Hypertension & CAD
when co-exist can attract complications...

In Hypertensives with symptomatic CAD
Telvas* - beta
Telmisartan & Metoprolol Succinate ER Tablets 25/50 mg

- Helps achieve target BP
- Offers end organ protection
- Helps reducing cardiovascular morbidity and mortality

The Alliance for Assured CV Protection
In Allergic Rhinitis and Chronic Urticaria...

Rule out RED

In Management of Hypertension

The Trusted Choice in Hypertension

Your Trusted Brand Since 2019

*Data on file. For the use of a Registered Medical Practitioner, Hospital or Laboratory only or as per the description under Form 46 of the Drugs & Cosmetics Act, 1940.
In Dyslipidemia

Revostat®
Rosuvastatin Tablets IP 5/10/20mg

The Revolutionary statin

₹ 4 / Tab
₹ 7 / Tab
₹ 13 / Tab

Launching Soon
Revostat GOLD 10/20
Rosuvastatin Calcium, Aspirin & Clopidogrel Bisulphate Capsules

Zuventus Lifestyle
Office No. 5119, 5th Floor, D-Wing, Oberoi Garden Estates, Chandivali, Andheri (E), Mumbai 400 072.
Contents

EDITORIAL

Fosfomycin: A Revisited Antibiotic for Urinary Tract Infections
Falguni S Parikh ................................................................. 11

ORIGINAL ARTICLE

Fosfomycin Susceptibility in Urinary Tract Enterobacteriaceae
Bhargav Patel, Kinjal Patel, Anjali Shetty, Rajeev Soman,
Camilla Rodrigues .......................................................... 14

A Study of Endothelial Dysfunction in Patients of Non-Alcoholic
Fatty Liver Disease
Vaibhav Shukla, Jalees Fatima, Saurabh Chaudhary, Mohsin Ali,
Ishan Mishra ............................................................... 18

Cardio-metabolic Risk profile in Women with Previous History
of Pre-Eclampsia
Jalees Fatma, Ritu Karoli, Zeba Siddiqui, HP Gupta,
Ashok Chandra, Mahima Pandey ...................................... 23

P. vivax Malaria presenting as Thrombotic Microangiopathy
Dharmendra Bhadauria, Harsh Vardhan, Anupma Kaul,
Raj Kumar Sharma, Amit Gupta, Narayan Prasad, Manoj Jain ...... 28

A Study of Genetic Markers in Patients of Rheumatoid Arthritis
and their Co-Relation with Severity of the Disease
Gauri Liyakat Ali, Suman Kapur, Sai Chinmayi, Qadir Fatima,
Harshal Pise, Asim Khan, Ambreen Liyakat, V Jiloo, Urvashi Dube ... 32

A Study of Clinical Profile of Patients presenting with
Complications of Acute Febrile Illnesses During Monsoon
Kaustubh Dilip Solare, Ravindra Nath Sahay, Amar R Pazeare,
Abhishek Dubey, Kunal K Marathe ........................................ 37

Pharmacological Reperfusion Therapy with Tenecteplase in 7,668
Indian Patients with ST Elevation Myocardial Infarction – A Real
World Indian Experience
SS Iyengar, Tiny Nair, Jagdish Hiremath, Anjan Lal Dutta,
Uday Jadhav, VK Katyal, Dayanand Kumbla,
Immoneni Sathymurmurthy, RK Jain, M Srinivasan,
Prasant Kr Shahoe .............................................................. 43

A Randomized, Controlled, Phase III Clinical Trial to Evaluate the
Efficacy and Tolerability of Risorinon with Conventional
Rifampicin in the Treatment of Newly Diagnosed Pulmonary
Tuberculosis Patients
Naresh Patel, K Jagannath, Agam Vora, Mukesh Patel, Anand Patel... 48

CONSSENSUS STATEMENT

Executive Summary: Association of Physicians of India: Position
Statement on Role of Chirally Pure Molecules in Clinical
Practice
Milind Y Nadkar, Mangesh Tiwaskar, Sanjay Kalra,
Siddharth N Shah, BR Bansode, Anjanal Dutta, Sarita Bajaj,
Sameer Aggarwal, Yatan Pal Singh Balhara, AK Das,
Puneet Dhamija, YK Gupta, Jubbin Jacob, Sundeed Mishra,
SN Narasinging, CK Pande, Ram Prabhaa, S Balakrishnan,
Manisha Sahay, RK Sahay, I Sathymurmurthy, Shilpa Tiwaskar,
Agam Vora ................................................................. 60

