary artery hypertension (PAH), can affect renal functions in many ways.[9]

Acute lung injury causes hypoxemia, which leads to organ dysfunction, including acute kidney injury. Direct effects of hypoxemia on the renal blood flow (RBF), as well as inflammatory mediators released due to hypoxemia, can be potential mechanisms of AKI in patients with ARDS.[10,11]

High tidal volumes on mechanical ventilatory support in a patient with lung injury increase the free radical injury, inflammatory cytokines,[12] chemokines, soluble FAS-L, and advanced glycosylation end products.[13] The inflammatory mediators released in the bloodstream due to ALI can amplify neutrophil activity by producing proteases, reactive oxygen products, platelet-activating factors, and leukotrienes, thus

worsening inflammatory status and leading to multiorgan failure, predominantly affecting kidney function. Hence, ALI and ARDS, irrespective of mechanical ventilation, can lead to acute kidney injury and mortality. It is thus an independent risk factor for AKI.

The hypercapnia and hypoxia seen in acute exacerbation of COPD activate the vasoactive system, resulting in renal vasoconstriction and reduced RBF.[10] Typically, the efferent arteriole constricts more than the afferent arteriole, leading to an increase in glomerular hydrostatic pressure and glomerular filtration rate (GFR). However, in the later stages of COPD, activation of compensatory mechanisms can cause a reduction in the GFR.

An increase in GFR leads to increased filtration fraction. This further reduces the hydrostatic pressure and increases the oncotic pressure in the peritubular capillaries, which leads to enhanced reabsorption of sodium and water from the renal tubules. Additionally, severe hypoxia, even in the absence of hypercapnia, triggers the release of vasoactive peptides and activates the adrenergic system. At the renal level, factors such as NO, angiotensin II, and endothelin induce renal vasoconstriction, thus reducing RBF and promoting sodium and water retention. The presence of hypercapnia accentuates the above pathways. In patients with COPD, sodium and water retention can also be due to chronically activated renin-angiotensin-aldosterone system (RAAS) in response to low volume status. Moreover, compensatory mechanisms dependent on natriuretic peptides are often ineffective in clearing sodium through the urine. Hypoxemia suppresses atrial natriuretic peptide synthesis, while renal tubules commonly exhibit resistance to antidiuretic hormone, further complicating fluid regulation in COPD patients.[10]

Pulmonary hypertension is another mechanism that is of critical importance in explaining the pathogenesis of renal dysfunction in patients with lung disease. Lung diseases can lead to PAH, which causes central venous congestion, raised renal interstitial pressure, and renal hypoxia, leading to a decreased GFR. Due to ventricular synchrony, right heart failure due to pulmonary pathology can cause left ventricular dysfunction, decreased cardiac output, stimulation of the renin-angiotensin system, and renal vasoconstriction, causing reduced GFR.[14]

Chronic kidney disease is a recognized comorbidity in patients with COPD, though it is often overlooked. Since many COPD patients are elderly and frail with normal serum creatinine levels due to malnutrition and reduced muscle mass, this association may go unnoticed, as it may render the eGFR formula unreliable. Common risk factors for CKD and COPD include elderly age and smoking.[14] Cigarette smoking, which is one of the leading causes of COPD, also damages kidney function as nicotine leads to an increase in oxidative stress, thereby promoting mesangial cell proliferation and extracellular matrix deposition. This contributes to renal and pulmonary fibrosis. Emerging inflammatory biomarkers indicate that significant chronic inflammation exists in CKD. This inflammation may cause organ damage directly or *via* endothelial dysfunction.[14]

Shared Mechanisms and Molecules

There are studies evaluating multiple molecules that have an interplay in lung-kidney interactions.

- Role of alpha klotho: Soluble alpha klotho is produced in the kidney and acts as an antiaging molecule with cytoprotective effects. There is a decrease in klotho levels in AKI and CKD. In rat models of AKI, which lead to ARDS, the lung injury was mitigated by repleting alpha klotho.[15]
- Angiopoietin 2: Angiopoietin 2 is released from endothelial Weibel–Palade bodies and is implicated in increasing vascular permeability in ARDS. Ischemia-reperfusion injury in renal transplant recipients leads to an increase in angiopoietin 2, which could lead to ARDS. The angiopoietin/Tie 2 signaling pathway is crucial during fetal glomerulogenesis and medullary maturation in adulthood.[16]
- Tumor necrosis factor-alpha (TNF-α), IL-6, and C-X-C motif chemokine ligand 1 (CXLCL-1): Inflammatory mediators that can lead to AKI in ARDS and vice versa.
- Indoxyl sulfate, a uremic toxin, is an inducer of IL-6 expression.[16]

Trans-vascular fluid in the lungs is collected in the interstitium, which is drained by lymphatics. The alveolar-epithelial barrier prevents alveolar flooding by interstitial fluid. The pneumocytes express sodium channels on the apical surface and sodium-potassium ATPase channels on the basolateral surface, which actively pump sodium into the interstitium, and due to the osmotic gradient through aquaporin channels, water is passively drawn, maintaining a balance between intra- and extracellular fluid.[17] Alterations in these sodium and aquaporin channels can affect alveolar fluid balance. Increased permeability increases protein and solute flux, raising oncotic pressure, favoring alveolar overflowing and impairing alveolar fluid clearance. There is evidence that suggests that acute kidney injury can cause pulmonary damage and alveolar edema even without volume overload. This is characterized by severe pulmonary vascular congestion, focal alveolar hemorrhage, and inflammatory cell infiltration. These effects are not only limited to the endothelium; there is also an alteration of sodium and water. In a study where rats underwent nephrectomy, uremia was responsible for salt and water transport alterations affecting lung functions.[17] Therefore, urea is an important connecting link between the two.

Many patients with SDB suffer from underlying comorbidities, including coronary artery disease and CKD, which worsen the fluid shift from the periphery to the rostrum during sleep. Such patients may also have difficulty controlling hypertension.

Inflammation and Immune Responses

Cytokines and chemokines, such as IL-6, IL-1, and macrophage inflammatory protein 2, play a major role in initiating and progressing renal and pulmonary impairment.[18] It was noticed that the administration of the anti-inflammatory cytokine IL-10 reduced pulmonary markers of injury and inflammation. Oxidative stress also played an important role in the AKI-induced pulmonary dysfunction. In a rhabdomyolysis-induced oxidative stress rat model, AKI was found to be associated with oxidative stress and inflammatory responses in the lung, with increases in lipid peroxidation and a decrease in antioxidants like reduced glutathione.[19] Unilateral renal ischemia or reperfusion injury was also found to decrease the release of antioxidants like superoxide dismutase, catalase, and glutathione from other organs. This suggests that ischemic kidney injury might compromise the host response to systemic oxidative stress.[20] Conversely, intratracheal instillation of lipopolysaccharide (LPS) caused renal inflammation,[21] suggesting that inflammatory changes in the lung cause similar changes in the kidney. Renal hemodynamics may be affected by hypoxemia, hypercapnia, and mechanical ventilation-associated high pressures. Although mechanical ventilation positively impacts kidney function, there are also some caveats.[22] The biotrauma due to mechanical ventilation releases proinflammatory cytokines into the systemic circulation. In an RCT comparing conventional lung volumes with a lung protective strategy, the levels of the cytokines TNF-α, interleukin-1

beta (IL-1β), IL-6, and interleukin-8 (IL-8) in the bronchoalveolar lavage fluid and plasma were found to be higher in the former group.[23] Additionally, it was found that the degree of multiorgan failure correlated with IL-6 levels.[24]

Neurohormonal Regulation

Kidneys filter extracellular fluid, and if there is excess extracellular fluid volume, renal sodium and fluid excretion will increase. Similarly, in volume-depleted states, more sodium reabsorption occurs.[25] Reduction in kidney function leads to increased circulatory volume due to decreased sodium and other solute excretion.[26] Fluid overload in these settings damages the alveolar membrane and leads to the accumulation of fluid near the airways, which impedes gaseous exchange.[27] Studies have shown that end-stage renal disease (ESRD)-associated fluid overload is associated with restrictive and obstructive abnormalities leading to chronic pulmonary dysfunction.[28]

Kidney and lung share several immune-mediated syndromes known as pulmonary-renal syndromes, including granulomatosis with polyangiitis, Goodpasture's syndrome, microscopic polyangiitis, eosinophilic granulomatosis with polyangiitis, and systemic lupus erythematosus. These are potentially life-threatening conditions defined as a combination of rapidly progressive glomerulonephritis and diffuse alveolar hemorrhage. They are characterized by neutrophilic infiltration of arterioles, venules, and capillaries, leading to the destruction of the vessel wall.[29]

It is essential to distinguish between the cross-talks occurring between the kidneys and lungs with pulmonary-renal syndromes, as these syndromes involve shared immunological mechanisms that may lead to the simultaneous involvement of both organs. In contrast, kidney-lung cross-talk emphasizes the pathways that affect one organ in the presence of the other.

Clinical Implications

Fluid management is the most important parameter that helps to prevent and treat pulmonary and renal dysfunction.[25] Acute or chronic renal dysfunction can easily lead to pulmonary edema, which can be corrected by providing diuretics and dialysis. Diuretics help shift the fluid from pulmonary to systemic circulation and remove it from the body through the renal system. Appropriate oxygenation to maintain saturation in patients with ALI can also help correct the renal dysfunction arising from hypoxia. Vascular endothelial growth factor receptors (VEGFR) can cause endothelial dysfunction. Fibroblast growth factor receptor (FGFR) is responsible for the elevation of fibroblast growth factor-23 (FGF-23) in patients with CKD. Nintedanib is a tyrosine kinase inhibitor approved for treating IPF; it inhibits VEGF, FGF, and platelet-derived growth factor (PDGF). FGFR1 inhibitors have shown to reduce FGF-23 levels seen in acute and chronic uremia.[30] This suggests VEGF inhibitors may be helpful in patients with CKD.[31]

Chronic kidney disease patients are in metabolic acidosis with low bicarbonate; its supplementation slows down the progression of CKD. However, the presence of COPD can lead to insufficient gas exchange and worsening hypercapnia, further worsening acidosis.[32] Therefore, further research is required to determine its use in the presence of COPD.

Vitamin D supplementation is used to control secondary hyperparathyroidism in patients with CKD.[33] Serum vitamin D has shown a positive correlation with lung function in patients with asthma.[34]

Antioxidants have been shown to reduce the risk of progression to ESRD in patients with stages 3 or 4 CKD or postrenal transplant patients; however, there was no reduction in cardiovascular complications.[35] Antioxidants have been used successfully in patients with COPD to reduce oxidative stress. Further studies are warranted to investigate antioxidant effects in patients with CKD and lung disease.

Studies are required to evaluate the role of providing dialysis and extracorporeal CO_2 removal in a patient with severe multisystem dysfunction so that both the pulmonary and renal systems can be corrected and the interplay can work toward a favorable physiology.

Future Directions and Research Avenues

As the interactions between the kidney and the lung in various diseases are complex and multifactorial, personalized management of all patients, along with providing equal attention to both organs, can help improve the patient's prognosis.

The treating physician should also remember that correcting one organ dysfunction can automatically help improve the other in certain situations. CKD patients undergoing regular maintenance hemodialysis will recover from pulmonary edema. Also, an ARDS patient who is oxygenated well and maintains body perfusion will recover from acute renal injury.

Future research on diagnostic tools, biomarkers, and research molecules targeting these biomarkers can help improve patient outcomes.

Conclusion

In conclusion, the intricate cross-talk between the kidneys and lungs is far from a one-way street. Lung disorders can provoke renal injury; conversely, kidney dysfunction can impact pulmonary health. In many disease scenarios, such as sepsis, heart failure, and systemic autoimmune diseases, both the lungs and kidneys can be simultaneously affected. Recognizing and addressing these multisystem involvements is paramount. The complex interplay between these two vital organs challenges healthcare professionals to adopt a multidisciplinary approach to patient care. Nephrologists and pulmonologists must collaborate closely to devise treatment strategies that consider the holistic well-being of the patient.

As we navigate this terrain of interconnected organ systems, it becomes evident that continued research is essential. Advancements in our understanding of the physiological and pathophysiological links between pulmonary and renal disorders are crucial for achieving optimal patient outcomes. By working together, sharing knowledge, and fostering a spirit of collaboration, we can offer patients a brighter, healthier future where the kidneys and lungs are not isolated entities but partners in sustaining overall health and well-being.

Availability of Data and Materials

The clinical data and the study materials available from the corresponding author on reasonable request.

Author Contributions

SM, PI, PP, SS, NV, VR, HV, and VK were involved in the literature search, planning, conduct, writing the original draft of the manuscript, and editing of the study. All the authors have agreed to the submitted manuscript. SS is the corresponding author and guarantor for all.

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REVIEW ARTICLE

Biologics and Tuberculosis Preventive Therapy

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Abstract

Biologics have revolutionized the management of systemic inflammatory disorders in the last few decades. The most common side effect associated with these agents is increased susceptibility to infection. Increased risk of tuberculosis (TB) reactivation in patients with latent tuberculosis infection (LTBI) has been recorded for anti-tumor necrosis factor (TNF) agents and, to a lesser extent, for the nonanti-TNFα targeted biologics. Use of both biologic agents and Janus kinase (JAK) inhibitors is associated with increased risk of TB disease. LTBI screening prior to initiation of a biologic agent or JAK inhibitor and treatment of positive cases significantly reduces the incidence of TB disease, though it does not eliminate it. Several recommendations and guidelines have been published, but none of them apply globally due to variable socioeconomic conditions and endemicity of TB in different countries. At present, we have a national guideline in India from the National Tuberculosis Elimination Programme (NTEP) in the form of Guidelines for Programmatic Management of Tuberculosis Preventive Therapy in India (PMTPT), which mandates TB screening and treatment for patients on immunosuppressive therapy and anti-TNF treatment. However, PMTPT is essentially a general recommendation. Clinicians need to be abreast of the integration of this approach with the variable risks of TB reactivation associated with different biologics in clinical practice.

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Biologics have revolutionized the management of systemic inflammatory disorders in the last few decades. These are large-molecule compounds produced from biological sources by genetic engineering, targeted to block specific parts of the immune system. Biotechnology enabled the development of closely related molecules, including Janus kinase (JAK) inhibitors, which are made from chemicals to also target specific enzymes involved in inflammation. The most common side effect associated with these agents is increased susceptibility to infection.

Use of both biologic agents and JAK inhibitors is associated with an increased risk of TB disease. The risk of TB and its timing of onset vary according to the agent. Screening for latent tuberculosis (LTB) prior to initiation of a biologic agent or JAK inhibitor and treatment of positive cases significantly reduces the incidence of TB, though it does not eliminate it.

Latent tuberculosis, recently termed tuberculosis infection (TBI), is a state of infection with *Mycobacterium tuberculosis* (MTB) with no evidence of clinically manifest active disease. Tuberculosis preventive therapy (TPT) by treatment of TBI is an important component of the National TB Elimination Program (NTEP) as part of the National Strategic Plan 2017–25 for Ending TB in India.[1]

Clinicians were abreast of the increased risk of latent TB reactivation with global immunosuppressants like corticosteroids and traditional immunosuppressive drugs over the years. Variable risks of TB reactivation associated with different biologics pose a new challenge in clinical practice.

Our age-old teaching was not to treat latent tuberculosis, basically because of the magnitude of the problem and utilizing limited national resources more meaningfully to combat active TB. NTEP, however, targets latent tuberculosis to deplete the epidemiological reservoir. Guidelines for Programmatic Management of Tuberculosis Preventive Therapy in India (PMTPT) advocates a nationwide phased implementation of TPT with prioritization of high-risk groups: people living with HIV (+ anti-retroviral therapy or ART), household contacts (HHC) of pulmonary TB patients notified in Nikshay (HHC of bacteriologically confirmed pulmonary TB patients get the priority). The expanded target population now includes those: (1) on immunosuppressive therapy, (2) having silicosis, (3) on anti-tumor necrosis factor (TNF) treatment, (4) on dialysis, (5) preparing for organ or hematologic transplantation.[2]

One of the concerns commonly expressed about the large-scale use of TPT is the potential risk of propagating drug resistance. These concerns have not been supported by high-quality evidence to date. Multiple trials have failed to find scientific evidence of a significant association between the emergence of drug resistance and the use of isoniazid or rifamycin for TPT. An increase in drug resistance is unlikely if good TPT practices are observed, that is, TPT is used in people without active TB disease. Individuals with TB infection have a small number of slowly and sporadically replicating bacteria in their body, and hence there is a low risk for TPT leading to drug resistance.[3–5]

Active TB must be ruled out in an individual clinically, bacteriologically, and radiologically before offering tests for TBI or TPT.

Tuberculosis infection is essentially a clinical diagnosis. PMTPT is a public health measure with a general recommendation not exactly addressing the nuances and variability of biologics in causing immunosuppression. Also, the principle and practice of mandatory latent tuberculosis infection (LTBI) screening before prescribing biologic agents is still an alien concept in clinical medicine. A clinician's concern usually centers on deciding active TB or not TB and whether to treat or not to treat. Successful TPT implementation needs a change in this approach to cover TBI.

Risk of Progression for Tuberculosis Disease

Risk of progression of TB infection to active TB disease varies among susceptible populations. The national program at present prioritizes the highest-risk category consisting of people living with HIV and HHC of pulmonary TB patients. However, clinicians may be interested in the relative risk (RR) of different categories (not all covered by TPT at present).

Relative risk of TB disease among different high-risk population (Table 1).[6]

Tuberculosis Disease Risk in Children Following Exposure

It is high. In a systematic review and meta-analysis that included >1,37,000 children from 34 countries, the risk of developing TB disease following close exposure in the absence of preventive therapy among children <5 years of age was 19%.[7]

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Table 1: RR of TB disease in various conditions

Condition	*RR*
HIV/AIDS	10–100
Close contact	15
Organ transplant	20–70
Chronic renal failure (CRF) on dialysis	6.9–52.5
TNF-α blocker	1.6–25.1
Silicosis	2.8
Fibronodular disease on chest imaging	6–19
Healthcare workers	2.5
Diabetes	1.6–7.83
Smoking	2–3.4
Use of steroid	2.8–7.7
Underweight	2–3

Tuberculosis Disease Risk in Steroid Users

Tuberculosis guidelines identify individuals receiving the corticosteroid drug prednisone (or its equivalent) at a dose of >15 mg/day for 2–4 weeks or more as a group at risk of TB if infected with MTB.[8] There is an eight-fold increased risk of developing active TB with such drugs at this dose.[9] In June 2014, a meta-analysis of RCTs was published by Dong et al. on ICS use and risk of TB in patients with COPD. Five studies were included; the author concluded that ICS use was associated with an increased risk of TB (OR 2.29; 95% CI 1.04–5.03; $p = 0.04$).[10]

Tuberculosis Risk Associated with Old Radiological Lesions

The presence of radiographic lesions consistent with old healed TB has been considered one of the risk factors for the development of TB disease.[11] The 5-year incidence of TB in tuberculin skin test (TST)-positive persons with old healed TB lesions on their chest X-ray (CXR) was 14.3 per 1,000 person-years. Among individuals with fibrotic lesions larger than 2 cm^2, the incidence was 21.3 per 1,000 person-years.[12] In another report, the presence of calcified nodular densities or fibrosis together with nodular densities in the mid and/or upper lung zones was associated with 8.8-fold higher odds for the subsequent development of active TB.[13] Persons with evidence of healed TB lesions, like calcified solitary pulmonary nodules, calcified hilar lymph nodes, and apical pleural capping, do not suffer increased risk for TB reactivation.

Diagnosis of Tuberculosis Infection

Diagnostic test for TBI is not a routine exercise, as a decision to test implies a decision to treat if the test is positive.

The currently recommended and available tests for assessing TB infection are the TST and interferon-gamma release assay (IGRA). Both measure immune sensitization (type IV or delayed-type hypersensitivity) to mycobacterial protein antigens. TST detects the reaction to purified protein derivative (PPD) of the mycobacterium.[14] IGRA measures the amount of interferon-gamma released *in vitro* by white blood cells when mixed with MTB antigens or the number of T-lymphocytes producing interferon-gamma. MTB-specific antigens, such as ESAT 6, CFP 10, and Tb7.7, are used in IGRA.[15] These antigens are absent in BCG and most nontuberculous mycobacterial infections (NTMs); hence, IGRA has higher specificity than TST in BCG-vaccinated populations and NTM.

Low sensitivity is found both in TST and IGRA among very young children, which might be explained by immune immaturity or by capturing a population with underlying conditions that may interfere with immunity, such as coinfections with helminths and malnutrition[16] So, TST or IGRA is not mandatory for child contacts to initiate TPT. This approach is called "window prophylaxis."[17]

Standard TST (PPD-RT 23 with Tween 80 of strength 2 TU) is recommended for use. Not available in the market.[18]

Increasing sensitivity of LTBI screening by combining IGRA and TST is not recommended by PMTPT. But studies have shown that dual testing with both TST and IGRA may reduce the probability of false negative results in the presence of severe immunosuppression.[19]

Duration of Tuberculin Skin Test and Interferon-gamma Release Assay Positivity in Patients with Past Tuberculosis

It is variable. As TST and IGRA measure the cell-mediated immunity to tuberculous antigens, they may remain positive for a long duration in a patient who has already suffered from TB disease. If there is repeated exposure to the antigen, the tests will remain positive for a long duration. So, the test positivity duration will differ between endemic and nonendemic areas.[20]

Mantoux test can boost IGRA results.[20] more common in patients who are already IGRA positive. The boosting usually occurs after 3 days of Mantoux test and can be seen up to 3 months.[21] A previous MT can also boost the reaction size to the subsequent MT for up to 1.5 years. To declare this as a new infection, there should be an increase of at least 10 mm from the first test if done within 1.5 years, provided the first test result was <10 mm.[22]

PMTPT guidelines do not recommend follow-up IGRA or TST.[2]

Biologics and Tuberculosis Preventive Therapy

Patients with immune-mediated inflammatory diseases on biologics (TNF agents and others) are at increased risk of developing active TB with a higher likelihood of extrapulmonary or disseminated TB. Most represent reactivation of latent TB (occurring early after the initiation of a biologic) compared to a minority representing newly acquired infection that occurs later. Identification and treatment of LTBI is thus important in this group before commencing biologics. There is increased risk of nontuberculous mycobacterial infection as well.[23]

Tumor necrosis factor-alpha (TNF-α) plays a key role in the host defense against MTB. TNF-α is a cytokine involved in the pathogenesis of several inflammatory and autoimmune diseases. TNF-α blockade is used therapeutically in these disorders for control of symptoms. But the cytokine signaling by TNF-α is important in defense against TB infection. Studies have suggested that TNF-α helps to maintain granulomas, and any blockade of TNF-α may increase the chances of reactivation or new infection with TB. In addition, TNF-α blockade leads to unabated intracellular growth of TB bacilli within macrophages.[23]

Do All Tumor Necrosis Factor-α Inhibitors Increase Chance of Tuberculosis?

Tumor necrosis factor-α inhibitors are divided into TNF-α blockers and TNF-α receptor inhibitors. Studies have shown that TB incidences are higher with TNF-α blockers like infliximab and adalimumab, whereas a comparatively lower incidence of TB was seen

Table 2: Risk of TB with various immunomodulators

Drug class	*Name*	*Disease used*	*Risk of TB*	*References*
JAK inhibitor	Baricitinib, tofacitinib	RA	Not increased	28,29
IL-6 receptor blocker	Tocilizumab	Connective tissue disorders	Not increased	30,31
IL-1 receptor antagonist	Anakinra	RA	Not increased	32
Anti CD 20	Rituximab	Connective tissue disorders	Not increased	33
Biologics in asthma	Omalizumab, mepolizumab, benralizumab	Asthma	Not increased	34

with TNF-α receptor blockers like etanercept. Overall, a 4-fold or more increase in TB risk is associated with TNF blockade.[24] Two-thirds of the TB disease in patients on TNF-α blockade are extrapulmonary, and half of those are disseminated.[25]

What are the Challenges in the Diagnosis of Tuberculosis Infection in Patients on Biologics?

The main challenges are:

- Patients with rheumatoid arthritis (RA) may have impaired cell-mediated immunity and false negative TST or IGRA, regardless of the presence of immunosuppressive medications.[26]
- Patients on TNF-α blockade are often on steroids or methotrexate, which may result in false negative TST/IGRA.[27]

Discordant results between TST and IGRA add to the confusion, but providing TPT with the "either test positive approach" in such patients has been shown in some studies to decrease the rate of active TB in patients with TNF-α blockade.[19]

What is the Risk of Development of Tuberculosis with Other Biologics?

The immunological modulations with these drugs may place an individual at higher risk of TB in high-endemic countries. A plausible risk is given below in Table 2.

How to Manage Tuberculosis Infection before Considering Biologic Therapy?

When TB infection (TBI or LTBI) is diagnosed before biologic therapy, the LTBI treatment should be completed before commencing biologic therapy. If there is a pressing clinical need to start biologics, it can be started at least 1 month after starting TPT.[35]

What Should be Done When Patients Develop Tuberculosis Disease While on Biologic Therapy?

When such occurs, the biologics should be stopped, and a full course of anti-TB treatment should be initiated. The biologics can be resumed at least 1–2 months after starting anti-TB therapy or after completion of TB treatment.[35] Sometimes, a patient develops IRIS (immune reconstitution inflammatory syndrome) on abrupt stoppage of biologics while on TB disease treatment. It can be treated with steroids or resumption of biologics after 1–2 months of TB treatment.[36]

Clinical Scenario

A 23-year-old male, HLA B27 positive, is diagnosed with spondyloarthritis. Biologics are suggested. He has a history of moderate left pleural effusion 4 years ago, treated with antitubercular drugs (ATD). Aspirations were done twice; no corticosteroids were given. At present, the pulmonologist opines there is no evidence of clinically active TB. A CT chest is normal at present.

Interferon Gamma Release Assay is positive. What is the next course of action?

Response

Guideline advocates TPT before biologics in MT/IGRA-positive patients after ruling out active TB. However, the exact management strategy before initiating biologics in patients with adequately treated TB disease remains undetermined. MT/IGRA in these patients are likely to remain positive for a long duration. Symptoms, imaging (CXR/CT chest), sputum examination, and the opinion of a specialist might be sought for decision-making. The usual practice point would be confirming the adequacy of earlier treatment, ruling out active TB, and continuous monitoring.

Biologics also vary in their degree of immunosuppression (see Table 2). Preference may be given to the use of a non-TNF inhibitor biologic to lower the risk of TB development. An individual risk-benefit approach is warranted. One may opt for an online calculator to determine the risks and benefits as given below. Mostly, it tallies with clinical decision-making.

Online calculator: Online TST/IGRA interpreter.[37]

There is an online tool: Online TST/IGRA Interpreter. The calculations are based on the subject's age, recent contact, country of birth, comorbidity, and BCG vaccination status, among others. Based on Styblo's formula, this has been validated in a cohort of more than 37,000 foreign-born individuals in Canada.

For our above case:

The likelihood that this is a true positive test (PPV) is 98%.

The annual risk of development of active TB disease is estimated to be 0.52%.

The cumulative risk of active TB disease, up to the age of 80, is 29.89%.

If treated with INH, the probability of clinically significant drug-induced hepatitis is 0.3%, and the associated probability of hospitalization related to drug-induced hepatitis is 0.1%.

Conclusion

As the benefits of prophylaxis are more than the adverse effects, the patient should be treated with INH prophylaxis.

Any suspicion of inadequate treatment earlier should prompt initiation of TPT before commencing biologics.

Patients with high risks of TB reinfection while on biologics should be monitored clinically every 3 months and with imaging when indicated. A repeat TST/IGRA annually has been advocated for those who are initially negative.

Take Home Message

Therapeutic efficacy of biologics and other immunomodulators come with variable risks of TB reactivation.

Guidelines for PMTPT mandate TBI screening and treatment for patients in high-risk groups, including those on immunosuppressive therapy and on anti-TNF treatment.

Clinicians need to prudently adopt and apply the recommendations prior to the initiation of biologics.

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REVIEW ARTICLE

Plastic Pollution and One Health Crisis: A Burning Issue in Environmental Medicine

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Abstract

Awareness of plastic pollution is poor among the general population and medical professionals. It is impossible to understand the detrimental effects of plastics without knowing basic facts about plastics and their additives and sorbents. As the topic of plastics is vast, it is difficult to grasp by a physician. So, I have tried first to concise the basic facts of plastics in this article, followed by detailing its impacts on health and the ecosystem. As plants, animals, and humans are interdependent, the impact of plastic pollution on one group affects the others. So, a healthy balance of all components is essential. For controlling pollution, basic needs are reduction of plastic production, reuse and recycling of plastics, and safe disposal of wastes. Considering the nature of pollution, global intervention is essential. Physicians should spread awareness, take preventive measures, and plan mitigation strategies against health hazards and environmental impacts of plastics.

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Introduction

Plastic products are used widely as shopping bags, water bottles, clothing, food packaging, medical supplies, electronic goods, construction materials, automotive, electrical, and agricultural applications, etc. Because of increasing restrictions on fossil fuel combustion, fossil fuel companies are investing in plastic production more and more. In parallel to plastic production and usage, a huge plastic waste is also generated, which is indiscriminately dumped, landfilled, or incinerated. Plastic wastes either cause pollution of the terrestrial environment or migrate to the ocean, damaging the marine ecosystem.[1]

Definition of Plastics and their Properties

Plastic refers to the property of plasticity, that is, the ability to deform without breaking. Plastic polymers are derived from petrochemicals and are composed of various elements such as carbon, hydrogen, oxygen, nitrogen, sulfur, and chlorine. The properties of plastics and their low cost have made them favorable for indiscriminate uses. Plastics are thermally and electrically insulating, chemically stable, good impact and wear-resistant, highly durable, light in weight, nonrustable, and often have good transparency. Thermoplastics can be heated and molded repeatedly, while thermosetting polymers solidify into a permanent shape. Examples of thermoplastics are polyethylene (PE), polyethylene terephthalate (PETE or PET), polypropylene (PP), polycarbonate (PC), polystyrene (PS), polyvinyl chloride (PVC), acrylonitrile-butadiene styrene (ABS), Teflon, acrylic, polyamide (PA), etc. Examples of thermoset plastics include epoxy, silicone, polyurethane (PU), and phenolic, etc.

Microplastics

Larger plastic materials gradually decompose into smaller particles such as microplastics (MP) and nanoplastics (NP). MPs are <5 mm in length, and NPs are <1 µm. MPs resulting from the breakdown of larger plastics are called secondary MPs, while MPs produced as such by design purposefully are called primary MPs.

Primary MPs include microbeads, plastic pellets (nurdles), and plastic fibers. Microbeads are microspheres used as exfoliating agents in cosmetics and cleansing agents, like toothpaste, body scrubs, face wash, etc. Primary MPs are also used in industrial abrasives. Plastic fibers are used in synthetic textiles, for example, clothing made from polyester, nylon, etc., car tires, fishing gear, etc. Plastic pellets are about the size of lentils and are used to make larger plastic items after melting down and shaping into a final product. Primary MPs enter the environment when personal care products are washed or when there is unintentional loss from spills during manufacturing at industry or during transport.

Secondary MPs arise from synthetic textiles, tires, plastic ropes, road markings, etc. Synthetic textiles made of polyester, nylon, rayon, acrylic yarns, etc., shed millions of MPs during washing, and they are major contributors of MPs in the ocean. Sources of secondary MPs also include plastic packaging, wrapping paper, containers, toys, fishing nets, paint (acrylic) fragments (e.g., abrasion of paint), cigarette filters, household products, electronic and electrical equipment, etc. Single-use face masks and personal protective equipment kits were major sources of MPs during the COVID-19 era.

Apart from polluting the terrestrial environment, plastic wastes migrate to oceans or water bodies through rivers, shorelines, boats, etc., or they are directly disposed of in water bodies by humans (Figs 1A and B). Degradation of larger plastics to MPs occurs in either place by different factors like heat, sunlight, ultraviolet radiation (UVR), oxidation, hydrolysis, pH of the aquatic environment, wave action, wind abrasion, etc. Microorganisms (e.g., *Bacillus cereus*, *Actinobacteria* sp., *Pseudomonas* sp., *Aspergillus* sp., etc.) also help in degradation through the production of different enzymes.

Microplastics are now ubiquitous and are detected in water bodies, soils, plants, animals, humans, tap water, food, beverages, etc. They are easily ingested by animals and humans because of their micro-level sizes. They move easily through the food chain. Humans consume MPs not only through seafood but also *via* tap water, soft drinks, and terrestrial foods, or by inhaling MPs *via* air. The bioavailability of MPs is high because of their small size. Buoyant plastics and MPs float and are carried by ocean currents and wind across the environment.

Microplastics adsorb toxic chemicals and microbes on their surface and transport additives, sorbents, and microorganisms to the human body as the "Trojan Horse effect." Detrimental effects of MPs seem to be higher than macroplastics because of their higher surface area to volume

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Figs 1A and B: Indiscriminate disposal of plastics. (A) Roadside discarded plastics at hilly picnic spot at Ajodhya Pahar, Purulia; (B) plastics thrown in water body at Saheb Bandh, Purulia, West Bengal

ratio and favorable surface properties like hydrophobicity, porosity, surface topography, surface charge, or functional groups, etc.[2] Surface characteristics help concentrate toxic chemicals on MPs.

Different Plastics and their Uses

Commonly used plastics include PE, PP, PETE, PVC, PS, acrylic or polymethyl methacrylate (PMMA), PC, and ABS (Table 1).

PE is used most commonly. Different PE densities are low-density polyethylene (LDPE) (e.g., in plastic bags), medium-density PE (e.g., in gas pipes), high-density polyethylene (HDPE) (e.g., piping for water and sewer), and ultra-high molecular weight PE (UHMWPE) (e.g., in military body armor). As LDPE does not contain any harmful additives, its usage is safe for humans as packages for food and beverages. HDPE also does not contain phthalates or bisphenol A (BPA). However, its safety is untested. PP is heavier and stronger than PE. PP containers are also considered safe for food and beverages, though safety is untested.

Polyethylene terephthalate is the most common thermoplastic resin of the polyester family. It has low manufacturing costs. PETE is used for producing beverage and water bottles, polyester fabrics for clothing, and in the automotive and refrigeration industries, etc. It is anti-inflammatory, waterproof, and antiair (preventing the entrance of oxygen). Antimony trioxide is used as a catalyst for the production of PETE. PETE at high temperatures leaches toxic additives such as acetaldehyde, antimony, and phthalates. Antimony is a possible carcinogen.[3] Generally, PETE products are manufactured for single use only. With its reuse, toxic chemicals leach into food and beverages. PETE is easily recyclable.

Polyvinyl chloride is the third most produced synthetic polymer after PE and PP. It has rigid and flexible properties. PVC contains heavy metals, dioxins, nonylphenol, BPA, and phthalates.

Polystyrene is made of styrene monomers. Styrene often remains as an impurity in PS products. Prolonged exposure to styrene has neurotoxic and carcinogenic effects (lymphohematopoietic cancers).[4] PS products also contain BPA. Thermocol is an example of expanded PS, while styrofoam is extruded PS. Apart from PS (styrofoam), foamed plastics can also be produced from PU, PE, and HDPE. An Indian study showed that anthropogenic marine litter on the Indian coast in Kerala is mainly plastics (77.6%), and thermocol consists of 13% of all.[5]

Polycarbonates are used for packaging consumer goods, suitcases, and applications requiring optical clarity, like automotive lighting, safety goggles, and electronic display screens. PC contains BPA. ABS is hard and is a tough substitute for metal. ABS can decompose at high temperatures into its components styrene, butadiene, and acrylonitrile, which are carcinogenic. ABS can form ultrafine particles (UFPs) at low temperatures (such as 3D printing), which can damage the kidneys, lungs, and intestine. PA (nylon) is used for making ropes, clothes, toothbrushes, etc.

Additives and Sorbents

Additives are mixed with plastic polymers to make them easier to process and to improve their properties, like flexibility, strength, safety, cleanliness, color, and stability. Commonly used additives include plasticizers, flame retardants, antioxidants, acid scavengers, lubricants, light and heat stabilizers, colorants, antistatic agents, anti-inflammatory agents, slip compounds, fillers, and reinforcements (e.g., glass and carbon fibers). Additives are usually not chemically bound to plastics, so they can leach into the environment. Plasticizers improve the flexibility of plastics, particularly during thermoforming, shaping, and molding. They are most often used in PVC. Stabilizers extend the lifespan of polymers by preventing degradation from exposure to light, heat, humidity, or microorganisms. Fillers like mica, talc, kaolin, clay, calcium carbonate, barium sulfate, etc., improve the performance of plastics or reduce cost. Antioxidants protect plastics from oxidative degradation.

Additives and impurities of plastics are often toxic and found above recommended levels in different products. They are released into the environment during manufacture, use, or after discarding. Plastic particles adsorb, concentrate, and transport toxic chemicals, heavy metals, persistent organic pollutants (POPs), and emerging organic contaminants (still lacking published health criteria). Heavy metals (e.g., lead, mercury, chromium, cadmium, cobalt, antimony, titanium, etc.) are toxic, and they are either additives (like inorganic colorants) and/or sorbents. POPs are additives and/or sorbents and include short-chain chlorinated paraffins (SCCPs), polychlorinated biphenyls (PCBs), polychlorinated naphthalenes (PCNs), polybrominated diphenyl ethers (PBDEs), perfluoro-octane-sulfonic acid (PFOS), and perfluoro-octanoic acid (PFOA). POPs accumulate in fatty tissues of animals and humans and cause endocrine disruption, reproductive disorders, immune dysfunction, neurobehavioral disorders, genotoxicity, and carcinogenesis. Table 2 shows different additives, impurities, and sorbents of plastics and the health hazards related to them.

Table 1: Types of plastics, their properties, uses, and safety

Plastic code	*Polymer type*	*Property*	*Example of use*	*Recycling?*	*Safety, hazards, misc.*
1	PETE	Clear, tough, solvent resistant; barrier to gas, moisture and fluid; soften at 80°C	Beverage bottles, polyester fabrics, biscuit trays, salad dressing containers	Yes	Release EDCs like acetaldehyde, toxic antimony, phthalate
2	HDPE	Hard to semiflexible, resistant to chemicals and moisture. Waxy surface. Opaque. Soften at 75°C	Milk, juice and detergent bottles, shopping bag, food container, bottle cap, shampoo bottle, bucket, rigid agricultural pipe, plastic surgery	Yes	Safety untested
3	PVC-U (unplasticized)	Tough, can be clear, solvent welded, soften at 80°C	Plumbing pipe, siding, signs, roof sheeting, clothing, shower curtain, insulation, furniture	No	highly toxic, leaches phthalates, dioxins, etc.
	PVC-P (plasticized)	Flexible, clear, elastic, can be solvent welded	Blood bag and tubing, films, cable sheathing, garden hose, shoe soles, toys		
4	LDPE	Soft, flexible, waxy surface, translucent, scratches easily, soften at 30°C	Plastic wrap, shopping bag, refuse bag, baby bottles, laminates, snap on lids; packaging of milk, frozen foods and juices	No	Safe to use
5	PP	Hard but still flexible, waxy surface, translucent, solvent resistant, versatile, soften at 140°C	Packaging, stationeries, baby bottles, packaging yoghurt and beverages, diapers, textiles, carpets, potato chip bags, microwave dishes, kettles, straws, garden furniture, rope, lunch box	Yes	Safety untested
6	PS	Clear when not pigmented, may be opaque, glossy, semi-tough; affected by animal fat, acids and solvents but withstand alkalis and salt solutions; low water absorption; odor and tastes free; soften at 95°C	Egg containers, plastic cutlery, imitation glassware, protective packaging, foam drink cup, food insulation, packing peanuts, styrofoam packaging, DVD case	No	Leach BFR, BPA Styrene- neurotoxin, carcinogen
	PS-E (expanded)	Special types			
7	Others: PC, styrene acrylonitrile (SAN), ABS, PA	Property depends on plastic types SAN-resistant to boiling water PC-high impact resistance, high tensile strength and excellent clarity	Depends on plastics	Depends on plastics	Often contains toxic additives (e.g., BPA in PC) ABS- damage kidney, lung and intestine by building of UFPs

Phthalate

Phthalates are plasticizers that make plastics soft and flexible. They are commonly present in PVC. A small amount is present in PS. High molecular weight phthalates [e.g., di(2-ethylhexyl) phthalate (DEHP)] are used in the manufacture of food packaging, raincoats, clothes, medical devices, toys, hoses, vinyl flooring, shower curtains, etc. Dibutyl phthalate (DBP) and diethyl phthalate (DEP) are low molecular weight phthalates that are used as solvents in the manufacture of lacquers, coatings, varnishes, and personal-care products (e.g., cosmetics, perfumes, and lotions), etc. Phthalates are endocrine-disrupting chemicals (EDCs). They mimic estrogen and antagonize testosterone. Phthalates can cross the placenta. They can cross the blood-brain barrier (BBB). A developing fetus is highly vulnerable. Prenatal exposure causes premature births, disorders of the reproductive system (e.g., male sexual development disorders like cryptorchidism and shortened anogenital distance in boys), and intellectual development.[6] Postnatal phthalate exposure reduces vaccine response in newborns.[7] Phthalate exposure is linked to decreased sperm count, quality, and motility; infertility, obesity, diabetes, hypertension, asthma, and breast cancer. Infants and children are vulnerable because of frequent mouthing of objects like plastic toys and fingers, and direct skin contact with phthalate-containing substances. Butylbenzyl phthalate causes rhinitis and eczema in children and is a possible carcinogen. Replacement plasticizers like di-isononyl cyclohexane-1,2-dicarboxylate (DINCH), di(2-ethylhexyl) adipate (DEHA), and acetyl tributyl citrate (ATBC) are used as alternatives to phthalate plasticizers, but still, they can cause endocrine disruption, at least with high doses.[8]

Bisphenol A

Bisphenol A is an antioxidant and is used to make a hard and clear plastic (e.g., PC). BPA is found in epoxy resin, which acts as a protective inner lining of food and beverage cans. BPA can leach from plastics into drinks and food and release into house dust breathed in. The process of leaching is accelerated by storing acidic or basic items in plastic containers, at high temperatures, and with repeated washing. BPA is an EDC that mimics estrogen. Women exposed to BPA have polycystic ovarian syndrome (PCOS), obesity, recurrent miscarriages, and infertility. It reduces spermatogenesis and sperm viability. BPA causes hypothyroidism, affecting metabolism and development. Developing fetuses, neonates, and children are more vulnerable to BPA exposure compared to adults. Changes in serum lipid profiles and increased incidence of hypertension due to BPA increase the subsequent risk for cardiovascular disease (CVD) and stroke.[9] Higher urinary BPA concentration in humans is associated with CVD, hypertension, type 2 diabetes mellitus (T2DM), and hepatic dysfunction.[10,11] BPA is associated with neurobehavioral disorders (e.g., autism), abnormal male urethra/penile

Table 2: Additives and sorbents, and health hazards related to them

Additives	*Uses*	*Health hazards*	*Plastic types*
Phthalates	Plasticizer, fragrances	EDCs mimicking estrogen, interfere with testosterone, reduce sperms count and motility	PVC, PS
BPA	Antioxidant, can-liner	EDC, infertility, PCOD, miscarriages, obesity, T2DM, hypothyroidism, hypertension, dyslipidemia, CVD, stroke, disorders of neurobehavioral (e.g., autism) and urogenital development (boys), female early sexual maturation; breast, prostate, ovary and colon cancers	PC, PVC
BFRs	Electrical and electronic appliances, synthetic textiles	EDC, obesogen, hypothyroidism, developmental disorders of nervous and reproductive systems, carcinogenesis	PVC
Styrene monomers	Structure of PS. Remain as impurity in PS products	Neurotoxicity, can form DNA adducts, carcinogenesis	PS
Dioxins	Produced during combustion of PVC	EDC, disorders of brain and reproductive development, immune dysfunction, carcinogenesis	PVC and all plastics
PCBs	Stabilizer, plasticizer, flame retardant, dielectrics in electrical equipment or electronic manufacture	EDC, hypothyroidism, neurotoxins, carcinogenesis	PE, PP and all other plastics
Nonylphenol (alkylphenol)	Antistatic, antifog, surfactant, flame retardant	EDC, obesogen	PVC, PS
PFAS	Coating plastic products	EDCs, infertility; LBW, diabetes, obesity, thyroid disease, immune dysfunction; kidney and liver damage; testicular cancer	Teflon
Paraben	Antimicrobial preservative	EDC, obesogen, thyroid dysfunction, carcinoma breast	PA, PETE, PS, PE, PVC
DBT	Stabilizer, antifouling agent and pesticide	EDC, obesogen, neurotoxicity, DNA damage	PVC, PE
Polycyclic aromatic hydrocarbons	Used in making pesticides	Developmental and reproductive disorders, mutagenic, carcinogen	All plastics
Polyaromatic hydrocarbons	Produced when fossil fuels are burned	Developmental and reproductive disorders	All plastics

development, female early sexual maturation, and hormonally mediated cancers (e.g., breast and prostate cancers). Bisphenol S and bisphenol F have similar applications and similar endocrine-disrupting effects.

Flame Retardants

Flame retardants are added to plastics to prevent burning easily. They are used in electric and electronic equipment (e.g., computers, phones, and televisions), upholstery, synthetic textiles, etc. Flame retardants are POPs as they don't break down easily in nature. Brominated flame retardants (BFRs) in plastics include tetrabromobisphenol A (TBBPA) and PBDEs. BFRs are EDCs (like estrogen). They are also obesogens. They affect thyroid hormones and cause developmental disorders of the reproductive and nervous systems. PBDEs are reported to cause neurobehavioral abnormalities.[12,13]

Parabens

Methylparaben and propylparaben are antimicrobial preservatives that are used in pharmaceutical and cosmetic products and food packaging. They are EDCs and obesogens. They can cause thyroid dysfunction, breast carcinoma, and telomere shortening. They are emerging environmental contaminants and are adsorbed on MPs of PA (porous), PETE, PS, PE, and PVC.

Pesticides

Pesticides have an obesogenic effect and are adsorbed to MPs.

Alkylphenols

They are used as antioxidants, surfactants, antistatic agents, and flame retardants. Nonylphenol belongs to alkylphenols and is used in PVC production. Nonylphenol is an EDC and obesogen. Alkylphenols cause testicular damage, decrease sperm count and quality, and cause infertility in males.

Per- and Poly-fluoroalkyl Substances

Per- and poly-fluoroalkyl substances (PFAS) are "forever chemicals." They are used to coat plastic products and synthetic textiles. PFAS can also be adsorbed on MPs. They are EDCs. Health risks of PFAS include infertility, low birth weight (LBW), diabetes, obesity, thyroid disease, immune dysfunction, prostate, kidney, and liver damage, and kidney and testicular cancers. Polytetrafluoroethylene (PTFE), a thermoplastic fluoropolymer, also known as Teflon, belongs to polymeric PFAS and is used to make products with nonstick, waterproof, noncorrosive, and nonreactive surfaces. PFOA and PFOS were previously used as additives in PTFE. PFOA and PFOS belong to nonpolymeric PFAS, which are more toxic than polymeric PFAS. PFOA is linked to growth and developmental defects, hypothyroidism, LBW, hypertension, especially in pregnancy, immune deficiency, reduced vaccine response in children, kidney and liver disease, and carcinogenesis. PFOA activates PPAR receptors and causes hypercholesterolemia. Teflon nonstick cookware manufactured on or before 2013 contains PFOA. Teflon coating is now PFOA-free. Nonpolymeric PFAS can still be released into the environment from fluorinated polymers because of degradation. Inhaling fumes of Teflon may lead to fever, chills, headache, and body aches 4–10 hours after exposure, which persist for 12–48 hours. It is known as polymer fume fever or Teflon flu.

Organotins

Organotins are used in PVC or PE as stabilizers, antifouling agents, and pesticides. Examples include tributyltin (TBT) and dibutyltin (DBT). They are POPs. They are EDCs mimicking or antagonizing estrogen. They are also obesogens. DBT has neurotoxicity and can cause DNA damage. TBT (used in ship bottom painting as an antifouling agent) is found

to cause imposex, where female sea snails develop male sex organs (due to inhibition of aromatase, which converts androgen to estrogen). It is the best example of an EDC in wildlife.[14]

Dioxins

When plastics are burned in the air, dioxins are released. Dioxins are highly toxic and are important problems of medical waste incineration.[15] They are POPs. Brominated dioxins are EDCs. They affect the development of the brain, cause immune dysfunction, and are carcinogenic. Dioxins appear as impurities during the manufacturing of plastics like PVC containing BFRs.

Polychlorinated Biphenyls

They are dioxin-like substances with similar toxicities. They are used as stabilizers, plasticizers, or flame retardants in PE, PP, etc. They can be adsorbed to MPs. Marine food webs, particularly seabirds, are polluted with PCBs. PCBs are EDCs, neurotoxins, and carcinogens. PCBs are detrimental to marine life even at low concentrations and make seafood unfit for consumption. Prenatal and childhood exposures to PCBs cause neurotoxicity, leading to lower intelligence and motor skills, poor attention, and memory defects.[16,17]

Stabilizers

Stabilizers in plastics mainly include UVR and heat stabilizers. Benzotriazole ultraviolet stabilizers are EDCs, and they can also damage the liver, heart, kidney, etc. Metal salt blends are the main heat stabilizers, such as Pb, Ba, or Zn, which cause oxidative stress.

Polyvinyl Chloride

Polyvinyl chloride is very toxic and has additives like phthalates, BPA, BFRs, DBT, etc., which are EDCs and obesogens. PVC contains human carcinogen vinyl chloride.[18] Burning vinyl chloride produces dioxins and many dioxin-like compounds. While PVC and PETE both are toxic, PVC is more harmful as it is nonrecyclable.

Hazards of Plastics and Microplastics

Plastics cause damage to the environment, animals, plants, and human lives. Hazards are magnified as all of them are interdependent (Fig. 2).

Plastics pollute the environment from the beginning of their life cycle. Mining of petroleum resources and chemical extraction of plastics produce multiple toxins, hydrocarbons, volatile organic compounds, and particulate matter, which cause air and environmental pollution.[2] The process of plastic production utilizes energy from fossil fuel combustion, which elevates greenhouse gases. Carbon dioxide and methane are also released into the air when plastic wastes decompose biotically or abiotically. Incineration of plastics releases carbon dioxide and toxic substances such as heavy metals, dioxins, PCBs, and furans into the air.[19] Air pollution also occurs from dust containing MP fibers generated in households (e.g., from synthetic textiles) and industries. Uncontrolled dumping of plastics or landfilling leads to leaching of additives, causing soil and water contamination. Indiscriminate disposal of plastic waste causes natural beauty deterioration. It also causes sewage system blockage.

Habitats of marine animals are reduced by ocean garbage patches containing plastic debris. Plastics reduce the habitat of land animals also. Marine animals like turtles, fish, birds, invertebrates, seals, and other mammals get entangled in discarded plastics like nets or bottles, leading to restricted movement, ulcers, lacerations, starvation, and death. Animals may choke on plastic debris. Land animals are also killed by being choked and tangled in plastics. Entanglement also prevents the escape of animals from their predators. However, plastic ingestion by animals is seen more frequently than entanglement. Animals often mistake plastic waste for food. For example, sea turtles often confuse discarded plastic bags with their food, jellyfish. Seabirds confuse plastic debris for fish (e.g., cuttlefish) or squid as their natural prey. Grazing animals also eat plastics. Plastics can block or damage the intestinal tracts of animals. Charlton-Howard et al. first recorded a novel, plastic-induced fibrotic disease of the stomach in wild animals like seabirds, which is defined as plasticosis.[20] When seabirds ingest small pieces of plastics, they inflame their digestive tract. Persistent inflammation and repeated injuries cause scarring of tissues, affecting digestion, nutrition, growth, and survival. Excessive scarring reduces the capacity of the stomach also. Plasticosis affects epithelial integrity, causing enhanced susceptibility to infection or parasite infestation. Plasticosis of seabirds also raises concerns for other animals and humans who ingest plastics or MPs.

Microplastics affect marine life in both benthic and pelagic ecosystems. They accumulate in bodies of plankton (both zooplankton and phytoplankton). From plankton, MPs migrate into higher predators. Marine organisms, like fish, crustaceans, mollusks, and echinoderms, ingest MPs. Subsequently, higher predators and humans ingest them. Animal studies revealed that MPs damage the gastrointestinal (GI) system, reproductive organs, lungs, liver, brain, kidneys, placenta, and developing fetus, and cause malnutrition, gut microbial dysbiosis, developmental, reproductive, and other endocrine disorders, and malignancies. Reduction of fertility and increased mortality reduce biodiversity. Additives, polymers, unreacted monomers, impurities (e.g., residual catalysts or reaction by-products), and sorbed contaminants are responsible for the hazards. Hydrophobic MPs bioaccumulate in fatty tissues and biomagnify in organisms higher up in the food chain (humans are at the highest level).

Plastics affect plant life by changing soil permeability and affecting symbiotic microbes (e.g., nitrogen-fixing bacteria) living in it.[21] By reducing water percolation and soil aeration, plastics reduce the productivity of land. MPs can stunt the growth of plants due to sorbed contaminants like cadmium.[22] MPs cause phytotoxicity and reduce the growth of crops by inhibiting photosynthesis, blocking stomata, and inhibiting water absorption and nutrient transportation.[23] Humanity depends on the ocean ecosystem for food and oxygen. MPs, by preventing photosynthesis, reduce the ocean's ability to absorb carbon dioxide and synthesize food for marine life. Coral reefs are damaged by dragging nets and other products along sea beds. Plastics cover coral reefs, and by entanglement and toxin release, kill corals and algae. By reducing light penetration in water, plastics reduce the photosynthesis of algae (zooxanthellae) living in coral reefs. Reefs account for 1% of the

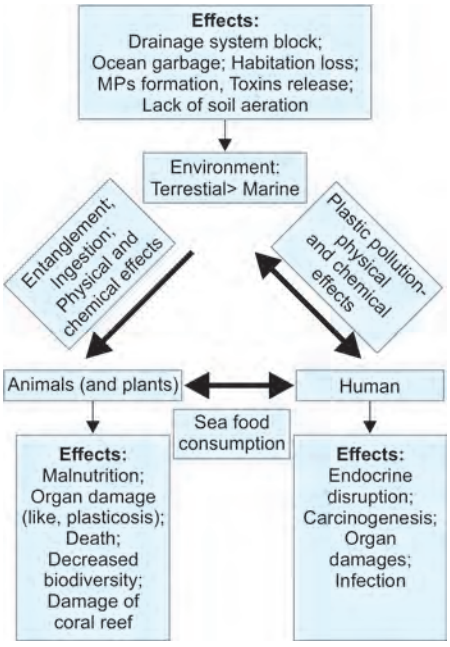

Fig. 2: Plastic pollution and its impact on One-Health

ocean floor but support 25% of marine species and provide 50% of the earth's oxygen. Loss of coral reduces the source of food and income for thousands of people and endangers the coastline from erosion, flooding, and storms. Plastics (like PVC) also damage the Prochlorococcus community (cyanobacteria identified in the last decade) of phytoplankton by leachates, which is a source of 10% of the earth's oxygen.[24]

Confirmed evidence regarding the human health hazards of MPs is rare. They are usually predicted from indirect evidence from *in vivo* animal studies or *in vitro* human studies. The lack of direct human studies is mostly due to the lack of a standardized method for quantifying MP exposure. Few epidemiological studies are present, which are mainly related to occupational exposure. It is unknown whether the toxicological impacts of MPs seen in animals translate to humans or whether MPs at levels now in the environment represent a real risk to humans. However, the continuous accumulation of MPs in the environment and their bioaccumulation and biomagnification are potentially threatening over time.

Damage to human health may occur at any stage of plastic's life cycle, like resource extraction, plastic production, waste generation, and degradation to MPs. MPs are highly threatening. Humans are exposed to MPs *via* food (e.g., seafood) and water consumption or inhalation of household and industrial dust. On average, humans ingest 0.1–5 gm of MPs weekly through various routes.[25] *Via* MPs, toxic substances, heavy metals (like arsenic, cadmium, mercury), insecticides, or pathogens migrate to humans. The human excretory system eliminates >90% of ingested MPs *via* feces. Retention and bioaccumulation occur depending on the size, shape, polymer type, and hydrophobicity of MP particles. MPs can harm human health *via* physical and chemical pathways, which depend on size, shape, surface functional groups, charge, hydrophobicity, additives, and adsorbed chemicals and microbes. Sharp MPs are physically more damaging. Weathered MPs are dangerous as they are prone to fragmentation, and have increased surface area, porosity, and altered chemical bonds. MPs/NPs are detected in different human tissues, including the gut, lungs, liver, spleen, kidneys, heart, bone marrow, brain, placenta, and bodily wastes like urine and stool.[26,27] Babies are exposed the most, as suggested by high levels of MPs in feces (especially PETE). MPs can enter the fetus *via* the placenta, infants *via* breast milk and baby foods, and children *via* food and liquid containers, toys, and synthetic textiles.

In vitro experiments with human cells and *in vivo* data generated with animals (e.g., mice, chicks, swine) showed that MPs cause oxidative stress (by synthesis of reactive oxygen species and inhibition of antioxidant enzymes like superoxide dismutase, catalase, and glutathione synthetase), immune activation (innate immunity), cell cycle arrest, necroptosis, apoptosis, autophagy, mitochondrial dysfunction, lipid metabolism disturbances, gut microbiota dysbiosis, and transfer of adsorbed chemicals and microbes.[28–31] Oxidative stress and inflammation are risk factors for T2DM, atherosclerosis, CVD, inflammatory bowel disease (IBD), etc.[29] Ingested or inhaled MPs can trigger local particle toxicity or cause metabolic, developmental, and reproductive disorders. MPs can cause genotoxicity, DNA adducts, and mutagenesis, which can lead to cancers.[32] Because of the exquisite sensitivity of developing fetuses, plastic exposures are linked to increased risks of prematurity, stillbirth, LBW, defects in reproductive and neurobehavioral development, and cancers. There is also the risk of different noncommunicable diseases later in life due to epigenetic modification in fetal life. Toxic chemicals in plastics potentially can damage fetuses, neonates, infants, and children at levels far below those that harm adults. EDCs are linked to infertility, obesity, T2DM, thyroid problems, and prostate and breast cancer. Thyroid-disrupting chemicals like BPA, phthalates, and PDBEs can harm pregnant women, developing fetuses, infants, and children.

Plastics can affect different organs throughout the body. Table 3 shows a list of potential health hazards of MPs as evident from *in vivo* animal, *in vitro* human, and some preliminary human studies. This list may help in the detection of novel cases in humans related to plastics.

Digestive System

Ingested MPs can cause physical irritation and injury to the mucous membrane of the GI tract. Inflammation and fibrosis can occur. Microbial infection can result from the weakening of the intestinal mucosal barrier. IBD and colorectal cancer (CRC) have an association with MPs. MPs are detected in the stool of IBD patients. Both *in vivo* animal and *in vitro* human studies revealed that MPs (e.g., PETE) induced gut microbiota dysbiosis.[7,33–36] Changes in gut microbiota have potential impacts on metabolism, immunology, and the gut-brain axis.

Endocrine

Additives are often hormonally active agents (EDCs) that cause endocrine, metabolic, developmental, and reproductive disorders (e.g., male and female infertility, PCOD, miscarriage, congenital malformations). As EDCs are lipophilic, they bioaccumulate in adipose tissue, persist there, and continue exposure. A subset of EDCs (additives and sorbents like POPs) is called obesogen. Obesogens reprogram the insulin-glucagon axis and increase the risk for obesity and T2DM. In this regard, MPs are thought to have a role in the pandemic of obesity spanning over the last few decades. The level of additives in MPs needs confirmation for their endocrine effects in humans. However, both animal and *in vitro* human studies revealed MP-induced ovarian and uterine fibrosis and testicular damage with reduced spermatogenesis.[37–39]

Respiratory

Sources of plastic microfibres in the air include synthetic textiles, building materials, waste-incineration byproducts, landfills, and house dust. Workplace exposure through inhalation occurs in the synthetic textile industry. MPs in sea salt aerosols are transmitted by sea waves and wind to the coast. MPs may cause oxidative stress, inflammatory damage, and fibrosis in airways and lung parenchyma.[40] High concentrations of PS and PP microfibres in the air cause the risk of COPD and interstitial lung disease (ILD) in long-term exposed workers.[41] Exposure to airborne microfibers among workers producing "flock" from nylon, polyester, polyolefin polyethylene, and PP causes flock workers' lung disease, which is characterized by fevers, asthma, ILD, hypersensitivity pneumonitis, chronic bronchitis, and lung cancer.[42] MPs are found to accumulate in both healthy and diseased lungs, which increase with aging and cause chronic inflammation, granuloma formation, ground glass nodules, and tumor formation.[43]

Toxicology

Potential toxicities of MPs are due to additives and sorbents, which include environmental toxins like heavy metals, pesticides, polycyclic aromatic hydrocarbons, and POPs.

Infectious Disease

Different parasites, bacteria (*Escherichia coli*, *Vibrio cholerae*), fungi, and viruses live together on MPs as a rich community, known as the "plastisphere." Many of these organisms are pathogenic.[44] The spread of organisms on buoyant plastics can occur *via* waterway or air. Microbes in waterbodies can colonize and form biofilm on plastic particles and spread waterborne diseases. Genetic transfer among microbes on plastic particles can develop resistant organisms. Stagnant water on plastic debris encourages arthropod-borne

Table 3: Potential human health hazards of MP

System	*Disorders*	*Details/pathogenesis*	*Prevention (major steps)*
Endocrine	Obesity, T2DM, hypothyroid, PCOD, infertility, changed pubertal timing	Due to EDC like BPA, Phthalates, etc.	Banning or restricting toxic additives
Congenital disorders	Male penile and urethral abnormalities	EDC, teratogenicity	Avoid MPs exposure at prenatal period
Gynecological and obstetrics	LBW, HTN in pregnancy, miscarriage, ovarian and uterine fibrosis	Inflammation, oxidative stress, EDC	Avoid MP exposure especially at prenatal period
Malignancy	Breast, prostate, testicular and liver cancer	Hormonally related. Genotoxicity. DNA adducts	Restriction of plastic and MPs exposure
GI tract	Plasticosis, microbiota dysbiosis, IBD, CRC, intestinal obstruction	Physical and/or chemical effects	Avoid plastic and MPs ingestions and restrict sea food ingestion
Nutrition	Malnutrition	Plasticosis, GI mucosal fibrosis	Avoid plastic and MPs ingestion
Infection	Malaria, dengue, cholera, *E. coli* infections	Breeding place and habitat of mosquitoes on stagnant water of discarded plastics. Plastics and MPs carry microorganisms	Proper waste disposal
Chest	Asthma, COPD, ILD	Inhalation of plastic microfibres > inflammation of airway and lung parenchyma > COPD/asthma/ILD	Prevent plastic incineration and dust generation (e.g., from synthetic textiles)
Brain	Parkinson's disease, Alzheimer's disease, autism, low IQ, ADHD, impaired fine motor development	Oxidative stress, inflammation, neurotransmitters alteration, decreased GFAP	Restriction of plastic usage and MPs exposure. Banning toxic additives
Psychiatry	Depressive disorders, manic depressive psychosis	Crossing of BBB by MPs/NPs. Effect on GFAP	Avoid consumption of MPs
CVS	CVD, hypertension	Atherosclerosis from chronic inflammation and dyslipidemias	Avoid consumption of MPs (PS)
Skin	Dermatitis	Contact with plastic with toxic additives	Avoid contact
Immunology	Activation of innate immunity, immunodeficiency	Loss of GI mucosal protection; chronic inflammation; immunotoxicity	Avoid consumption and inhalation of MPs
Others	Rhinitis, liver and kidney injury	inflammation, oxidative stress, mitochondrial dysfunction, apoptosis, physical effect	Avoid plastic incineration, inhalation and ingestion

diseases by providing a habitat and breeding place for mosquitoes like *Aedes aegypti* and *Aedes albopictus*, transmitting chikungunya, dengue, yellow fever, Zika virus, etc. Stagnant water in plastic debris also promotes the growth of bacteria such as *Leptospira* and harmful algae.

Immunology

Autoimmunity due to MPs has not yet been proved. In one *in vitro* human study, Lihua and Zhiyin showed that MPs have an increased risk of rheumatoid arthritis.[45] In an animal study (mice), Rawle et al. showed prolongation of chikungunya arthritis in the presence of MPs.[46] MPs can activate the inflammasome and cause pyroptosis.[47] MPs might influence IBD, as they are found in excess in the stool of IBD patients. MPs have potential effects on osteoporosis and osteoarthritis because of endocrine disruption and obesogenic effects.

Oncology

Microplastics potentially can cause breast, prostatic, and testicular malignancies. Cancers may occur due to genotoxicity and mutagenesis, or they may be hormonally related.

Neurology

Microplasticss can cross the BBB and cause oxidative stress and neurotoxicity. MPs (especially PS) can cause cognitive dysfunction and neurobehavioral changes by reducing acetylcholinesterase activity and increasing dopamine, 5-hydroxytryptamine, γ-aminobutyric acid, and acetylcholine levels.[28,48–50] MPs decrease glial fibrillary acidic protein (GFAP), which supports cell processes in the brain. A decrease in GFAP is associated with early neurodegenerative disorders like Alzheimer's disease and Parkinson's disease and can cause depression or major depressive disorder.[51–54] MPs can disrupt circadian rhythm and melatonin production, leading to sleep disturbance. Prenatal exposure can cause autism, attention deficit hyperactivity disorder (ADHD), and decreased intelligence.[55]

Cardiovascular System

The risk of atherosclerosis and CVD is increased due to MPs (e.g., PS)-induced lipid metabolism abnormalities and inflammation.[56]

Nutrition

Often, people consume clams and fish from local lakes as a major source of protein. So, the presence of LDPE and other plastics in lakes poses a threat of contaminating the food web of lakes.[57] Loss of coral and reduction of marine biodiversity also reduce food sources for people dependent on them.

Skin

Dermatitis can occur from direct contact with plastics or due to the leaching of additives or sorbents in water and the environment.

Allergy

Microplastics, their additives and sorbents, and products of incineration can lead to allergic contact dermatitis, asthma, rhinitis, sinusitis, and occupational allergic disorders.[58–60] Gut microbial dysbiosis causes immune dysregulation in children, which may precipitate allergy. MPs might increase the permeability of allergens by disrupting alveolar barrier function.[59]

Plasticenta

Microplastics can pass through the placenta. They cause ultrastructural alterations, like the narrowing of fetal capillaries and changes in mitochondrial and endoplasmic reticulum morphology in the human placenta.[61]

Occupational Disorders

Plastic production workers with vinyl chloride exposure are at increased risk of hepatic angiosarcoma and hepatocellular carcinoma.[18] Workers producing plastic textiles have an increased risk of bladder, lung, stomach, and esophageal cancers; mesothelioma and ILD.[62] Plastic recycling workers have increased rates of CVD, heavy metal poisoning, neuropathy, and lung cancer. Breast cancer risk and reproductive disorders have been reported in both women and men workers employed in the automotive and synthetic textile industries.[63] Flock workers' lung disease is seen among workers producing "flocks" from nylon, PE, PP, PETE, etc.[42]

People residing adjacent to plastic production and waste disposal sites experience increased risks of premature birth, LBW, asthma, COPD, childhood leukemia, CVD, and lung cancer. Thyroid and reproductive disorders, immune dysfunction, and physical and neurodevelopmental defects are reported in children living near e-waste recycling sites.[64]

Table 4: Prevention of plastic pollution

Method	*Explanation/details*
Reduce production	It reduces pollution from extraction to synthesis of plastics from petrochemicals; and controls supply and usage of plastics
Avoid toxic additives	Specifically for products associated with food, beverages and used for children like toys
Recycle	It reduces plastic wastes. Thin plastics are difficult to recycle
Alternatives of plastics	Products like, bamboo, paper, metals, natural fibers, silicone, etc. are better for ecosystem. Use alternatives of Teflon nonsticky utensils like, ceramic cookware
Bioplastics	Not generated from petroleum products. Better for recycling and composting. Environment friendly
Waste management	Proper landfilling and composting. Use of microbes and chemicals for decomposition, AOP, thermal degradation
Monitor plastic usage and MPs consumption	Restricted use of plastics especially single use plastics. Monitoring is essential for MP level in food and beverages, especially sea food
Remove plastics from environment to reduce secondary MPs generation	By collection, filtration and innovative methods. Use public transport and reduce tire erosion. Judiciously wash and dry synthetic textiles
Reduce MPs and toxin leaching procedure	Avoid microwaving, overheating, prolonged use of plastic containers with acid or corrosives

Prevention

Table 4 shows different methods of prevention of plastic pollution. Firstly, a cap on global plastic production is urgently required. Usage should be restricted, especially of single-use plastics and risky items. Safer choices of plastics include #2 HDPE, #4 LDPE, and #5 PP. BPA- and phthalate-free products should be used. Fragrance-free (phthalate-free) products are preferred. Waste generation should be reduced by reusing and recycling. Plastic disposal should be controlled. Plastic bags below 120 microns in thickness are banned in India. They are often single-use. Collection and recycling are difficult for them. Recycling costs are also higher. Thicker bags are reusable. Banned single-use plastic items in India include plastic cups, plates, cutlery, ice cream sticks, straws, wrapping, and thermocol. This banning needs strict implementation. The free provision of plastic bags at shopping stores should be stopped.

Plastic microbeads used for exfoliation in cosmetics are now being phased out in different countries. India also needs to ban them. Cosmetics containing "natural alternatives" to plastic microbeads, like pumice, oatmeal, or walnut husks, should be preferred. 100% virgin plastic production should be restricted, though production of virgin plastics becomes cheaper than recycled polymers with a fall in the price of petrochemicals.

The generation of secondary MPs should be reduced. Washers and dryers generate plastic microfibers from polyester and other synthetic textiles. Dryers generate more MPs than washers. Newer clothing sheds more microfibers. It should be used judiciously. Public or alternative transportation can reduce cars on the road. Car tires are major sources of MPs as they break down when driving. Dust particles around the home contain MPs. Air filters should be used for capturing MPs. Hard flooring is preferable, as carpeting releases large amounts of MPs. Reverse osmosis water filters can reduce MP ingestion. Consumption of shellfish should be reduced. It is of special concern as, in contrast to fish, shellfish is eaten entirely, including the stomach and intestines containing MPs. Farmers should reduce the use of plastic-coated fertilizers and pesticides, which are used for sustained effects.

The use of harmful additives in plastics that are in direct contact with food, beverages, and children should be banned or restricted. Prenatal exposure should be prevented. Microwaving food in plastic containers should be avoided as they leach toxins with heat. Ingredients of plastic are usually not mentioned on a product label, for example, on a shampoo bottle. Plastic product manufacturers or retailers should declare all ingredients of plastics and put a warning on them for potential health hazards. Importers, exporters, manufacturers, and retailers of plastic products should know environmentally safe product choices. Plastic producers should legally and financially be bound for the safety and end-of-life management of the products they produce and sell.

Waste Management

Thorough plastic waste collection, proper treatment, and safe disposal are essential. Indiscriminate disposal should be discouraged. Collection devices for discarded plastics should be placed in cities and along coasts. Macroplastics are collected easily, but MPs are difficult to remove. Options for wastewater management for plastic removal include advanced oxidation processes (AOPs), thermal degradation, adsorption, membrane treatment, and microbial degradation. AOP and thermal degradation accomplish rapid decomposition.[65] Microorganisms like bacteria (e.g., *Comamonas testosteroni* for PETE degradation), fungus, and microalgae (phytoplankton) help by enzymatically breaking down plastic polymers, which can be applied to sewage wastewater and other polluted places.

The scarcity of space for landfills is a major problem. Controlled landfilling is preferred. Uncontrolled landfills cause the leaching of harmful chemicals, polluting soil, air, and underground water. Landfills should be in a safe place to prevent environmental pollution and wildlife ingestion. Plastics in electronic waste (e-waste) have a large production volume. They should have proper disposal policies.

Plastic waste incineration is not favored as it causes atmospheric release of chemicals or fumes like halogenated additives, furans, dioxins, PCBs, different hydrocarbons, etc. They are often carcinogenic and damage the liver, spleen, bone marrow, and immune system, and have harmful effects on the eye, respiratory tract, skin, and nervous system.

Recycling of Plastics

Recycling is primary (mechanical reprocessing of plastics into a new product with equivalent properties), secondary

(mechanical reprocessing into a product with lower properties), tertiary (recovery of chemical constituents of plastics), and quaternary (energy recovery from plastics). Tertiary recycling is done by catalytic depolymerization or by controlled thermal degradation, such as thermolysis. Pyrolysis (plastics are heated without oxygen) and gasification (plastics are heated with limited oxygen) produce a range of hydrocarbons (liquid or gas), which can be used for energy. They also generate feedstock for repolymerization.[66] If toxic additives are present in plastics above permissible levels, the product should not be recycled.

Alternatives of Plastics

Jute, cotton, or paper should replace plastic bags. Nonplastic containers, for example, glass or metal like steel, are preferred for food and beverages. Paper cups and bamboo cutlery are preferred over plastics. However, paper cups are disposable and often are lined with a thin layer of PE, which generates MPs. Lots of trees are sacrificed, and recycling is difficult. Polylactic acid lining can make paper cups compostable. Clothing made of natural materials like cotton, silk, wool, hemp, and bamboo should be used instead of nylon or other synthetic materials. Bamboo is durable, sustainable, eco-friendly, grows rapidly, and has low production costs. Beeswax wraps are biodegradable and are natural alternatives to plastic wraps. Cardboard boxes are cost-effective, reusable, and are better for the environment. Instead of PFAS/Teflon-coated cookware, natural nonstick cookware alternatives like ceramic cookware, cast iron, carbon steel, etc., can be used. "Shola" can be used instead of thermocol.

Bioplastics

Though costly, bioplastics can replace petroleum-derived plastics in many applications. Instead of fossil fuel resources, wood, cellulose, sugar, corn starch, mushrooms, agricultural byproducts, and other natural substances are used for the production of bioplastics. Bioplastics are made by molecular and genetic engineering using microbes and plants. They are often biodegradable or compostable. However, most bioplastics do not break down in home composts and landfills but require commercial composting facilities. Bioplastics may also be nonbiodegradable and may contain significant amounts of conventional plastics. Polyhydroxyalkanoates are biodegradable bioplastics that are potential substitutes for thermoplastics.[67] Bioplastics are useful for controlled-release drug formulations and absorbable surgical sutures.

Silicone

Silicone is a safer and eco-friendly alternative to plastics, though expensive. Silicone is based on silicon atoms instead of the carbon atoms of conventional plastics. Silicon is extracted through heat from silica and mixed with hydrocarbons to create silicone. Silicone is used for electrical appliances, cooking products, and cosmetic and surgical implants to increase the size of body parts like breast implants or buttocks, or silicone hydrogel for optical lenses. Silicone, at least food-grade silicone, does not contain BPA, latex, lead, or phthalates. However, some silicone products still have EDCs or toxic monomers, for example, cyclotetrasiloxane (D4), cyclopentasiloxane (D5), cyclohexasiloxane (D6).[68] Silicone lasts longer, thus reducing waste generation. It is nonbiodegradable and can break into large pieces rather than MPs. Recycling is difficult but possible. It is safe to incinerate.

Tackling Injustice

Plastic wastes are often exported from high- to low-income countries. E-waste is of particular concern. Poor nations should be compensated for environmental harm, though plastic pollution is planetary in impact over time. Adverse effects of plastics disproportionately affect poor, marginalized people, manual workers in plastic production factories, fenceline communities, childbearing women, and children, who have little contribution and awareness of the pollution and lack political influence or resources to address it. The economic and social costs of plastic pollution are borne by citizens and taxpayers. Owners of petrochemical and plastic industries who benefit economically should bear their fair share for compensation of environmental and societal injustices.

Role of Physicians

Physicians should be vigilant in detecting plastic-induced health hazards, especially in exposed people, like persons consuming seafood and working in plastic factories. Special attention should be given to childbearing women and children, as they are more vulnerable. Research for evidence-making and clinical documentation is important. Clinicoepidemiological studies should be conducted. Despite the burden of treating multiple patients, the risk of planetary harm should not be neglected or forgotten, especially from activities in hospital settings. Plastics used in hospitals, like disposable gloves, intravenous bags, protective clothing, drapes, wipes, sharps, trays, syringes, connectors, tubing, pharmaceutical packaging, etc., cause exposure to toxic additives in patients. Also, the huge plastic waste generated in hospitals is incinerated, which causes air pollution. Physicians should decide on the judicious usage of plastics and alternatives to plastics. They should rethink reusable equipment (with decontamination) instead of single-use disposable products and should plan for the safe disposal of waste. Physicians should create awareness among people about plastic pollution and make people eco-conscious. They should treat vector- and water-borne diseases related to plastics and plan for mitigation strategies for potential health hazards. They should support environmentally sustainable policies and help campaigns, organizations, and initiatives that fight against plastics.

Future Direction

The extent of plastics-induced human health hazards needs evaluation. In-depth research is required to understand the mechanisms of MP toxicity and their movement in the human body. Toxicological studies commonly use synthetic microbeads, which are mostly uniform in size and shape. Studies should also be done with secondary MPs, which are of different sizes and shapes. Different polymers (apart from PS) should also be used. The concentration of MPs in foods needs evaluation to assess consumability. Additive and sorbed contaminants' bioavailability also needs evaluation. Determination of ingestion rate and total exposure of MPs by standardized methods is essential for human health risk assessment and planning mitigation strategies. General educational curriculums must include ways of plastic pollution reduction and waste management. Environmental medicine and climate medicine need incorporation into the medical curriculum. Public awareness programs are also important.

Conclusion

It is the ultimate time to be aware now to save the biodiversity of the world and the human species from the impacts of plastic pollution. As plants, animals, and humans are interdependent, the impact of plastic pollution on one group affects the others. So, the awareness of the "one health" concept is important to save the healthy balance in the environment. Plastics are continuing to accumulate. Even if we stop using plastics, accumulated plastics will continue to increase environmental MPs for decades. Now, global intervention to solve the problem is extremely important.

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POINT OF VIEW

Navigating the Artificial Intelligence Revolution: The Future of General Practice in India

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Abstract

This article explores the integration of artificial intelligence (AI) into general medical practice in India. It discusses global AI healthcare trends and India's strategic approach of leveraging AI for societal benefit through public service applications. The article examines Indian practitioners' skepticism and optimism regarding AI in enhancing diagnostics vs replicating nuanced clinical judgment. It highlights patients' data privacy concerns related to India's expanding digital health initiatives. Additionally, it identifies limitations in using AI for administrative tasks due to data constraints and the need for greater involvement of clinical users. Looking ahead, the article outlines future directions and challenges, including strengthening infrastructure, upskilling providers in AI, bolstering investment in translational research, and balancing technological innovation with ethical, human-centered healthcare delivery.

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Introduction

The integration of artificial intelligence (AI) into general practice signifies a transformation in healthcare, a change that is particularly pronounced in India. This article looks into the multifaceted role of AI in Indian healthcare, exploring its vast potential to enhance patient care, improve diagnostic accuracy, and streamline administrative processes. It also addresses the challenges inherent in adopting AI, such as data privacy concerns, the need for infrastructure development, and the importance of balancing technological innovation with the human touch in healthcare. Furthermore, the article looks ahead, considering the future trajectory of AI in India's healthcare landscape, where rapid technological advancements must align with the unique needs and dynamics of the Indian healthcare system. This exploration aims to provide a comprehensive understanding of how AI is reshaping general practice in India, offering insights into both the opportunities and obstacles presented by this technological evolution.

Artificial Intelligence in General Practice: Global Trends and Indian Context

Globally, AI is revolutionizing healthcare, offering unprecedented advancements in various aspects such as precision medicine, patient care, and operational efficiencies. In this global narrative, India has emerged as a leader, particularly in AI adoption by organizations, showcasing robust growth in AI innovation and contributions to AI research and publications. This leadership is reflected in India's remarkable ranking in these areas as per the Stanford AI Index 2022.[1]

In the Indian context, the government's "AI for All" initiative is pivotal. It represents a commitment to harness AI for broad-based, inclusive development across sectors, including healthcare. This initiative is not merely about technological advancement but also about ensuring that the benefits of AI reach every segment of society. An example of this commitment is evident in public service applications like the AI-enabled MyGov Helpdesk and the Umang app. These platforms demonstrate how AI can enhance government-citizen engagement by providing streamlined, accessible services. The MyGov Helpdesk, for instance, played a crucial role during the COVID-19 pandemic by disseminating vital information and facilitating vaccine-related services.[2,3]

These developments signify India's strategic approach to AI, where technology is not an end in itself but a means to achieve greater social good and inclusive growth. The government's focus on leveraging AI in public services reflects a vision where technology and governance converge to improve the quality of life and access to essential services for its citizens. This approach positions India not only as a significant contributor to the global AI landscape but also as a leader in demonstrating how AI can be harnessed for societal benefits, particularly in diverse and populous nations.[2,3]

Scepticism and Optimism among Practitioners

The integration of AI in healthcare has been met with a mix of skepticism and optimism among practitioners. While there is recognition of AI's potential in improving healthcare outcomes, there remains a level of caution regarding its capability to fully replicate the nuanced human judgment essential in medical practice. This skepticism particularly pertains to areas where physician-patient communication and clinical reasoning play a crucial role.[4] On the contrary, there is a growing sense of optimism about the role of AI in enhancing the quality and efficiency of diagnostics. This is especially true for the diagnosis of rare diseases, where AI's ability to analyze large datasets can aid in identifying patterns and conditions that might be challenging for human practitioners to detect. This dichotomy reflects the complex and evolving relationship between technology and traditional medical practice.[5]

Patient Perspectives and Data Privacy Concerns

The willingness of patients to share their health data for AI implementation is a complex issue, deeply intertwined with the trust and relationship they share with their general practitioners (GPs). This aspect of trust becomes even more critical in the context of India's rapidly expanding digital health initiatives. Data privacy and security concerns are paramount among patients, who are increasingly aware of the implications of their personal health information being used in AI applications.[6] Recognizing these concerns, the Indian government has prioritized the responsible adoption of AI and the cultivation of public

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trust. This is evident in the government's initiatives like the AI-enabled MyGov Helpdesk and Bhashini, which exemplify the careful integration of AI into public service delivery while respecting data privacy and security.[2,3] These initiatives reflect a concerted effort to balance technological advancement with ethical considerations and patient trust in a digital healthcare environment.

Artificial Intelligence in Administrative and Clinical Tasks

Research has identified certain limitations in the application of AI to administrative tasks in general practice. A key issue is the lack of standardized data sets, which hampers the development and effectiveness of AI applications. Moreover, there is a need for greater involvement of clinical users in the development process to ensure that AI tools are suitably tailored to the needs of healthcare practitioners.[7] Addressing these issues, the Indian government's IndiaAI program is a strategic initiative aimed at overcoming these barriers. By focusing on improving data quality, usage, and access, and fostering closer collaboration between AI developers and healthcare professionals, IndiaAI seeks to enhance the utility and effectiveness of AI applications in the healthcare sector.[3]

Future Directions and Challenges

The future trajectory of AI in general practice in India, while filled with potential, is not without its challenges. Key issues include data constraints, the need for robust technical infrastructure, and resolving medicolegal concerns. To harness the full potential of AI, a focused effort on upskilling healthcare providers in AI literacy and competencies is essential. Moreover, increased investment in translational research is critical for bridging the gap between theoretical AI advancements and their practical application in healthcare settings.[8] Ultimately, the successful integration of AI into general practice in India demands a well-rounded approach that equally weighs technological progress, human-centered care, ethical practices, and addressing practical on-ground challenges.

Conclusion

In summary, as we navigate through the AI revolution, it is clear that AI's role in general practice in India is a journey of innovation and adaptation. The landscape of healthcare in India stands on the cusp of significant transformation, driven by AI. This transformation requires a thoughtful and inclusive approach, harmonizing the cutting-edge capabilities of AI with the nuanced needs of human-centered care. Ethical considerations, infrastructural readiness, and legal frameworks form the bedrock upon which this AI-driven future must be built. By addressing these pivotal areas and fostering a synergistic relationship between technology and healthcare, India can set a global precedent in integrating AI into general practice, ultimately enhancing patient outcomes and revolutionizing healthcare delivery.

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CASE REPORT

Allergic Bronchopulmonary Aspergillosis, a Masquerader: Unveiling a Case of Nonresolving Pneumonia in an Asthmatic Patient

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Abstract

Background: Allergic bronchopulmonary aspergillosis (ABPA) is an immune-mediated hypersensitivity reaction to *Aspergillus*, a common environmental fungus. It is typically seen in asthmatic patients and those with cystic fibrosis. Lack of clinical suspicion and misdiagnosis often make the management of this condition difficult.

Case description: We are reporting a case of ABPA that was diagnosed and managed at Divisional Railway Hospital, Kharagpur, South Eastern Railway. The patient was a 66-year-old female who presented with fever, cough, and shortness of breath. She had been asthmatic since childhood and was on treatment for the same. On initial evaluation, her clinical and radiological features were suggestive of community-acquired pneumonia and were treated with antibiotics. However, the patient did not show improvement, and asthma also remained poorly controlled despite treatment. This raised the possibility of ABPA in this patient. The International Society for Human and Animal Mycology-ABPA (ISHAM-ABPA) working group criterion was used for making the diagnosis. She was successfully managed with low-dose steroids and itraconazole.

Conclusion: A high index of clinical suspicion is needed for timely detection of ABPA. Features of nonresolving pneumonia in the background of poorly controlled asthma raised the possibility of ABPA in this patient. Misdiagnosis and delay in initiating proper treatment can lead to permanent lung damage, such as bronchiectasis and lung fibrosis, which can even lead to life-threatening complications like cor pulmonale and respiratory failure.

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Introduction

Allergic bronchopulmonary aspergillosis (ABPA) is an often overlooked clinical entity. ABPA is an immunologic reaction to the inhaled spores of the fungus *Aspergillus*, which is described typically in patients with asthma or cystic fibrosis.[1] This condition is often misdiagnosed as tuberculosis, uncontrolled asthma, or pneumonia in the majority of patients.[2] We report a case of ABPA in a patient with nonresolving pneumonia and underlying asthma at Divisional Railway Hospital, Kharagpur, South Eastern Railway.

Case Description

A 66-year-old housewife came to the emergency department with a history of fever for 15 days, cough with expectoration for 10 days, and shortness of breath for 8 days (Fig. 1). The fever was low grade, not associated with chills or rigor. The cough was insidious in onset and gradually progressive, with no postural or diurnal variation. It was associated with whitish mucoid, mild to moderate amounts of sputum, which was not foul-smelling and not blood-stained. Shortness of breath was Modified Medical Research Council (MMRC) grade II, which progressed to MMRC grade III over 10 days, with an associated audible wheeze. Breathlessness was aggravated by exertion and coughing. For the above complaints, she was admitted to the local government hospital for 7 days, and since the symptoms didn't subside, she was referred to the Divisional Railway Hospital, Kharagpur, South Eastern Railway.

The patient is an asthmatic since childhood and was on metered dose inhaler (MDI) Formoterol 6 mcg + Fluticasone 250 mcg twice daily and as needed for the management of the condition. She had a history of repeated hospital admissions for similar complaints. She also had a history of allergic rhinitis and gastroesophageal reflux disease. Neither she nor her household contacts had tuberculosis in the past. The patient has had the habit of tobacco chewing for 50 years, and there is a family history of bronchial asthma in her grandmother.

On examination, she was found to have tachypnea. SpO_2 was 95%, and on auscultation, there was bilateral polyphonic wheeze and bronchial breath sounds in the right suprascapular area.

Chest X-ray posteroanterior (PA) view showed a heterogeneous opacity with air bronchogram, suggestive of consolidation in the right upper zone (Fig. 2). Her sputum tests for Gram stain showed no organism, and culture had no growth. Sputum Ziehl–Neelsen staining for acid-fast bacilli and GeneXpert test were done to rule out tuberculosis, but both were negative. Total counts at admission were 10,760 cells/mm^3 with neutrophil predominance. The absolute eosinophil count was 652 cells/mm^3.

She was treated with parenteral cefoperazone-sulbactam and oral clarithromycin initially, in line with the treatment for community-acquired pneumonia. However, as her symptoms were not subsiding, she also received a course of piperacillin-tazobactam, followed by meropenem and later linezolid. She also received nebulized salbutamol, ipratropium, and budesonide and took measures to optimize asthma control. Despite receiving the above treatment, her clinical symptoms and signs did not improve. Chest X-ray changes did not resolve, and newer infiltrates developed in the right lower zone (Fig. 3). A CECT thorax was done to rule out differential diagnoses like malignancy and ABPA. It revealed consolidation with air bronchogram in the apical and posterior segments of the right upper lobe and multiple patchy nodular shadows and ground-glass opacities in both lower lobes (right > left) (Figs 4A to C).

The background of asthma and the clinical picture raised ABPA as a probable cause and was investigated for the same. Her total immunoglobulin E (IgE) was 1769.60 IU/mL (>1000 IU/mL), *Aspergillus fumigatus-*

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Fig. 1: Photograph of the patient

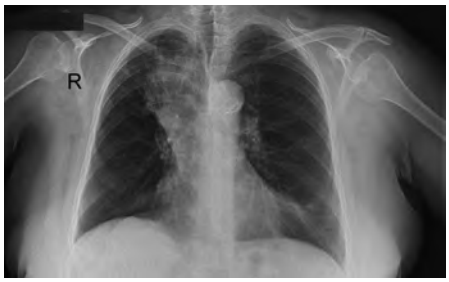


Fig. 2: Initial chest X-ray PA view revealing a heterogeneous opacity with air bronchogram in the right upper zone, suggestive of consolidation

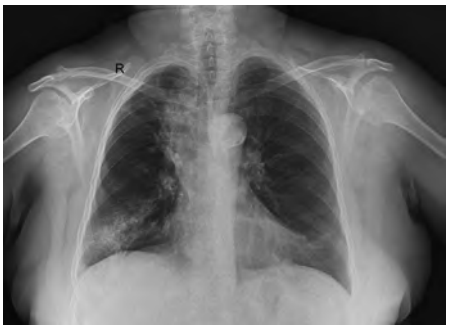
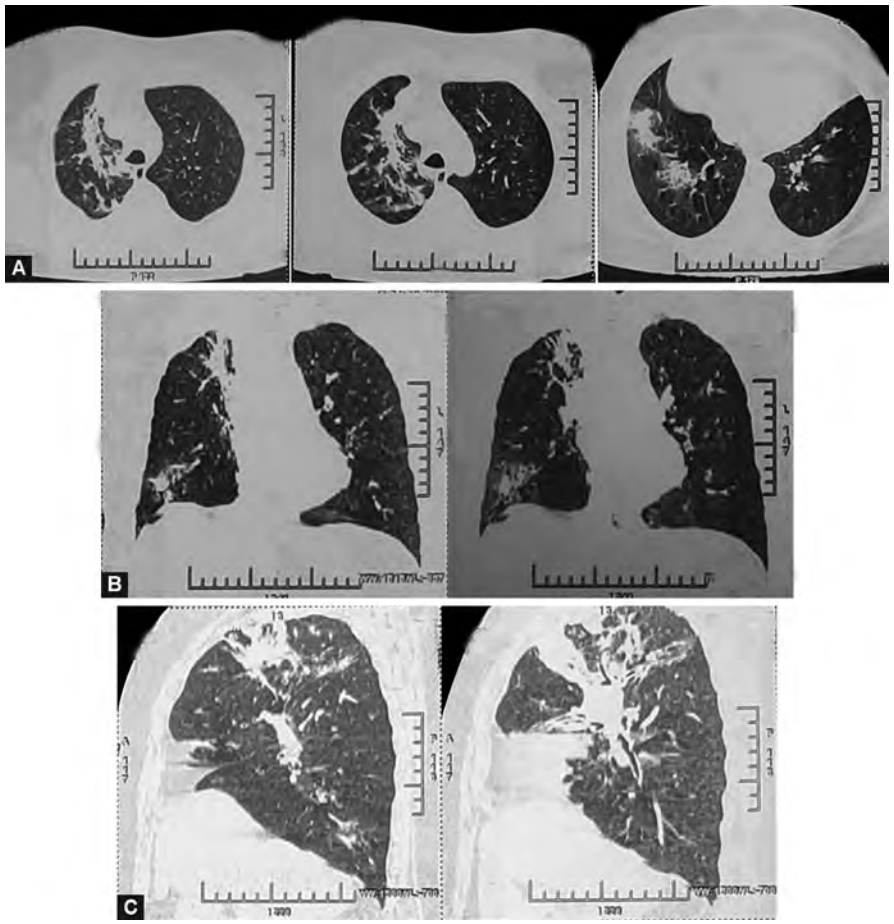


Fig. 3: Chest X-ray after 19 days showing persistent consolidation in right upper zone and appearance of new infiltrates in right lower zone



Figs 4A to C: CECT thorax done on 15th day showing consolidation with air bronchogram in apical and posterior segments of right upper lobe and multiple patchy nodular shadows and ground glass opacities in both lower lobes (right>left); (A) axial view; (B) coronal view; and (C) sagittal views

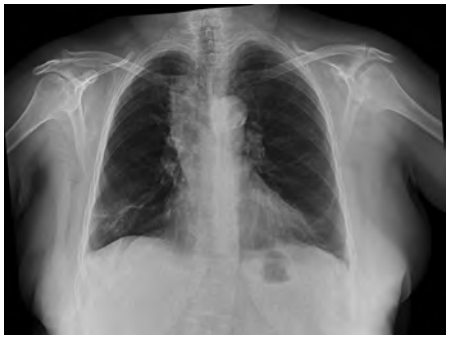


Fig. 5: Improvement in chest X-ray features after 1 month

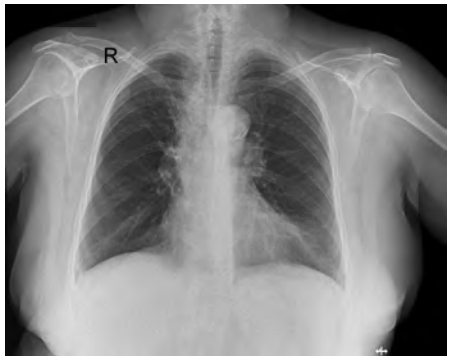


Fig. 6: Follow-up chest X-ray with complete radiological resolution after 6 months

specific IgE was 0.76 kUA/L (>0.35 kUA/L), and *A. fumigatus*-specific IgG was 16.58 U/mL (positive). The serum galactomannan antigen for *Aspergillus* was also raised (0.64 index). Her skin allergy testing reports from 2016 were reviewed. The diagnosis was made using the criterion put forward by the International Society for Human and Animal Mycology-ABPA (ISHAM-ABPA) working group (Table 1).[3] She was thus classified as stage 1 or acute ABPA, and treatment was initiated with low-dose steroids (Prednisolone 27.5 mg for the first 4 weeks, followed by 15 mg for the next 4 weeks, 7.5 mg for the next 4 weeks, and 5 mg for the last 4 weeks) and Itraconazole (200 mg twice daily for 24 weeks). On follow-up, her radiological picture, immunological parameters, and clinical symptoms improved, indicating she had responded to the treatment (Fig. 5). At 6 months, she was symptomatically better and showed radiological resolution (Fig. 6), and her absolute eosinophil count reduced to 190 cells/mm^3, with serum total IgE reduced to 495 IU/mL (>50% reduction). So, she was classified into stage 4 or the remission phase of ABPA.

Discussion

Aspergillus is a ubiquitous fungus that can lead to a wide variety of clinical manifestations. The lung diseases caused by *Aspergillus* range from aspergilloma, chronic necrotizing aspergillosis, and invasive pulmonary aspergillosis to ABPA (Table 2).[4] ABPA is a condition that is classically described in asthmatic patients and in those with cystic fibrosis.[3] Hinson et al., in 1952, first

Table 1: Criteria for diagnosis of ABPA, proposed by the ABPA-ISHAM working group[1]

Predisposing diseases
Asthma
Cystic fibrosis
Obligatory factors (both should be met)
A. Serum *A. fumigatus* specific IgE >0.35 kUA/L
B. Total IgE >1000 IU/mL
Additional factors (at least 2 out of 3)
A. Peripheral blood eosinophilia >500 cells/mm^3
B. Chest radiograph showing pulmonary infiltrates, which are transient
C. Presence of immunoglobulin against *A. fumigatus* (*A. fumigatus* specific Immunoglobulin G >27 mgA/L)

Table 2: Different lung conditions caused by *Aspergillus*[4]

Peculiarity of the host	*Clinical spectrum of pulmonary aspergillosis*
Normal individual	Absent sequel
Individual with cavitating pulmonary disease	
Chronic lung disease	Aspergilloma
Mildly immunocompromised person	Chronic necrotising aspergillosis
Immunocompromised individual	Invasive pulmonary aspergillosis
Bronchial asthma Cystic fibrosis	ABPA

Table 3: Staging of ABPA patients

Stage 0	Asymptomatic
Stage 1	Acute ABPA
1a	With mucoid impaction
1b	Without mucoid impaction
Stage 2	Response to ABPA
Stage 3	ABPA exacerbation
Stage 4	Remission phase
Stage 5	
5a	Treatment dependent ABPA
5b	Glucocorticoid dependent asthma
Stage 6	Advanced ABPA

described allergic pulmonary aspergillosis.[5] The overall burden of ABPA among patients with asthma in the world is estimated to be >4 million, according to a study conducted by Denning et al.[6]

The fungal species commonly implicated in this condition is *A. fumigatus*.[1] Fungal colonization in the airways of susceptible individuals leads to a chronic allergic inflammatory reaction characterized by IgE response and eosinophilic inflammation. This Th2-mediated reaction eventually causes tissue injury, airway remodeling, bronchiectasis, and fibrotic changes in the lung. The exact reason behind susceptibility to ABPA in certain individuals is not fully identified, though genetic factors play a role.[1,7–9]

Clinical features include poorly controlled asthma, shortness of breath, wheezing, fever, tiredness, coughing out plugs of brown-colored mucus, and rarely hemoptysis.[3] The identification of ABPA requires proper clinical suspicion. In a study by Kristen et al., in Munich, the average diagnostic latency from the start of symptoms to identification of ABPA was around 10 years.[10] Tuberculosis is a major confusing entity in developing countries, which accounts for around 33% of the misdiagnosed cases.[11] There are several reports of misdiagnosis of ABPA as pulmonary tuberculosis, especially from India.[2]

In our case report, the asthmatic patient had clinical features similar to those of nonresolving pneumonia, with a lack of improvement despite antibiotic therapy. The asthma remained poorly controlled even with optimization of asthma treatment. We recommend that, in patients with nonresolving pneumonia and an underlying asthma, the possibility of ABPA should be considered and investigated in that line as well. The diagnosis of ABPA is not obtained from a single test. It involves a combination of clinical workup, laboratory investigations, and imaging studies to rule out other potential differential diagnoses.

Even though there are different diagnostic criteria put forward, the ISHAM-ABPA working group criteria are from an Indian context and encompass the main features of the condition.[3] The diagnostic criterion is described in Table 1. The array of tests in the identification of ABPA are serum total IgE, *A. fumigatus* specific IgE, *A. fumigatus* specific IgG, and blood eosinophil count. *A. fumigatus* specific IgE is the preferred screening test for ABPA in asthmatics, as it is the most sensitive test (100%) and has good specificity (70%). Total IgE is not a good screening test, as it has low specificity (24%), but is a good tool in the diagnosis as well as follow-up of patients with ABPA.[2] Common radiological manifestations in acute ABPA are transient and fleeting opacities. Transient opacities can be in the form of consolidation, toothpaste opacities, finger-in-glove shadows, circular shadows, and atelectasis.[12] Bronchiectasis, which is typically central in location, develops in the later stages of ABPA. Even peripheral bronchiectasis can also occur. Other findings include high-attenuation mucus, mucoid impaction, and centrilobular nodules. According to a study by Agarwal et al., in 50% of ABPA patients, chest radiography was normal.[13] There are certain case reports of ABPA presenting as mass-like consolidation.[14]

The ISHAM working group has described seven stages for ABPA[1] (Table 3). Most of the patients are diagnosed in the acute stage, with symptoms suggestive of ABPA and fulfilling the diagnostic criteria. The acute stage can occur with or without mucoid impaction of airways. A response to ABPA treatment involves improvement of clinical and/or radiological features and reduction in serum total IgE by ≥25% from baseline within 2 months. The definition of exacerbation involves worsening of clinical and/or radiological features and an increase in total IgE by ≥50% from the new baseline value. An individual is in the remission stage if there is sustained improvement in clinical and radiological features and ≤50% increase of total IgE from the new baseline. Individuals who require treatment with steroids for control of ABPA or asthma are defined as treatment-dependent ABPA and glucocorticoid-dependent asthma, respectively. If not diagnosed and treated in time, advanced ABPA will result, where there is bronchiectasis and fibrosis amounting to permanent lung destruction. This can lead to cor pulmonale and respiratory failure.[15]

The two arms in the management of ABPA are corticosteroids for reduction of inflammation and antifungals for reduction of airway fungal load.[16] Several studies were done regarding the dose of steroids, and the ABPA-ISHAM working group proposes a dose of prednisolone as 0.5 mg/kg for the initial 4 weeks and then gradual tapering to 0.25 mg/kg for the next 4 weeks, 0.125 mg/kg for the next 4 weeks, and taper by 5 mg every week for a total duration of 16 weeks.[3] The preferred antifungal used in ABPA is itraconazole. Management of ABPA also includes optimization of asthma management.

Immunomodulatory therapies are in trial stages for the treatment of ABPA.[1] Patients should be monitored for clinical, radiological, and functional improvement, along with monitoring of serum IgE every 8 weeks.

Conclusion

A high degree of clinical suspicion is the key for timely detection of ABPA. If it is not diagnosed and treated in a timely manner, it will progress to advanced ABPA with irreversible bronchiectatic changes in the lung parenchyma, along with cor pulmonale and respiratory failure. ABPA should be in mind when a clinician is dealing with a patient of poorly controlled asthma in a background of peripheral eosinophilia, presence of radiological infiltrates, nonresolving pneumonia, or bronchiectasis. The absence of a single diagnostic test often makes the diagnosis difficult. Early diagnosis and proper treatment can result in a better prognosis of the patient's condition.

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CASE REPORT

Pseudomedian Claw Hand in Cortical Infarct: A Case Report

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Abstract

Isolated hand weakness due to stroke is rare and is often misdiagnosed as a peripheral lesion. Isolated central hand and finger weakness can present as pseudomedian, pseudoulnar, and/or pseudoradial nerve palsy. Here, we describe a patient who presented with a median claw hand due to cortical infarct.

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Case Description

A 57-year-old man presented with left hand weakness since 2 am. There was no dysarthria, difficulty in lifting the limb, or walking difficulty. He was a smoker and had a family history of diabetes mellitus. On examination, his vitals were normal. There was clawing of the index and middle fingers (median claw hand) (Fig. 1). In addition, he had weakness of all intrinsic hand muscles, long flexors of fingers and thumb, and extensors of fingers and thumb. Wrist extension, wrist flexion, elbow, and shoulder movements were normal. There was no arm drift or pronator drift. Deep tendon reflexes were normal. Plantars were flexor. The sensory system was normal. Gait was normal. There was no carotid bruit. Blood glucose at admission was 698 mg%. Electrocardiogram (ECG) was normal. Echocardiogram (ECHO) showed left ventricular hypertrophy. Computed tomography (CT) of the head showed subtle hypodensity in the right frontal region. Magnetic resonance imaging (MRI) of the brain showed acute infarct involving the right precentral gyrus lateral to the hand knob region (Fig. 2). Magnetic resonance (MR) angiography did not show any major vessel stenosis or occlusion. Nerve conduction study was not done due to typical clinical presentation and imaging findings. Moreover, examination showed mild weakness of ulnar and radial innervated muscles.

Fig. 1: Left hand showing flexion of proximal and distal interphalangeal joints of index and middle fingers with extension of MCP joints (median claw hand)

Discussion

Isolated hand weakness due to stroke is rare and is often misdiagnosed as a peripheral lesion. Isolated central hand and finger weakness can present as pseudomedian, pseudoulnar, and/or pseudoradial nerve palsy. Claw hand is a condition that causes curved fingers that appear like a claw of an animal. It is characterized by hyperextension of metacarpophalangeal (MCP) joint and flexion of interphalangeal joints. It is commonly caused by ulnar nerve palsy (ulnar claw hand), but it can also be caused by median nerve palsy (median claw hand) or any other diseases selectively affecting intrinsic hand muscles. It is characterized by overaction of long finger extensors and long finger flexors and underaction of proximal interphalangeal (PIP) and distal interphalangeal (DIP) extensors (lumbricals and interossei). Ulnar claw hand is characterized by flexion of PIP and DIP joints of the ring and little finger with hyperextension at MCP joint. Median claw hand is characterized by clawing of the index and middle fingers.

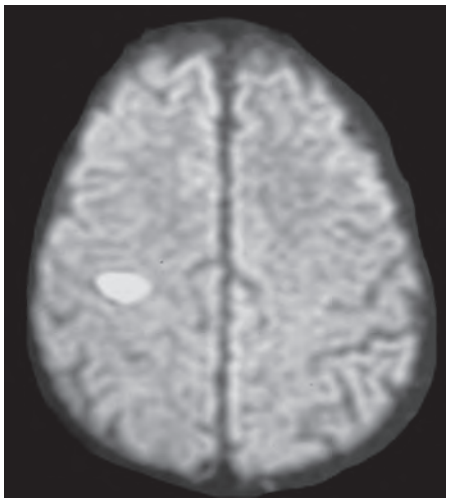

Fig. 2: Magnetic resonance imaging of the brain axial diffusion weighted image showing infarct over the right hand knob area

Isolated pure motor distal hand palsy is often due to precentral hand knob lesion.[1] Hand knob stroke accounts for 0.9% of all strokes. It has been pointed out that finger paralysis caused by a cortical lesion can be partial, with only few fingers involved, producing a so-called pseudoradicular pattern. There was a difference in the severity of paralysis between radial side and ulnar side, and this seemed to be a characteristic of motor paralysis of fingers caused by a cortical lesion. This may be important for differentiating hand paralysis due to a cortical lesion from that caused by pyramidal tract lesions at other sites.[2] Although our patient presented with a median claw hand-like presentation, examination suggested a more proximal involvement. A small cortical infarct should be suspected in cases of acute median claw hand-like presentation when examination suggests involvement of muscles outside median nerve territory. There are only a few reports of cortical infarcts presenting as pseudomedian claw hand.[3]

Conclusion

Small infarcts in hand knob area of motor cortex can present like a median nerve palsy, and often the acuteness of presentation and involvement of other nonmedian innervated muscles clinches the diagnosis.

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CASE REPORT

Progressive Disseminated Histoplasmosis with Primary Adrenal Insufficiency in Immunocompetent Person: A Case Report

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Abstract

Histoplasmosis, also referred to as Darling's disease, is mainly caused by the thermally dimorphic fungus *Histoplasma capsulatum*. It is usually contracted by inhaling fungal spores found in soil contaminated with bat or bird droppings, often during activities like cave exploration. Although endemic in certain regions of India, such as the eastern part, and sporadically in southern and northern states, histoplasmosis can manifest with varied clinical presentations, ranging from asymptomatic to severe disseminated disease affecting multiple organs. Adrenal involvement, though relatively uncommon, can lead to adrenal insufficiency, especially in immunocompetent individuals, with bilateral adrenal enlargement being a characteristic feature in imaging studies. This report discusses the case of a 51-year-old farmer from Haryana, India, who was diagnosed with progressive disseminated histoplasmosis (PDH) resulting in primary adrenal insufficiency. Although tuberculosis or malignancy was initially suspected, imaging studies and biopsy results confirmed histoplasmosis as the root cause. This case emphasizes the necessity of including histoplasmosis in the differential diagnosis of primary adrenal insufficiency, especially in endemic areas, and highlights the importance of early detection and appropriate management of this potentially life-threatening disease.

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Introduction

Histoplasmosis, also known as Darling's disease, is caused by the thermally dimorphic fungus[1] *Histoplasma capsulatum*. It is typically contracted through the inhalation of microconidia or hyphal fragments present in soil contaminated with bird or bat droppings, often during cave exploration. In India,[2] the disease is endemic in certain regions of the east, including parts of West Bengal, Assam, and the Gangetic plains, with sporadic cases reported from southern to some northern states. Clinical manifestations range from asymptomatic infection to systemic involvement, including fever, malaise, hepatosplenomegaly, lymphadenopathy, pancytopenia, disseminated intravascular coagulation, skin lesions, encephalopathy, focal parenchymal lesions, renal failure, and adrenal insufficiency, particularly in severe and disseminated cases via hematogenous spread, depending on the patient's immune status.

Progressive disseminated histoplasmosis[3] (PDH) can affect multiple organs, with the lungs, bone marrow, spleen, liver, adrenal glands, meninges, brain, and mucocutaneous membranes being the most commonly involved. In individuals with a healthy immune system, disseminated histoplasmosis is rare. However, when widespread disease occurs in immunocompetent individuals, as seen in our patient, the adrenal glands are the most frequently affected organ.[4]

Adrenal histoplasmosis typically presents on imaging as bilateral adrenal enlargement, distinguishing it from the bilateral adrenal atrophy seen in autoimmune adrenalitis. When bilateral adrenal enlargement is identified in a patient with primary adrenal insufficiency, the differential diagnosis includes tuberculosis, primary or metastatic malignancy, lymphoma, infiltrative disorders, and bilateral adrenal hemorrhage. In our patient, a definitive diagnosis was established through an image-guided biopsy.

Adrenal histoplasmosis is an uncommon cause of adrenal insufficiency. Studies[5] indicate that approximately 30% of patients with disseminated histoplasmosis exhibit adrenal involvement, though only a small proportion (15–20%) progress to adrenal insufficiency. While early systemic symptoms of disseminated histoplasmosis may mimic those of adrenal insufficiency, significant adrenal gland destruction leading to hypofunction is typically a late manifestation of chronic disseminated disease. Laboratory findings, vital signs, and physical examination features of primary adrenal insufficiency may include hypoglycemia, dehydration, orthostatic hypotension, and hyperpigmentation.

Case Description

A 51-year-old farmer from the Rewari district of Haryana, India, presented with a 6-month history of reduced appetite, significant weight loss (20 kg), generalized myalgia, fatigue, salt cravings, mild abdominal discomfort, and skin darkening. He had no known comorbidities or travel history but reported a history of alcohol consumption, tobacco use, and hookah smoking. Family history was insignificant. On examination, the patient had a Glasgow Coma Scale (GCS) = E4V5M6, pulse rate of 88/minute, blood pressure (BP) = 98/60 mm Hg, random blood sugar (RBS) = 105 mg/dL, and was maintaining a saturation of 98% on room air. Hyperpigmentation could be appreciated on the sun-exposed areas, palmar creases, and tongue (Fig. 1). No lymphadenopathy or hepatosplenomegaly could be appreciated.

He was worked up for the abovementioned complaints. Labs were suggestive of anemia, hyponatremia, hyperkalemia, normal thyroid stimulating hormone (TSH), and erythrocyte sedimentation rate (ESR) = 44 mm/hour. Serum cortisol levels were on the lower side (76.2 nmol/L).

Human immunodeficiency virus (HIV) status was nonreactive. Chest X-ray was grossly normal. The patient had HbA1c of 7% and was diagnosed as a case of type 2 diabetes mellitus, although he was not compliant with the treatment.

Upper gastrointestinal endoscopy (UGIE) was suggestive of duodenitis.

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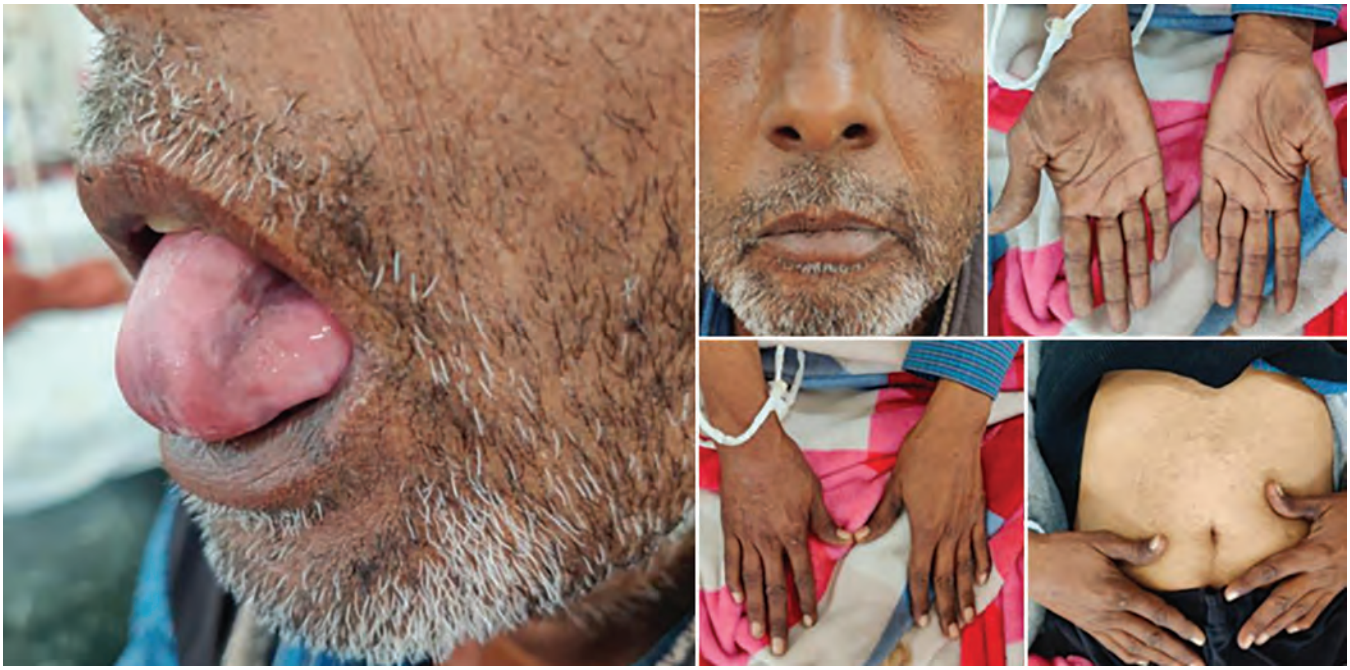

Fig. 1: Hyperpigmentation was noticed on sun-exposed areas, palmar creases, and the tongue

Contrast-enhanced computed tomography (CECT) abdomen revealed bilateral adrenal soft tissue nodular mass lesions showing mild contrast enhancement with subcentimetric periportal lymph nodes with mild mesenteric panniculitis. The liver and spleen were grossly normal.

Differential diagnoses of tuberculosis and malignancy were kept. CEA and CA-19.9 levels were normal.

Positron emission tomography-computed tomography (PET-CT) scan was planned, which showed mildly enhancing hypodense Space-occupying lesions (SOLs) having a lobulated outline, symmetrically involving bilateral adrenal glands, likely representing a sequela of granulomatous inflammatory etiology (representing a possibility of either tuberculosis or histoplasmosis) rather than a neoplastic cause (Fig. 2). Numerous tiny subcentimetric, enhancing nodules within bilateral cerebral hemispheres (parietal-temporal with no involvement of the pituitary gland) likely represent sequelae of central nervous system (CNS) involvement by similar granulomatous inflammatory etiology with few, small size to mildly enlarged, abnormally fluorodeoxyglucose (FDG) avid lymph nodes within the level IB of bilateral cervical regions and level II of the left cervical region.

Lumbar puncture was done, although it was inconclusive.

Imaging-based biopsy was taken from the adrenal SOL, which showed a large number of yeast forms of Histoplasma species (Gomori Methenamine silver stain was positive) (Fig. 3).

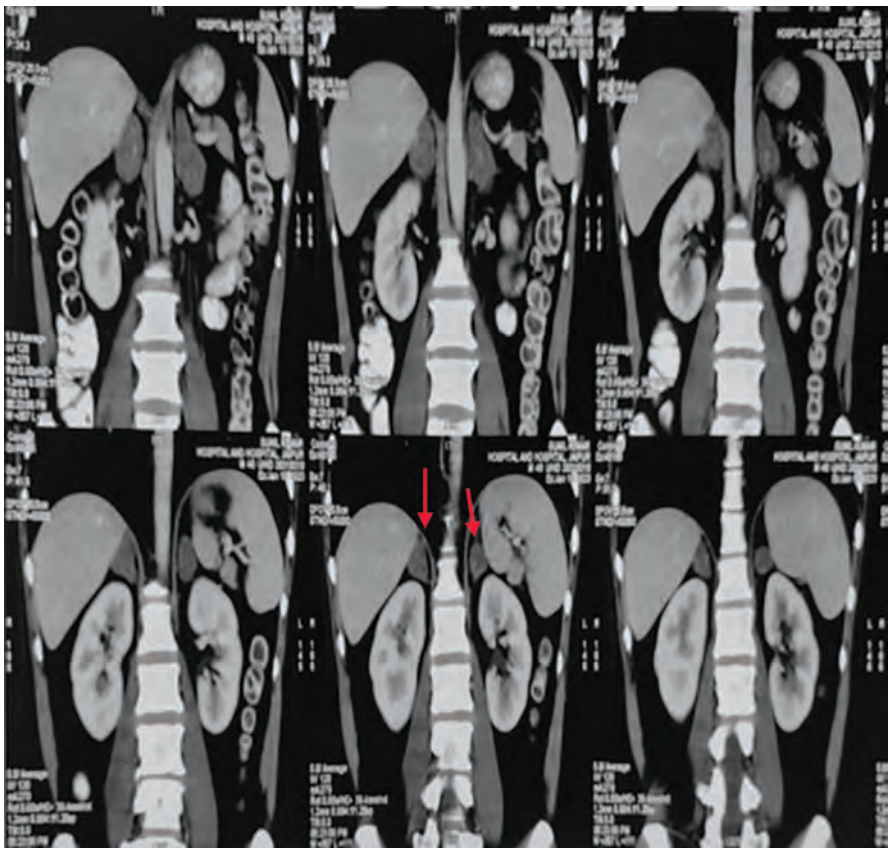

Fig. 2: Mildly enhancing, hypodense SOL symmetrically involving bilateral adrenal glands (red arrows)

He visited us with all the above reports in outpatient department (OPD) and was admitted for the treatment of primary adrenal hypocortisolism (PDH). He was treated with liposomal amphotericin B (5 mg/kg/day) for 4 weeks, along with glucocorticoid and mineralocorticoid supplementation for primary adrenal insufficiency. Upon discharge, he was prescribed oral itraconazole (200 mg twice daily) for 1 year.

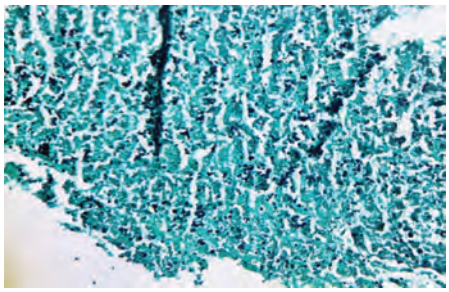

Fig. 3: A large number of yeast forms of histoplasma species (Gomori methenamine silver stain was positive)

CE-MRI brain showed multiple granulomatous lesions in both temporal lobes, right basal ganglia, and left parietal lobe with minimal perilesional edema along with chronic ischemic microangiopathic changes.

Discussion

We present a case of PDH in an apparently immunocompetent farmer from Rewari, Haryana, India. The patient manifested with primary adrenal insufficiency, most likely resulting from PDH—a rare occurrence in immunocompetent individuals. Diabetes may have been a potential predisposing factor.

Disseminated histoplasmosis can present in acute, subacute, or chronic forms, typically characterized by symptoms such as weight loss, weakness, fever, malaise, and anorexia—symptoms that may be attributed to a fungal infection but could also indicate adrenal insufficiency.

Adrenal involvement[5] occurs in approximately 30% of patients with disseminated histoplasmosis. However, adrenal insufficiency in the context of histoplasmosis is relatively rare, affecting only about 15–20% of those with adrenal involvement. Primary adrenal histoplasmosis and adrenal involvement during dissemination are more frequently observed in males,[6] although the reason for this is still unclear. It typically presents as bilateral adrenal masses, appearing as symmetrical adrenomegaly with preserved adrenal contours, central hypodensity, and peripheral enhancement, as observed in our patient.

Central nervous system involvement[7] occurs in 5–10% of individuals with disseminated histoplasmosis. It typically presents[8] with symptoms such as headache, confusion, altered mental status, ataxia, and visual disturbances. Imaging studies often reveal focal mass lesions, ventricular enlargement, meningeal enhancement, and T2/FLAIR signal abnormalities.

Advanced diabetes mellitus can lead to an immunocompromised state. However, in our patient, we considered him immunocompetent, as his HbA1c was 7% and he had no signs of micro- or macrovascular complications associated with diabetes. Additionally, his retroviral screening was negative, and he did not report any history of recurrent infections. Given these factors, we did not pursue further investigations to assess his immune status.

Individuals such as farmers and poultry keepers, whose occupations involve handling soil—especially soil contaminated with bird and bat droppings—are at a higher risk of acquiring infections like histoplasmosis.

Conclusion

Disseminated histoplasmosis is a significant but rarely reported cause of primary adrenal insufficiency in immunocompetent individuals. Although factors in our patient suggested tuberculosis or malignancy as the primary differential diagnoses, characteristic imaging and laboratory findings, along with the detection of *H. capsulatum* on biopsy from the adrenal mass, pointed to histoplasmosis as the most likely underlying cause. This case underscores the importance of considering disseminated histoplasmosis in the differential diagnosis of primary adrenal insufficiency.

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CASE REPORT

A Stitch in Time Saves Nine

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Abstract

Endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) procedure is nowadays routinely used for diagnostic sampling of mediastinal lymph nodes. Fracture of the needle during the procedure has rarely been reported in the past.

This reports the successful retrieval of the broken fragment of the needle using a snare through a fiberoptic bronchoscope. The accidental breakdown of the needle was encountered while performing EBUS-TBNA from the subcarinal lymph node.

The cardinal management in such emergencies in resource-constrained settings can be accomplished by maintaining calm, using multiple instruments judiciously in different combinations, and tapping the potential expertise of the team to the fullest.

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Introduction

The procedure of endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) has become an integral part of the diagnostic work-up in the routine practice of respiratory physicians. Ever since its introduction in 2003, the technique has revolutionized our approach toward the assessment of mediastinal lymphadenopathy.[1] Over the years, the use of EBUS has increased, as the procedure is easily tolerated, cost-efficient, safe, and less invasive than other procedures like mediastinoscopy or core-needle biopsy.[2]

Cases of lung abscess, empyema, mediastinitis, and mediastinal abscess after EBUS-TBNA have been reported in the past. Needle breakage also finds mention.[3] Here, we report a case of breakage of the needle during the procedure of EBUS-TBNA. The complication was managed successfully with the use of available equipment and resources.

Case Description

A male patient, 67 years of age, presented with complaints of generalized weakness, weight loss, and loss of appetite over the past 2.5 years. It was accompanied by breathlessness and a dry cough for the last 1.5 years. He was nondiabetic and a nonsmoker. On examination, the patient also had an enlarged cervical lymph node in the neck. On respiratory system examination, the patient had reduced breath sounds in the right mammary and right infrascapular regions. Chest radiograph showed a right peri-hilar homogeneous opacity. Contrast-enhanced computed tomography (CECT) of the thorax reported bilateral lung field hyperinflation with extensive centrilobular emphysema and a mass-like opacity in the right middle lobe (medial segment). It also showed low-density areas within the right middle lobe (medial segment) with cutoff of segmental bronchi, suggestive of bronchiectasis with mucus impaction/malignancy. Multiple discrete lymph nodes were present in the right lower paratracheal, paraaortic, subcarinal, right hilar, and left hilar regions. Fine needle aspiration cytology (FNAC) from the cervical lymph node was suggestive of reactive neutrophilic leukocytosis.

EBUS-TBNA was performed with a convex probe EBUS scope (EB-530US; Fujifilm Healthcare, Lexington, Massachusetts, United States) under conscious sedation from station 7 (subcarinal lymph node) using a 19 G Olympus ViziShot flex needle. Three passes with the needle were taken. The needle moved smoothly inside the lymph node in all the initial three passes. While taking the fourth pass, the needle was intact, and motion was well visualized in the ultrasound view. However, when the needle assembly was removed, a broken segment of the needle was localized at the point of insertion, as seen directly through the endobronchial view of the bronchoscope (Fig. 1). The needle assembly was removed gently along with the EBUS scope. The expertise of the team in performing fiberoptic bronchoscopy was utilized. The fiberoptic bronchoscope (BF-H190; Olympus Medical Systems, Shinjuku-ku, Tokyo, Japan) was introduced through the oral route immediately, followed by a snare through its working channel to retrieve the broken needle, thus preventing further complications (Fig. 2). The postprocedure period was uneventful. The size of the broken segment was 19 mm (Fig. 3). There was no damage to the EBUS scope or fiberoptic bronchoscope. The patient was kept overnight under observation and discharged the next morning without any further complications. The EBUS-TBNA-guided FNAC report was inconclusive.

Discussion

Needle breakage as a complication of the EBUS-TBNA procedure is rare. The Japan Society for Respiratory Endoscopy carried out a nationwide survey specifically on complications associated with EBUS-TBNA procedures. Breakage of the needle was reported in 0.20% of cases.[4] Although rare, EBUS needle assembly breakdown can occur due to numerous reasons, such as

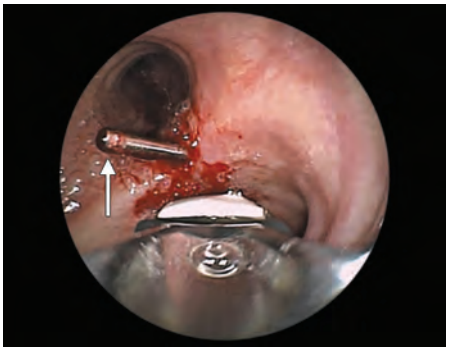

Fig. 1: Showing the broken fragment of the needle (white arrow) through EBUS scope

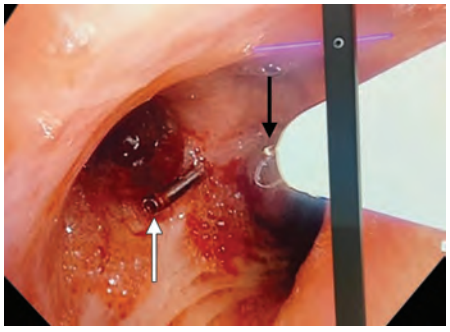

Fig. 2: Showing the broken fragment of the needle (white arrow) and the snare (black arrow) through fiberoptic bronchoscope

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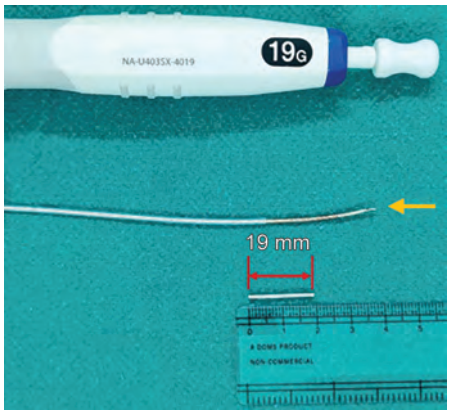

Fig. 3: Showing the broken fragment of the needle (19 mm) retrieved through the fiberoptic bronchoscope with the use of a snare and the remaining assembly of the 19 G needle (yellow arrow) used through the EBUS bronchoscope

hard cartilaginous rings and calcified lymph nodes, the tangential position of the needle in sampling nodes requiring higher angulation, manufacturing defects at the juncture of the needle tip with the sheath, kinking at the weakest point in the needle assembly, and multiple punctures.[5] Needle breakage has been reported after the second, third, or even after multiple passes in the past.[2,3,5]

According to previous case reports, successful removal of the broken needle was possible in the majority.[2,3,6–10] In a few cases, unsuccessful retrieval attempts were seen, with broken fragments migrating further down into the dependent lobe of the lung (later expelled out by coughing) or migrating to the GI tract (later expelled out along with feces).[5,11–13] Inflammatory reaction, migration, perforation, vascular disruption, and embolization are the various possibilities if the broken needle fragment is not expelled but stays retained.[12,14] In one case report, inflammatory changes and mucosal thickening occurred within the lymph node, where the broken needle was retained during the procedure. The fragment could not be taken out, and further consequences of the fragment retention remained unknown.[14] In another case, there was needle breakdown requiring mechanical ventilation due to near-fatal hemorrhage.[12]

Thorough visual inspection of the needle assembly and its integrity before and after every pass, along with avoidance of excessive needle bending, is an integral part of the standard operating procedure for minimizing the risk of needle breakage. In this case, the sudden breakage of a segment of the needle occurred even after exercising all the caution and following every step with respect to needle usage. Timely removal of the broken segment with a snare through the fiber-optic bronchoscope helped prevent further complications and referral of the patient to a higher center.

To overcome the complications with the needles routinely used with EBUS systems and provide additional safety, EBUS needles composed of an alloy named nitinol (nickel and titanium) have been recently introduced in the market. Kinks and bends do not occur even when angulated, and integrity is maintained even after taking multiple passes. Twist-lock technology helps in tracing the sheath precisely and making adjustments in needle length. However, they are costly, and their availability is extremely limited.

In a resource-poor setting like ours, where the affordability of the patient is already compromised, such complications lead to morbidity and may result in mortality in the rarest circumstances. The serendipity of our team in utilizing the available equipment at our center helped prevent catastrophe associated with possible morbidity, referral, surgical intervention, and expenditure. Panic and haste in such emergency situations may lead to wrong decisions, further loss of confidence, and additional negative consequences. We need to always remember that the use of a variety of instruments in different combinations can help in easy sailing through such stormy emergencies.

Conclusion

The rarest of the complications associated with any interventional modality can be dealt with minimal resources. The preference for utilization of one instrument over another in such emergencies should be guided by the ease and expertise of the operator. Team effort and confidence in using various tools available at hand in combinations can prevent catastrophes.

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CASE REPORT

Biatrial Myxoma Twins with Acute Myocardial Infarction—A Malady of Rarities!

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Abstract

We describe a young male patient who suffered myocardial infarction and was discovered to have a biatrial myxoma where stalks originated from opposite sides at the same point of the atrial septum, also described as "myxoma twins". The rarity of having a biatrial mirror image myxoma among cardiac myxomas, complicated by an even rarer event of coronary embolism in such milieu, prompted us to present the following case report.

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Introduction

Secondary cardiac tumors are more common than primary cardiac tumors and result from metastasis from other body sites. Most primary cardiac tumors are benign, with myxoma being the most common type. Myxomas occurring in a biatrial location account for <2.5% of all cardiac myxomas. Despite its benign nature, a cardiac myxoma is a potentially fatal tumor due to its embolic potential to several vascular territories. Myxomas from the left heart embolize in 45–60% cases, while it is 8–10% for a right heart location.[1,2]

Case Description

A young 24-year-old male who had an acute ST segment elevation (STEMI) anterior wall myocardial infarction (MI) was referred for echocardiography following thrombolysis with tenecteplase from a satellite secondary care center. The patient denied smoking and addiction and had no other risk factors for premature atherosclerosis. On clinical examination, the patient was pain free and had normal vital parameters. His electrocardiogram had minimal ST segment elevation of 0.5–1.0 mm with T wave inversion in leads V4–6, I, and aVL (Fig. 1A). Transthoracic echocardiography revealed:

- An echogenic mobile mass in the left atrium (LA), measuring approximately 3.3 × 3.3 cm attached to the interatrial septum. Another mirror image mobile mass measuring approximately 3.0 × 2.8 cm was detected in the right atrium (RA) that was also attached to the interatrial septum at the same location (Fig. 1B).
- Both masses were freely mobile and had villous surfaces. The biatrial masses partially prolapsed through the mitral and tricuspid orifices during diastole. Other vital cardiac structures such as pulmonary veins, superior and inferior vena cava, left atrial appendage, and coronary sinus were free from tumor mass. The patient also had moderate mitral regurgitation with an eccentric posterior-directed jet (Figs 1C and D).
- Regional wall motion abnormality (RWMA) was noted in the left anterior descending artery (LAD) territory with severe hypokinesia of interventricular septum, left ventricular free wall, and the left ventricular apex. No mural clot or pericardial effusion was seen. LV ejection fraction was 30–35%.

A case of biatrial myxoma with coronary myxoembolism in the LAD territory was suspected. Clinical examination related to the familial Carney complex was not found.[3] Coronary angiography done later revealed right coronary artery dominance with embolic occlusion of the distal LAD (Fig. 2A). As myocardial RWMA was out of proportion to the distal location of thrombus in LAD, it suggested the possibility of proximal occlusion of LAD first, followed later by distal migration of the myxomatous emboli. The patient was then shifted for emergency cardiac surgery.

Surgical Course

Following midline sternotomy, a biatrial approach consisting of right and left atriotomy with transseptal incision was adopted (Fig. 2B). A dumbbell-shaped, dark red-brown colored, gelatinous tumor mass with villous projections was removed, including the intervening septal attachment (Fig. 2C). The interatrial septum was closed with autologous pericardium. Cross-section of the tumor mass revealed gelatinous, myxoid stroma with patchy areas of hemorrhage. The patient's postoperative course was uncomplicated.

Microscopic examination of a myxoma shows polygonal myxoma cells with eosinophilic cytoplasm embedded in loose ground substance (Fig. 2D—not from the patient, adapted from an online histopathology image).

Discussion

Despite benign histology, myxomas are complicated by venous obstruction, valvular regurgitation or stenosis, atrial arrhythmias, and peripheral embolism.[4] The probability of myxoma forming emboli is related to its villous surface and fragility. A cardiac myxoma mostly embolizes to the cerebrum, followed by peripheral arteries and the mesentery. Coronary embolism is an even rarer event, with coronary cusps guarding any embolism besides the lower diameter of the coronary arteries. Coronary embolism in such cases may present as syncope, acute MI, or sudden cardiac death.[5,6] The absence of atherosclerotic disease in other coronary arteries, young age, and the absence of cardiac risk factors suggest that myxoembolism from the tumor was the cause of the patient's acute MI. Besides coronary embolism, other nonatherosclerotic coronary causes of MI in young patients are congenital coronary anomalies, coronary arteritis (e.g., Kawasaki disease), coronary spasm (variant angina, cocaine induced), etc.

The surgical removal of a myxoma requires full-thickness resection with clear margins of cardiac tissue to minimize the risk of recurrence. A biatrial approach for tumor removal was adopted over atrial

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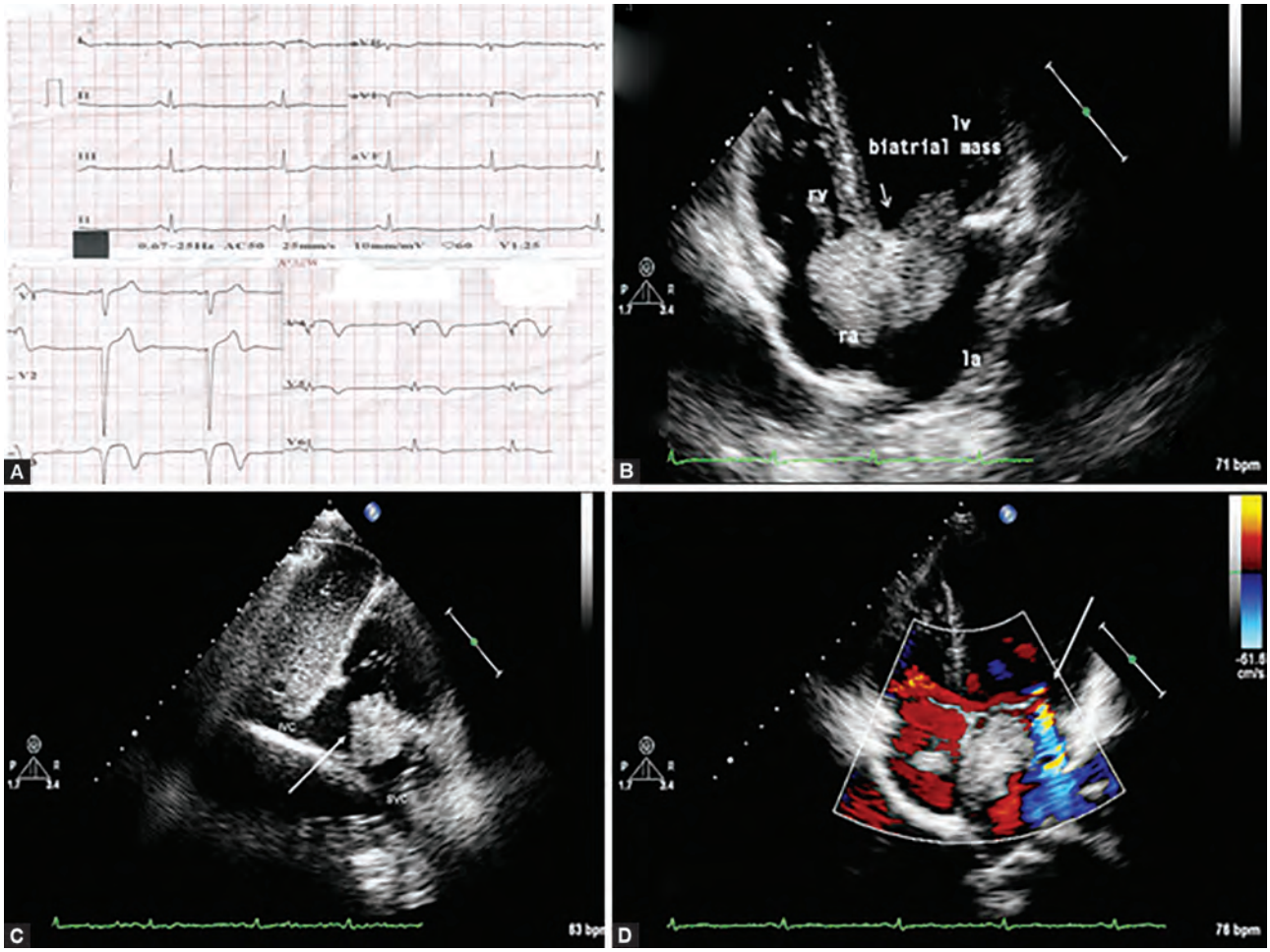
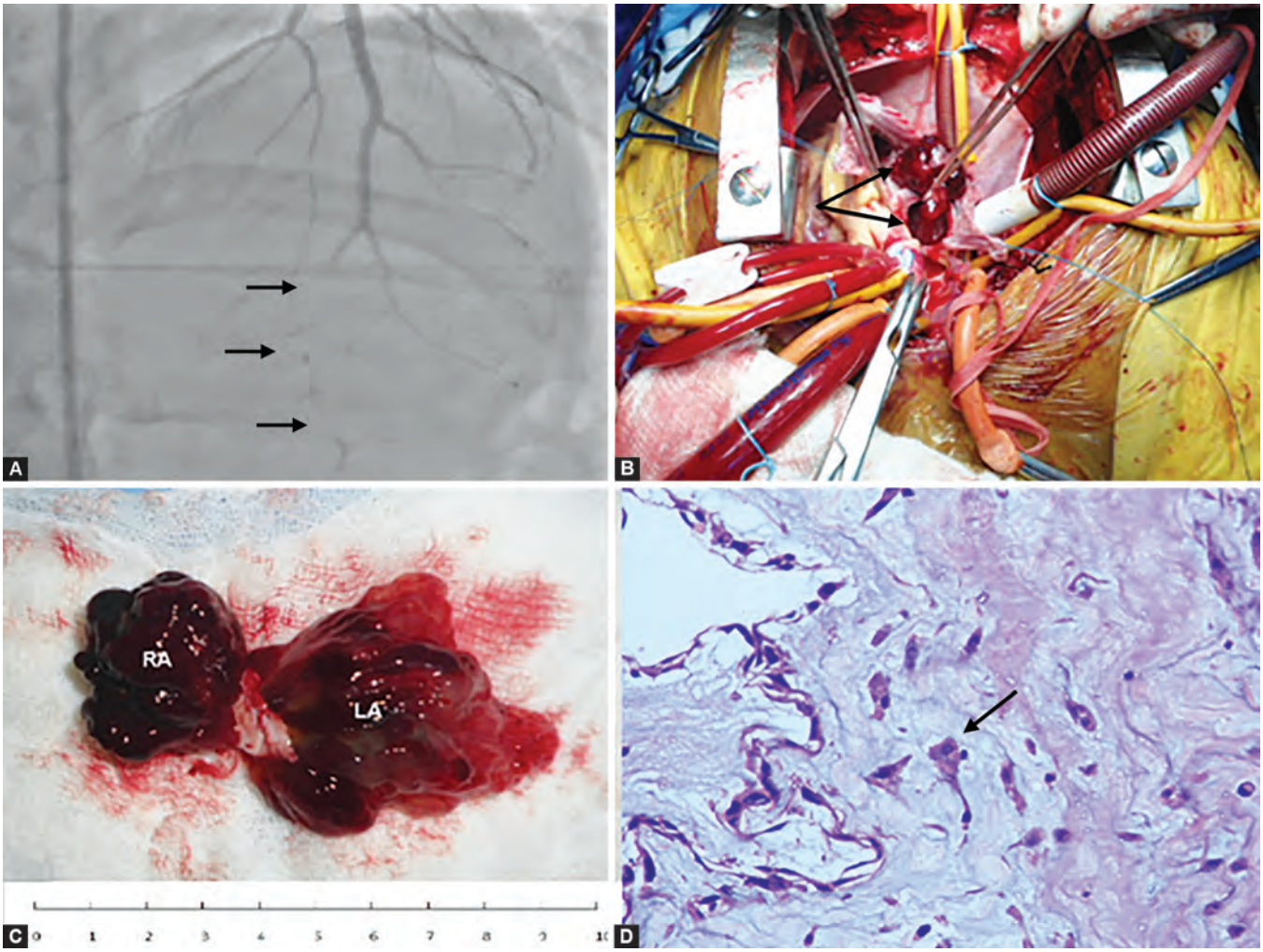


Figs 1A to D: (A) Patient's electrocardiogram 2 days after thrombolysis suggesting postdiagonal occlusion in LAD territory; (B) Apical 4 chamber view on 2D-echo showing biatrial mirror image mass attached to the common location at the interatrial septum, partially prolapsing through mitral and tricuspid orifices (RA = right atrium; LA = left atrium; RV = right ventricle, and LV = left ventricle); (C) Subcostal bicaval view on 2D-echo showing tumor-free entry of inferior (IVC) and superior vena cava (SVC) (arrow); (D) Apical 4C view with color Doppler echo showing moderate mitral regurgitation (turbulent blue jet marked by arrow)



Figs 2A to D: (A) Coronary angiogram showing multiple filling defects in distal LAD suggesting its embolic occlusion (multiple arrows); (B) Biatrial approach of myxoma resection showing right and left atriotomy (arrows) with tumor mass excision; (C) Excised biatrial tumor mass (RA = right atrial; LA = left atrial) with intervening septa having villous surface that predisposes to myxoembolism; (D) Polygonal myxoma cells (arrow) embedded in ground substance. Hematoxylin and eosin stain at 40× magnification

approach due to better visualization of all four cardiac chambers and atrioventricular valves, tumor removal with clear margins, exclusion of tumors at other cardiac sites, and prevention of intraoperative embolization.[7]

Conclusion

The desire for early reperfusion often overlooks clinical examination in the setting of an acute MI. While atherosclerotic coronary artery disease with plaque rupture is the most common cause of STEMI, a differential of coronary embolism arising out of intracardiac tumor mass should always be considered.

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CASE REPORT

Cellulitis that was NOT Cellulitis

Aditi D Punwani[1*], Keyur K Dave[2], Yuti Sheth[3], Rahul Shah[4], Tejas Parekh[5]

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Abstract

Cellulitis is a common bacterial skin infection characterized by erythema, swelling, and pain of the affected skin and subcutaneous tissues. The lower limbs are a commonly affected area due to microtrauma and gravity-dependent stagnation of blood. We describe a case of a male patient with an extensive travel history who presented with left lower limb cellulitis, hyperbilirubinemia, and acute kidney injury. When workup for the usual causes of cellulitis did not provide a clearer picture, we had to consider the unusual. Considering his travel history, an exotic tropical zoonotic disease was considered, and an eschar was searched for. Upon further investigation, he tested positive for the Weil-Felix test and responded very well to doxycycline. Our case emphasizes the need to suspect scrub typhus in travelers, even with unusual presentations, for timely diagnosis and treatment to prevent the development of various complications and ensure earlier recovery of patients. It usually presents as an acute febrile illness, but the diagnosis is often missed due to similarities with other tropical febrile infections.

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Introduction

Cellulitis is an acute affliction of the dermis and subcutaneous layers of the skin. *Streptococcus* species and *Staphylococcus aureus* are the most common Gram-positive cocci that cause this infection.

The common risk factors include trivial skin injuries, venous stasis, obesity, lymphoedema, and other skin infections (including tinea pedis).

Approximately 30% of cellulitis patients are misdiagnosed, as per various studies.

Alternate diagnoses to be considered include eczema, lymphoedema, psoriasis flare-ups, or aggravation of connective tissue disorders.[1]

During examination of a patient suspected of cellulitis, the entire body should be uncovered, and micro-abrasions, insect bites, pressure ulcers, and injection sites should be considered as the source of zoonotic illnesses that present with cellulitis.

Scrub typhus is an acute, febrile, infectious illness caused by *Orientia* (formerly Rickettsia) *tsutsugamushi*, an obligate intracellular gram-negative bacterium. It was first described in China in 313 AD.

In endemic areas, also called the "tsutsugamushi triangle," it is estimated that approximately 1 billion people may be infected at some point in their lives, and of those, 1 million symptomatic cases are documented annually.[2]

At the site of infection, a small painless papule appears and enlarges gradually. Then central necrosis increases, followed by eschar formation. At the initiation of the fever, the eschar is well-developed.

The rash, a history of travel to endemic areas, and the presentation of the eschar or sore can be diagnostic of scrub typhus, but it may still remain difficult, as many tropical infections have overlapping features.

Case Description

A 62-year-old man came to us with symptoms of left lower limb swelling, redness, and pain. He had developed these symptoms during his flight to Ethiopia, which progressively increased during his travel, lasting 8 days (Fig. 1).

He had preexisting diabetes mellitus (HbA1c 5.8%) and had received treatment for psoriasis in the past.

During the initial examination at the casualty department of our hospital, all his parameters were normal. His temperature was 99°F, heart rate was 76 beats/minute, and blood pressure was 110/70 mm Hg.

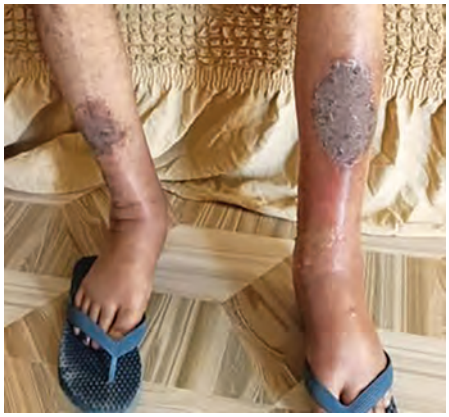

Fig. 1: Psoriatic scars with left leg edema and erythema at landing in Ethiopia

Oxygen saturation was 98% on room air. On auscultation, the chest and cardiovascular system were clear.

He had no visible eschar, active rash, or palpable lymphadenopathy (Fig. 2).

He was started on a piperacillin-tazobactam combination with metronidazole, along with regular dressing and elevation of the leg. His investigations revealed acute kidney injury with a creatinine of 3.4 mg%, along with hyperbilirubinemia (total bilirubin 14 mg% with direct bilirubin of 8.4 mg%) and a procalcitonin level of 11.95 ng/mL (for a normal of <0.05 ng/mL).

Worsening thrombocytopenia with leukocytosis was seen, but blood culture, immunology workup, and tests for malaria, leptospirosis, and dengue were negative.

Bilateral lower limb arterial and venous Doppler studies showed triphasic flow but no luminal obstruction, with subcutaneous edema suggestive of cellulitis. Computed tomography of the abdomen and pelvis showed liver parenchymal disease with portal hypertension and mild to moderate ascites. His CA-125 and CA-19 levels were borderline high.

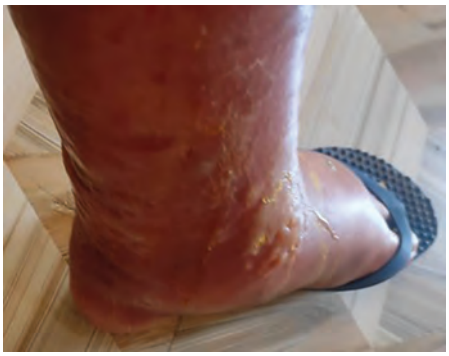

Fig. 2: Left leg cellulitis on departure from Ethiopia (day 8 of symptoms)

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Esophago-gastro-duodenoscopy revealed a lax lower esophageal sphincter with a massive necrotic ulcer at the D1 level with no active bleeding. No esophageal varices were found.

He developed hypotension; hence, he was transferred to the intensive care unit, and antibiotics were increased to meropenem, along with inotropic support and a continuous pantoprazole infusion for the ulcer. On repeat questioning, a list of countries he had visited recently was obtained. Keeping in mind tropical zoonotic diseases, the insect bites, wounds, and psoriasis scars were examined minutely, which led to the discovery of an eschar on the dorsum of the left foot at the center of the cellulitis (Fig. 3).

Weil–Felix test was sent, which was positive for OX-K (agglutination 1:80), and he was started on doxycycline (dose adjusted as per creatinine clearance).

He gradually improved with regular dressing of the leg and was discharged with creatinine and bilirubin on declining trends.

Discussion

Zoonotic diseases are spread from an animal host to humans, even though the host may remain unaffected by the pathogen, be it bacteria, virus, parasites, or fungi.

Various methods of spread include direct or indirect contact with contaminated bodily fluids, or vectors, food, or waterborne transmission.

Scrub typhus is spread to people through bites of infected chiggers (larval mites). The name is derived from the type of vegetation that harbors the vector.

The chigger bite is the method of inoculation and is often painless, remaining unnoticed. The incubation period lasts from a minimum of 6 days to a maximum of 20 days. Symptoms then include headache, lymphadenitis, conjunctivitis, fever, anorexia, and generalized malaise.

The interesting fact about our case was that the patient never complained of fever, but instead had only leg pain, swelling, and generalized malaise.

A small, painless papule initially appears at the site of infection and enlarges gradually. An area of central necrosis develops and is followed by eschar formation.[3]

The eschar, initially a small papule, is a painless lesion at the site of the bite and is considered pathognomonic.[3] It is seen a few days after the chigger bite, but before disease presentation. Target cells, the main type of cells affected by *O. tsutsugamushi*, are endothelial cells, leading to symptoms of pneumonitis, hepatitis, tinnitus, rash, disseminated intravascular coagulation, and meningoencephalitis.[4]

It is underdiagnosed in India due to its nonspecific clinical presentations, low index of suspicion among clinicians, limited awareness, and limited diagnostic facilities.

The maximum number of cases in India has been reported from the months of September to October, as the mites are more active during the rainy season.

The Weil–Felix test is widely used in the diagnosis of rickettsial diseases, but this test is neither sensitive nor specific in the diagnosis of these diseases. The result may be negative during the early stage of the disease because the agglutinating antibodies are detectable only during the 2nd week after the onset of the illness. Some of the more specific immunological tests include the microimmunofluorescence test, which is considered the best approach, followed by latex agglutination (LA), indirect hemagglutination (IHA), immune-peroxidase assay (IPA), and enzyme-linked immuno sorbent assay (ELISA). These specific immunologic tests are not easily available in India.[5]

Leptospirosis has been reported to be a common coinfection and confusing to the clinician due to the overlap of symptoms, history of exposure to the vectors, and the presence of transaminitis on test results.

Drugs available for the treatment of scrub typhus include azithromycin and doxycycline. In a multicentric open randomized controlled trial conducted in Thailand, 296 adult patients were studied. In conclusion, doxycycline was shown to be an affordable and effective choice for the treatment of both leptospirosis and scrub typhus. Azithromycin was better tolerated than doxycycline but is more expensive.[6]

Identification of the eschar, along with a high index of clinical suspicion, helps to hasten diagnosis and reduce the incidence of complications and end-organ damage.

Conclusion

India is an endemic nation for dengue and malaria, among other tropical febrile illnesses.

Scrub typhus remains a diagnostic dilemma for most, as the lack of clinical experience in dealing with these cases is a real problem.

An atypical presentation such as this, with only cellulitis without fever or lymphadenopathy, represents a conundrum for the treating physicians.

Only a multispecialty approach, with careful clinical examination and observation, helped us solve this case, and it served as a reminder that in clinical practice, the learning never ends (Fig. 4)!

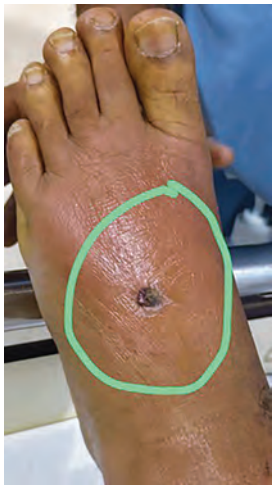

Fig. 3: Eschar on dorsum of left foot

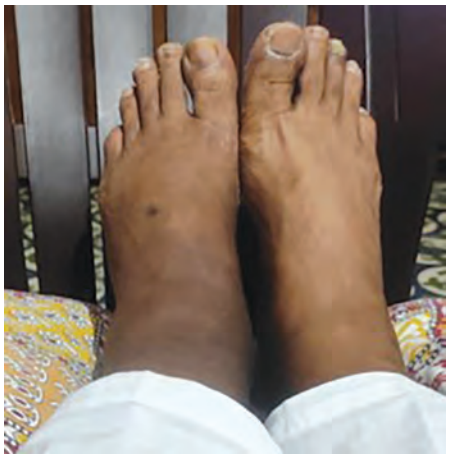

Fig. 4: Resolution of cellulitis and eschar after completing 14 days of doxycycline therapy

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CASE REPORT

A Rare Presentation of Rheumatic Heart Disease: Severe Pulmonary Tricuspid and Mitral Stenosis Successfully Treated by Triple Balloon Valvuloplasty

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Abstract

This case report describes a unique occurrence of rheumatic heart disease (RHD) with severe mitral, tricuspid, and pulmonary stenosis in a 17-year-old female. The patient presented with progressive exertional dyspnea and dependent edema. She had a history of acute rheumatic fever and joint pain 5 years ago. Evidence of congestive heart failure, such as pitting pedal edema, hepatomegaly, and elevated jugular venous pressure, was noted on presentation. The electrocardiogram (ECG) revealed important diagnostic information and signs consistent with right ventricular and right atrial enlargement. Chest radiography revealed cardiomegaly with an uplifted cardiac apex and elongation of the right heart border (enlargement of the right atrium and right ventricle). Echocardiography was suggestive of severe pulmonary, tricuspid, and mitral stenosis with mild mitral and tricuspid regurgitation. The patient's prognosis remained challenging, but she had dramatic symptomatic improvement after percutaneous triple valve balloon valvuloplasty. She was discharged after 5 days without any complications.

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Introduction

Rheumatic heart disease (RHD) is a systemic immune condition resulting as a sequela of single or repeated rheumatic fever due to streptococcal infection (beta-hemolytic) of the throat. It continues to be a significant global health problem, particularly in regions with limited access to healthcare resources.[1,2] While the prevalence of RHD has decreased in many parts of the world, it still remains the most common acquired heart condition in individuals under 25 years of age across the globe, predominantly affecting children in low- and middle-income countries.[2] The condition is characterized by valvular damage due to an abnormal immune response to the infectious agent.[3] The mitral valve is the most commonly affected valve in patients with RHD. The most common presentation of RHD is mitral regurgitation, and RHD is reported to be the most common cause of mitral valve stenosis.[4]

Its unique and challenging presentations remain a subject of clinical interest. This case report sheds light on an extraordinary manifestation of RHD, where a 17-year-old female from a rural community with lower socioeconomic status presented with severe tricuspid, mitral, and pulmonary stenosis. RHD, a sequela of untreated streptococcal throat infections, can lead to debilitating cardiac complications. There have been various case reports in the literature of triple valvular involvement, but involvement of the pulmonary valve, as seen in this case, is a unique and rare presentation of RHD. The early detection and management of RHD are crucial, and this report not only discusses the clinical aspects but also emphasizes the enduring challenges that persist in underprivileged communities. By highlighting the need for early diagnosis, antibiotic prophylaxis, and access to specialized cardiac care, this case underscores the ongoing battle against RHD in resource-limited settings.

Case Description

A 17-year-old female, belonging to a lower socioeconomic class and residing in a rural area, with no history of any cardiac diseases in the past, presented with progressively worsening shortness of breath (New York Heart Association functional class II dyspnea) and fatigue, along with edema of the lower extremities for 2 years. She had a history of fleeting joint pain during childhood, 4–5 years ago. A history of diabetes or other systemic illness was negative. Clinical examination revealed a regular pulse rate of 92 beats per minute, blood pressure of 94/70 mm Hg, and oxygen saturation of 95% on room air. Evidence of congestive heart failure, such as pitting pedal edema, hepatomegaly, and elevated jugular venous pressure, was present. A predominantly loud ejection systolic murmur was heard over the left parasternal second to fourth intercostal space on cardiac auscultation, and on respiratory auscultation, bilateral crepitations were heard.

Investigations

On routine pathological and biochemical investigations, the liver function test was found to be abnormal. Cardiac evaluation was done. The 12-lead ECG revealed important diagnostic information and signs consistent with right ventricular and biatrial enlargement. It showed normal sinus rhythm, prolonged PR interval, Himalayan P-waves (right atrial enlargement), R/S wave ratio >1 in lead V1 [right ventricular hypertrophy (RVH)], and a biphasic P-wave with a terminal negative portion >40 ms and >1 mm deep, suggestive of left atrial enlargement (Fig. 1).

Thorax radiography revealed cardiomegaly with uplifting of the cardiac apex and elongation of the right heart border (enlargement of the right atrium) (Fig. 2).

Echocardiography was done and revealed an aortic diameter of 29.4 mm, left atrium diameter of 32.2 mm, and a right ventricle measured at 33.3 mm with concentric hypertrophy. The ejection fraction was 60%. Severe pulmonary stenosis was noted (mean pressure gradient 40 mm Hg), and the pulmonary annulus measured 22 mm. Other echocardiographic findings included severe tricuspid stenosis (mean pressure gradient 11.8 mm Hg), severe mitral stenosis [MV mean pressure gradient (PG) 10.4 mm Hg] with a grossly dilated right atrium, mild mitral regurgitation, and mild tricuspid regurgitation [normal pulmonary artery systolic pressure (PASP)], along with thickened valves of rheumatic origin (Figs 3 to 6).

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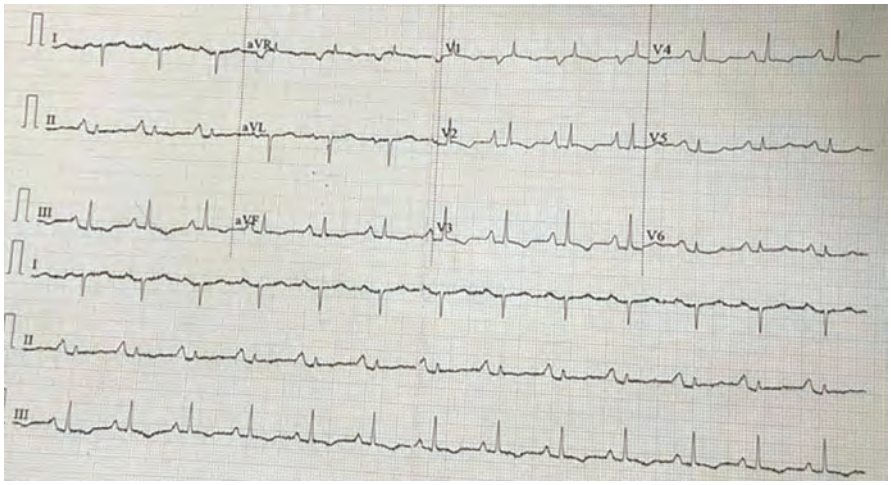

Fig. 1: 12 lead ECG

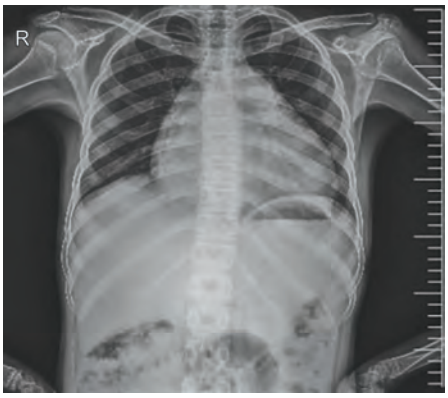

Fig. 2: Chest X-ray showing cardiomegaly with uplifting of cardiac apex, elongation of right heart border (enlargement of right atrium and right ventricle)

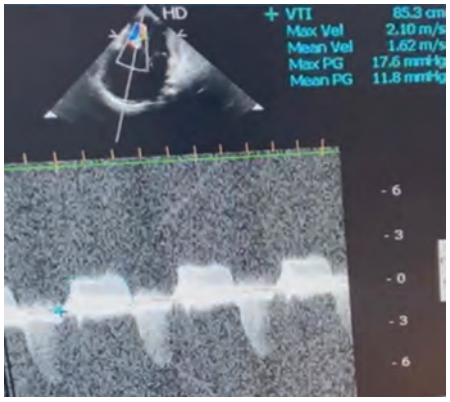

Fig. 4: Severe tricuspid stenosis (mean pressure gradient 11.8 mm Hg)

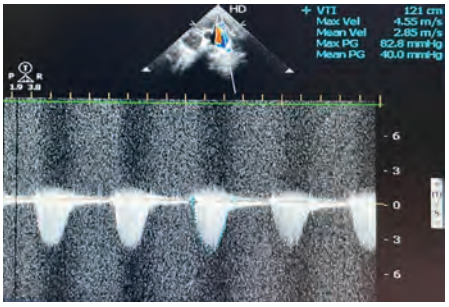

Fig. 3: Severe pulmonary stenosis (mean pressure gradient 40 mm Hg)

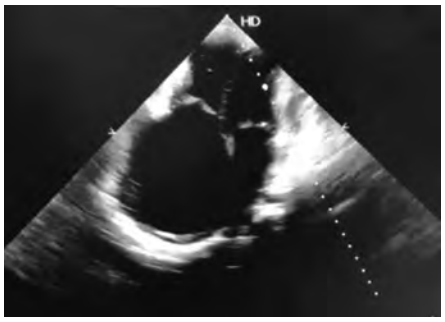

Fig. 5: Apical four-chambered view showing grossly dilated Rt atrium

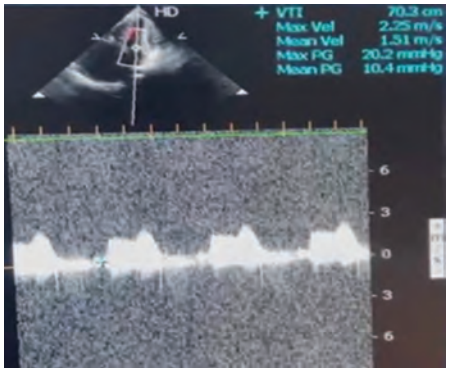

Fig. 6: Severe mitral stenosis (MV mean PG 10.4 mm Hg)

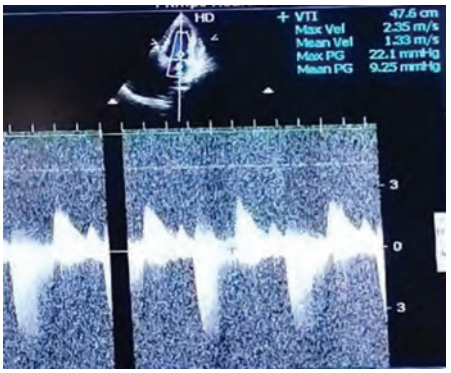

Fig. 7: Postoperative echocardiography showing mitral valve (MV mean PG 9.2 mm Hg)

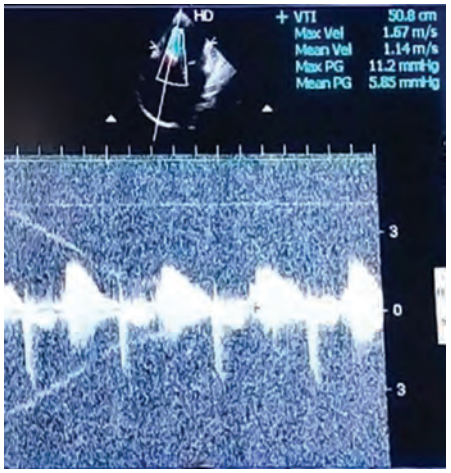

Fig. 8: Postoperative echocardiography showing tricuspid valve (mean PG 5.85 mm Hg)

Treatment

The patient was admitted to the cardiac care unit and started on diuretics for symptom relief. Due to the severe nature of the mitral, pulmonary, and tricuspid stenosis, the patient was considered for surgical valvular intervention but underwent valvuloplasty rather than valve replacement due to severe right ventricle dysfunction and deranged liver function tests in a specialized cardiac center. As the patient was diagnosed with severe pulmonary, tricuspid, and mitral stenosis with mild mitral and tricuspid regurgitation, the patient underwent triple valve balloon valvuloplasty, in which a hollow flexible catheter with a balloon tip was inserted percutaneously under local anesthesia through the right femoral vein using a guidewire. After reaching the required position, the balloon was inflated to relieve the stenosis of the valves, and then the balloon was deflated and the catheter was removed. Postoperatively, the patient improved symptomatically. Echocardiography showed a decrease in peak velocity in the mitral from 2.75 to 2.35 m/s, in transpulmonary from 4.55 to 3.07 m/s, and in transtricuspid from 2.10 to 1.57 m/s, and the mean transmitral gradient, mean transpulmonary gradient, and transtricuspid gradient from 10.4 to 9.2 mm Hg, 40 to 20.5 mm Hg, and 11.8 to 5.85 mm Hg, respectively, as shown in Figures 7 to 9.

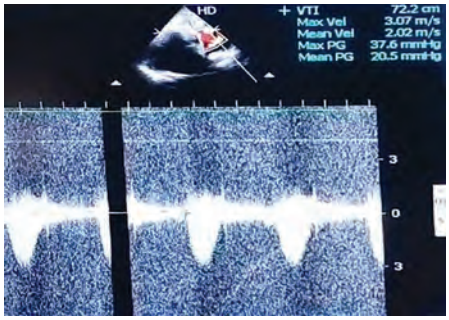

Fig. 9: Postoperative echocardiography showing pulmonary valve (mean PG 20.5 mm Hg)

Outcome and Follow-up

The patient's prognosis remained challenging, but she was relieved of her symptoms dramatically after the valvular intervention. She was discharged after 5 days without any complications. On the subsequent three follow-up visits postprocedure, the patient was completely symptom-free with no edema.

Discussion

Rheumatic heart disease is one of the most critical acquired conditions of the heart among children and young adults, especially in developing countries, and it has been mainly attributed to poor living conditions, poverty, and inadequate access to health care. In endemic regions, this condition may be responsible for heart failure in 15–20% of the affected cases.[5] According to a systematic review and meta-analysis, the prevalence of silent RHD was documented to be 21.1 per 1,000 people, and it was documented to be much higher compared to clinically manifest RHD (2.7 per 1,000 people). The prevalence is documented to increase from 4.7 per 1,000 children to 21 per 1,000 children at 5 and 16 years of age, respectively.[6]

Our case was a 17-year-old female resident of a rural community (difficult-to-reach area), belonging to a low socioeconomic status. Though the history of rheumatic fever was present only 5 years ago, within such a short span of time, she had exacerbated features of congestive cardiac failure (CCF) such as chronic progressive dyspnea, lower limb pitting edema, hepatomegaly, raised jugular venous pressure, and severe valvular stenosis. Mitral valve stenosis with mitral regurgitation is a common feature of this condition,[1] however, our patient presented with severe stenosis of three valves, that is, tricuspid, mitral, and pulmonary, along with mild tricuspid regurgitation and mitral regurgitation. There have been various case reports in the literature of triple valvular involvement, but involvement of the pulmonary valve, as seen in this case, is a unique and rare presentation. The diagnosis of RHD was established based on the clinical history of rheumatic fever in the past and typical findings of thickened leaflets associated with RHD on echocardiography.[1] The valvular changes result from an abnormal immune response to the pathogen causing acute rheumatic fever, that is, group A beta-hemolytic streptococci, causing progressive fibrosis of the valves of the heart and ultimately causing rheumatic valvular heart disease.[1]

Electrocardiogram and chest X-ray were suggestive of the features of biatrial enlargement and RVH due to back pressure effect with severe stenosis of the affected valves. Pulmonary stenosis may be associated with RVH.[7]

Our patient was symptomatic due to severe stenosis of the mitral valve, tricuspid valve, and pulmonary valve, though there have been case reports of triple valve involvement undergoing valvuloplasty.[8] However, involvement of the pulmonary valve, as evident in our patient, is rare. Since the tricuspid and mitral regurgitation were mild, and the patient's age was less (17 years), we preferred a less invasive method for surgical management, that is, triple balloon valvuloplasty (mitral, pulmonary, and tricuspid) rather than valve replacement surgery. In this era, where the focus is on primary prevention (in patients with group A streptococcal pharyngitis) or secondary prevention (in patients with acute rheumatic fever) of RHD by giving penicillin prophylaxis, our patient presented with severe stenosis of three valves with features of CCF. Though the patient recovered well, stenosis in all the valves decreased and clinical improvement was evident, the cost and morbidities faced by the patient were a traumatic experience for not only the patient but also for the family. This case highlights the enduring challenges associated with RHD and was a rare presentation involving severe mitral, tricuspid, and pulmonary stenosis. Prevention through early detection and regular antibiotic prophylaxis remains the cornerstone of RHD management, and resource disparities can significantly affect patient outcomes.

Learning Points/Take Home Messages

- Rheumatic heart disease remains a pressing issue in underprivileged communities with limited healthcare resources.
- Triple valve stenosis with no previous cardiac manifestation, presenting with features of CCF despite a history of rheumatic fever, was a rare presentation.
- Though valve replacement surgery is preferred over balloon valvulotomy in the management of severe tricuspid stenosis, we used a comprehensive strategy that included early diagnosis, penicillin prophylaxis, and early triple balloon valvuloplasty with close cardiac monitoring, which helped in mitigating the impact of RHD.
- Patients must be followed up for a prolonged period to detect the recurrence of RHD.

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ANCA Negative Vasculitis Manifesting as Pulmonary-Renal Syndrome in a Patient with Chronic Osteomyelitis

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A man in his early 60s, with a history of obstructive airway disease and hypertension, had a fall from a height 1 year ago. He developed a fracture of the left distal tibia and fibula, for which open reduction and internal fixation (ORIF) was done. Since then, he has had persistent pain and discharge from the implant site, for which multiple antibiotics were given and debridement was done numerous times. Three months ago, he was admitted to an outside hospital with similar complaints, and a pus culture grew methicillin-resistant *Staphylococcus aureus*. The patient gave a history of sudden onset right upper and lower limb weakness associated with slurring of speech, which recovered in <24 hours. A magnetic resonance imaging (MRI) of the brain revealed multiple thromboembolic acute infarcts. The patient now presented with high-grade fever, cough with expectoration, and shortness of breath (grade 3 mMRC) for 5 days. On examination, he was febrile, tachycardic, with a saturation of 92% on room air. Systemic examination revealed bilateral infrascapular crepitations and a mid-ejection systolic murmur in the aortic area. Laboratory investigations revealed leukocytosis, raised creatinine, and inflammatory markers. A chest X-ray done on day 1 revealed cardiomegaly. An X-ray of the left lower limb revealed changes of chronic osteomyelitis (Fig. 1). Blood, urine, and sputum cultures were sterile. An ultrasonography (USG) of the whole abdomen showed a splenic infarct with 190cc liquefaction. A 2D echocardiography revealed severe aortic stenosis. A plain computed tomography (CT) of the chest/abdomen showed moderate pleural effusion bilaterally with collapse/consolidation in both lungs. There was evidence of hypodense fluid density with internal hyperdense content and lobulated margins seen in the spleen. An USG-guided splenic infarct aspiration was done, which was sterile. Sequestration and debridement of the lower limb wound were done, and the culture revealed *Acinetobacter baumannii*. On day 12, the patient had an episode of macroscopic hematuria, which resolved spontaneously. The coagulation profile was normal. On day 14, a similar episode reoccurred. In view of hematuria, resistant hypertension, worsening fluid overload, rising 24-hour urinary protein, and creatinine, a differential of nephrotic vs nephritic syndrome was made. The patient was stabilized with antibiotics, blood transfusion, and dialysis, and we proceeded with a kidney biopsy. The kidney biopsy revealed crescentic glomerulonephritis (Figs 2A and (B). Mild tubular atrophy and inflammation, as well as fibrosis of the interstitium, were also seen. Immunofluorescence revealed IgM positivity, and the rest (mesangial, IgG, IgA, C3, C1q, Kappa, and Lambda) were negative. ANA (IF), ANA profile, c-ANCA, p-ANCA were negative, and ASO titers were normal. The patient then developed massive hemoptysis. The coagulation profile and platelet counts were repeated, which were

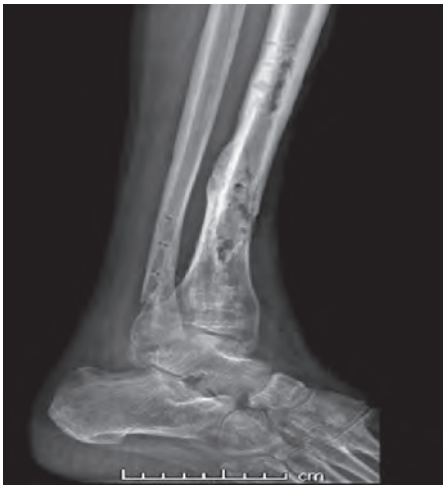

Fig. 1: Lower limb showing changes consistent with chronic osteomyelitis in the left lower limb

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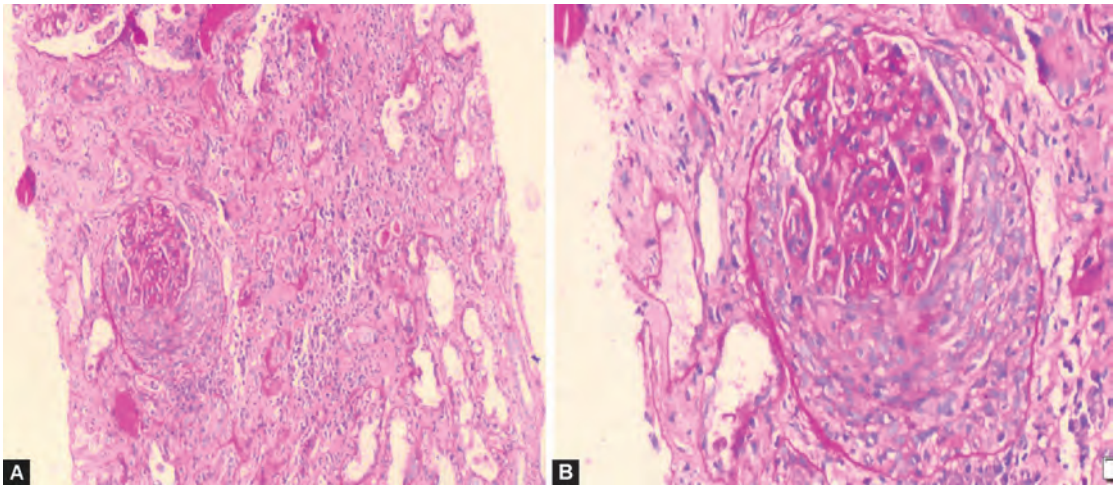
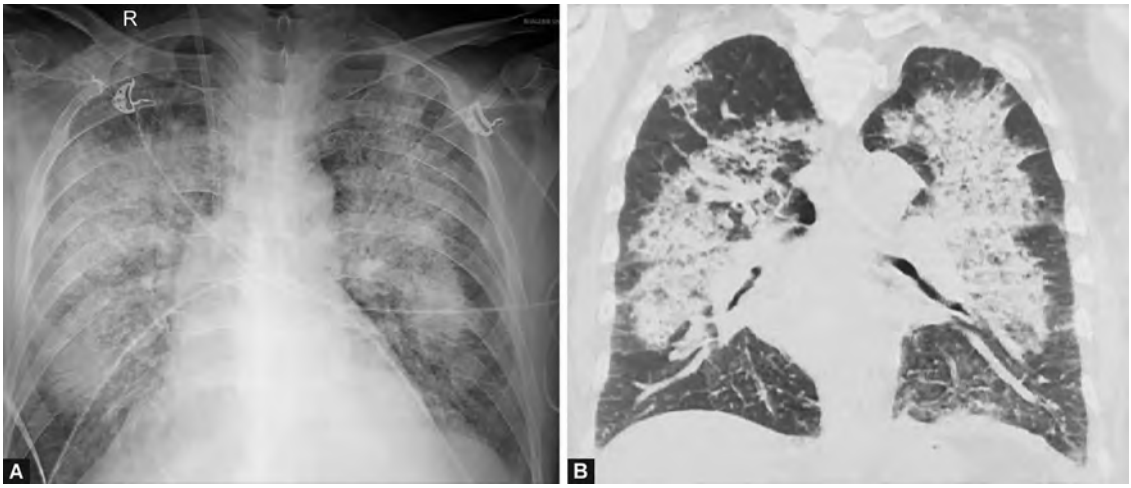


Figs 2A and B: (A) Low power field kidney biopsy showing crescent formation; (B) High power field kidney biopsy showing crescent formation



Figs 3A and B: (A) Chest X-ray showing changes of diffuse bilateral infiltrates; (B) HRCT chest showing bilateral alveolar opacities with interlobular septal thickening, s/o alveolar hemorrhage

normal. A chest X-ray, done immediately, revealed diffuse bilateral infiltrates (right > left) (Fig. 3A). An urgent high-resolution computed tomography (HRCT) chest was done, which showed alveolar opacities in the medial aspects of both lungs with interlobular septal thickening and pleural and pericardial effusion, with a high possibility of alveolar hemorrhage (Fig. 3B). Hemoglobin showed a significant fall from 8.8 to 6.2 gm/dL. A diagnosis of pulmonary renal syndrome with the following possible etiologies was made:

- Anti-glomerular basement membrane (GBM) disease/Goodpasture syndrome.
- Immune complex glomerulonephritis/postinfectious glomerulonephritis.
- Pauci-immune glomerulonephritis/ANCA-associated vasculitis.

Anti-GBM antibodies were negative on two occasions (1 week apart). Immune complex or pauci-immune glomerulonephritis were ruled out with a negative autoimmune panel, c/p-ANCA, and biopsy report showing no immune complex deposits. With pauci-immune glomerulonephritis and negative ANCAs, we arrived at the diagnosis of ANCA-negative vasculitis. The patient was treated with high-dose methylprednisolone (500 mg) for 5 days and received 2 doses of intravenous cyclophosphamide (750 mg). After he had the episode of hemoptysis, the patient was initiated on plasmapheresis and received 6 cycles of the same. Despite antibiotics, IV cyclophosphamide, steroids, dialysis, and plasmapheresis, the patient continued to be critical. He was intubated in view of worsening respiratory distress. In view of ongoing sepsis, he underwent left lower limb below-knee amputation. After about 60 days of admission, the patient persisted in having rapidly progressing glomerulonephritis. Despite all efforts, he succumbed to death after 2.5 months of hospitalization and treatment.

Discussion

According to an Indian study, rapidly progressive glomerulonephritis (RPGN) is the most common cause of renal failure in elderly patients.[1] Pauci-immune variety is commonly linked to the presence of ANCA-associated vasculitis. However, approximately 10% of pauci-immune cases have been found to be negative for serological markers and are labeled as ANCA-negative pauci-immune RPGN.[1] Classical pauci-immune cases cause destruction of endothelial cells, whereas ANCA-negative vasculitis has neutrophilic activation, which occurs through alternate pathways.[2] Recent studies suggest 100% homology of LAMP-2 epitope with fimbrial adhesin (FimH), which is seen in gram-negative bacteria.[3]

Pulmonary involvement is the second most common after renal involvement. Pulmonary capillaritis, leading to diffuse alveolar hemorrhage, is a serious complication and has a very poor prognosis.[4]

Management involves an induction (3–6 months) and maintenance phase with IV methylprednisolone followed by oral prednisolone and cyclophosphamide/rituximab.[5] Plasma exchange is indicated in cases with serum creatinine >4 mg/dL, pulmonary hemorrhage, coexisting anti-GBM, or those needing dialysis. The efficacy of plasma exchange is uncertain in patients with severe diffuse alveolar hemorrhage.

This case represents one of the biggest dilemmas that treating physicians face when autoimmune disease and infection present together. The decision to perform a renal biopsy and administer immunosuppressants in view of renal worsening for ANCA-negative vasculitis in the background of ongoing osteomyelitis was a challenge.

Our case highlights the importance of treating the infection timely and the seriousness with which it can exacerbate if left untreated.

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Enzymes and Virus Protein Pioneers

JV Pai-Dhungat

John Northrop—Nobel Prize in Chemistry 1946. Gabon, 1995

Eduard Buchner—Nobel Prize in Chemistry 1907. Gabon, 1995

Eduard Buchner (1860–1917) proved that biochemical processes do not necessarily require living cells but are driven by special catalyst substances. He called the catalyst substance enzyme zymase (Nobel Prize 1907).

James Sumner (1887–1955), a US-born biochemist in Canton, obtained his PhD from Harvard in 1910 and became an Assistant Professor at Cornell University Medical College (1914). Sumner studied the enzyme that breaks down urine into ammonia and carbon dioxide; he called it urease. While trying to extract the enzyme from jackfruit beans, he obtained a number of tiny urease crystals that had precipitated out (1926). Sumner confirmed that they were pure urease enzyme crystals.

John Howard Northrop (1891–1987), born in New York, obtained his PhD in chemistry in 1915 and joined the Rockefeller Institute for Medical Research. There, he isolated the proteolytic enzyme pepsin from gastric juice in pure crystalline form in 1930 and confirmed its protein nature beyond doubt. Northrop went on to isolate trypsin and several other proteolytic enzymes from the pancreas; during the course of the studies, he isolated several inactive precursors of these enzymes in pure forms in 1932. He further studied complete enzyme kinetics. Northrop also purified and estimated bacteriophage protein.

Wendell Meredith Stanley (1904–1971), born in Ridgeville, Indiana, obtained his PhD from Illinois in Chemistry (1929). After postdoctoral studies in Germany, he went to the Rockefeller Institute in 1931. Stanley crystallized tobacco mosaic virus (TMV), which causes TMV disease in tobacco plants. By 1937, he recognized that TMV crystals were actually nucleoproteins and ribonucleic acid (RNA), which displayed TMV activity.

COVID-19 virus particles made 2020 a deadly pandemic year. Serbia, 2020

The apparently lifeless nucleoprotein RNA in crystallized form sprang back to life and multiplied when reintroduced into tobacco. This criterion seemed to poise the virus on the boundary between life and nonlife. This revolutionary discovery was not acceptable to many, but later workers showed nucleic acid RNA to be infective.

In 1946, half of the Nobel Prize in Chemistry was jointly awarded toNorthrop and Stanley "for their preparation of enzymes and virus proteins in a pure form," and the other half was awarded to Sumner "for his discovery that enzymes can be crystallized."

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Why Medical Doctors Hesitate to Write for Scientific Journals?

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Even after publishing numerous articles in various journals, I often feel the need for a bit of extra motivation before starting to write for a scientific journal. Does this happen to all medical professionals? If so, what could be the reason, and how can this inertia be overcome? To explore this, I formally engaged with a wide range of healthcare professionals, from postgraduate medical students to senior consultants, as well as academics and researchers from various institutions. Additionally, after reviewing relevant literature, I discovered that several factors contribute to a loss of interest in writing for scientific publication. These include time constraints, the complexity of the publishing process (such as the cumbersome submission procedures and delayed journal responses), and the lack of formal training in research and writing.

Medical doctors, despite being highly trained professionals with extensive experience in patient care and clinical practice, often hesitate to write for scientific journals, probably due to the following reasons:

- Complexity of the publishing process: Especially during my interaction with clinicians, they always talked about the complexity of the process of publication. The process of publishing in a peer-reviewed journal is complex and very time-consuming. There are several complicated steps involved, starting from registration at the journal website to submission of the manuscript as per the journal's predecided format. Several documents need to be updated in different formats and sizes. The challenge starts with the right selection of the journal. Doctors who are unfamiliar with these steps often find the process overwhelming. Doctors frequently report frustration with the administrative and procedural hurdles involved in getting their work published. The submission process itself is also time-consuming, requiring careful attention to the journal's guidelines, formatting, and submission protocols. For busy doctors, these extra steps can be major obstacles. Many doctors initiate the process but drop in between because of the complex nature. Even after successful submission, the peer review process takes several weeks to months, sometimes years, for their reply, and in most cases, authors lose their interest in publication. In a few journals, the publication charges are exorbitant, which are beyond the scope of young researchers.[1]
- Time constraints: Medical practice, especially in clinical settings, is highly demanding, leaving little room for nonclinical activities. Doctors often work long hours, managing emergencies, including nights and weekends, making it challenging to dedicate the necessary time for research and writing. Additionally, medical doctors often prioritize patient care over academic pursuits. The clinical environment demands immediate attention to pressing health issues, leaving less time for activities like conducting research, reviewing literature, or crafting manuscripts.[2]
- Lack of formal training in research and writing: While medical schools rigorously train doctors in clinical knowledge and patient care, the training in research methodology and scientific writing is often limited. Many medical doctors are unfamiliar with the intricate processes involved in preparing and submitting papers to peer-reviewed journals. The lack of writing experience can make the process hard. The language barrier presents a general challenge for those who are not fluent in English. Writing for scientific journals requires a precise, structured approach, which can be challenging for those who are not accustomed to the format. Furthermore, many doctors are unfamiliar with the process of navigating peer review, handling revisions, and responding to critiques, which can further dissuade them from submitting their work.[3]
- Fear of rejection and criticism: The fear of rejection or receiving harsh critiques from peers is another reason why medical doctors might hesitate to write. The competitive nature of publishing, combined with the lengthy and rigorous review process, can deter doctors from even attempting to submit their work.[4]
- Challenges in finding relevant research opportunities: Physicians who are not directly involved in academic institutions or research centers may struggle to find opportunities to engage in research. In many clinical environments, there is limited access to research resources, such as funding, support staff, and research networks. Without institutional support or collaboration with academic researchers, many doctors find it difficult to initiate and complete research projects suitable for publication. This lack of access to research opportunities makes the prospect of writing for journals even more challenging.

Conclusion

Medical doctors face numerous barriers when it comes to writing for scientific journals, from the overwhelming demands of their clinical roles to a lack of formal training in academic writing. To address these challenges, there is a need for greater institutional support, more comprehensive training in research methods and writing during medical education, and a cultural shift within the healthcare system that values and rewards scholarly contributions. Journals should make their submission process easier and should review and reply to authors within timelines. Additionally, journal reviewers should assess the manuscript with a positive mindset so that the author will not lose interest in publication.

Workshops related to research should be planned and executed, possibly supported by pharmaceutical industries. Mentoring programs should be developed, as they play a significant role in guiding, encouraging, and supporting novice researchers.[5]

Young researchers can be motivated by giving awards, small grants for publication, free registration to attend conferences, etc., to promote a research culture in society. The societies, institutes, and even pharmaceutical industries can provide different resources for researchers, like EndNote for reference citation support, software for analysis, statistical analysis support, diagrams, plagiarism checking, and language editing services. Workshops can be conducted on how to select the right journal for the right manuscript, maintaining academic independence to preserve the integrity of the scientific articles clinicians publish.[6] By alleviating these barriers, the medical community can better integrate clinical knowledge and experience into the scientific literature, ultimately enhancing both medical practice and research.

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Pulse Corticosteroid Therapy and Bradycardia

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Dear Editor,

High-dose intravenous methylprednisolone (IVMP) is widely used in managing systemic lupus erythematosus (SLE), myositis, and vasculitis. While the long-term adverse effects of chronic glucocorticoid use are well documented, acute adverse effects from high-dose IVMP are often overlooked.

Cardiac arrhythmias, including bradycardia, atrial fibrillation, and ventricular tachycardia, have been reported during and after pulse corticosteroid infusions. Asymptomatic bradycardia is not uncommon, as highlighted by 2 cases presented here.

Case 1

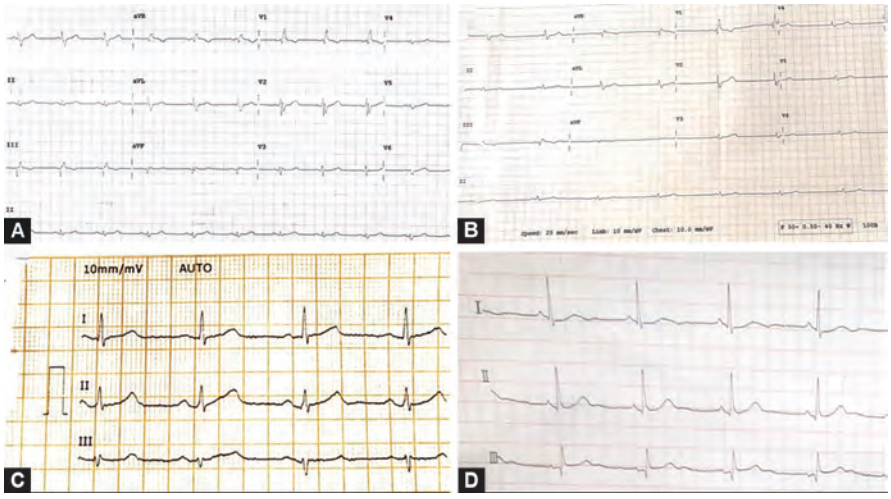
A 60-year-old male with ANCA-associated vasculitis for 2 years was in remission. He had an asymptomatic right bundle branch block (Fig. 1A) with normal echocardiography. Following a flare in the left middle ear with facial nerve palsy, hearing loss, and pachymeningitis, he received three doses of IVMP (500 mg). After the 3rd pulse, he complained of dizziness. On examination, his pulse rate was 42/minute. Blood pressure was 90/60 mm Hg, and ECG showed sinus bradycardia (Fig. 1B). The patient was administered a single dose of atropine. Dizziness gradually improved. Thyroid function tests, cardiac enzyme levels, and serum electrolyte levels were normal. His pulse rate improved spontaneously within a week.

Case 2

A 36-year-old female with class IV lupus nephritis in remission presented with a mucocutaneous and nephritic flare. She was treated with IVMP for 3 days and cyclosporine. The patient had no known cardiac illness. Baseline ECG was normal (Fig. 1C). During the 3rd dose of IVMP, she developed asymptomatic bradycardia (pulse rate: 56/minute), which persisted even after the infusion. An ECG suggested sinus bradycardia (Fig. 1D). The patient's thyroid function tests, electrolytes, and 2D echocardiography were normal. Her heart rate improved gradually over the next four days.

Pulse IVMP administered over a short period of time is thought to be useful in avoiding the chronic adverse effects of steroids. However, clinicians should be aware of the adverse events caused by them, including cardiac arrhythmia and sudden death.[1,2] Bradycardia, atrial fibrillation, atrial flutter, ventricular ectopic beats, and ventricular tachycardia have been reported during and after infusion. A systematic review found bradycardia to be the most common condition and could be asymptomatic.[2] Few case reports have described sinus bradycardia after oral steroids.[3]

The pathophysiology of steroid-induced bradycardia is multifactorial, potentially affecting myocardial membrane and alteration in responsiveness to catecholamines. Other causes include sudden electrolyte shifts and baroreceptor activation due to plasma volume shifts affected by changes in salt and water balance.[4]



Figs 1A to D: (A) Case 1 baseline ECG showing right bundle block; (B) Case 1 ECG showing sinus bradycardia after infusion with methylprednisolone; (C) Case 2 baseline normal ECG; (D) Case 2 ECG showing sinus bradycardia after pulse methylprednisolone

Rapid rates of IVMP infusion (typically <30 minutes) and underlying cardiac or renal disease make patients prone to bradycardia.[5]

Pulse IVMP has been associated with rare but potentially serious cardiac arrhythmias, which can be fatal. Thus, it is imperative for physicians to exercise heightened vigilance and consider the existing comorbidities of patients and the infusion rate when treating them with steroids. Strict monitoring protocols are paramount during the administration of pulse steroids to promptly detect any signs of cardiac arrhythmias and to intervene as necessary.

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