REVIEW ARTICLE

Pancreatic Exocrine Insufficiency in Type 1 and 2 Diabetes:
Therapeutic Implications
Rupjyoti Talukdar, D Nageshwar Reddy ............................... 64

PLATFORM PRESENTATION

Presenting Research Paper: Learning the steps
Sandeep B Bavdekar, Varun Anand, Shruti Vyas ....................... 72

STATISTICS FOR RESEARCHERS

Principles of Interim Analysis
NJ Gogtay, UM Thatte ....................................................... 78

PICTORIAL CME

Mets Here, Mets There, Mets Everywhere....
Amey Beedkar, Rohan Parikh, Pradeep Deshmukh ................. 84

Termination of Ventricular Tachycardia by Anti Tachycardia
Pacing-An Uncommon Diagnosis on 12 Lead Surface ECG
Vaibhav M Dedhia ............................................................ 86

CASE OF THE MONTH

An Interesting Case of Recurrent Pyelonephritis
Achintya Dinesh Singh, Siddharth Jain, Agrima Mian,
Surabhi Vyas, Neeraj Nischal, Pankaj Jorwal ......................... 88

CASE REPORT

CMV Pneumonitis following Bendamustine containing
Chemotherapy
Sumeet Vimal Kishor Singhania, Pujan Parikh, Sandeep Goyle .... 92

Eosinophilic Ascites-Rarest Presentation of a Rare Disease,
Eosinophilic Gastroenteritis
Iqbal Bagasrawala, JK Maniar, Abizer Manked,
Hozefa Runderawala ...................................................... 93

Hereditary Haemorrhagic Telangiectasia with Severe Anemia
and Recurrent CNS Infections
NRushen Peesapati, PBPR Naidu, S Sunitha, PY Sivaram ......... 96

Paraneoplastic Inverse Myasthenic Syndrome as a Presentation
of Bronchogenic Carcinoma
GS Chowdhary, Malav Jhala ............................................. 98

DRUG CORNER

Role of Clarithromycin in Acute Exacerbations of Chronic
Obstructive Pulmonary Disease
Agam Vora ........................................................................ 100

MEDICAL PHILATELY

Sneezing – Physiological Facts and Beliefs
Geeta Gore, Aparna Verma .................................................. 106

CORRESPONDENCE

Drug Interaction between Acenocoumarol and Linezolid
Kinjalka Gosh, Kanakshka Gosh ........................................ 107

Rising Levels of Antibiotic Resistance in Bacteria:A cause for
Concern
Rathindranath Sarkar, Rudrajit Paul, Debodita Roy,
Indranil Thakur, Jayanti Roy, Tanmay Jyoti Sau, Kunal Haldar,
Jayati Mandal ................................................................. 107

A Patient with Dilated Cardiomyopathy and Portal
Hypertension:Which Beta-Blocker to Use?
Rathindranath Sarkar, Rudrajit Paul, Debodita Roy, Asim Saha,
Tanmay Jyoti Sau, Jayati Mandal ...................................... 108

ANNOUNCEMENTS

39th CME in Internal Medicine ........................................... 16
Workshops during CME APICON 2018, Bengaluru ................. 27
15th International Conference on Cardiology, Diabetology,
Electrocardiology, Echocardiography & Critical Care-2017,
Bhopal ................................................................. 109
Manage HbA1c, Blood Pressure & Cholesterol of CV AD

For your T2DM patients, think metformin, use metsmall®
the smart decision

For Dyslipidemia in T2DM Patients
ROZAT™
Lead the Lipid Revolution

In Hypertensive Patients
Stamlo®
Once-a-Day
Amlodipine 2.5 mg / 5 mg / 10 mg tabs.
leader at heart

In Diabetic Hypertensives uncontrolled on Monotherapy
Stamlo-T®
Amlodipine 5 mg + Telmisartan 40 mg tabs.
Powerful & Consistent BP Control

For the use of a Registered Medical Practitioner, Hospital or Laboratory only or as per the description under Form 46 of the Drugs & Cosmetics Act, 1940

Dr. Reddy’s Laboratories Ltd., Global Generics - India,
7-1-27, Ameerpet, Hyderabad - 500 016, India; www.drreddys.com
Editorial Board (2017-2018)

EMERITUS EDITORS
VR Joshi • Shashank R Joshi

EDITOR-IN-CHIEF
Milind Y Nadkar

EXECUTIVE EDITOR
Siddharth N Shah

ASSOCIATE EDITORS
Sandhya A Kamath • Gurpreet Singh Wander
Amar Pazeer • Rajeev Soman

ASSISTANT EDITORS
RR Chaudhary • Falguni Parikh
Agam Vora • Vikram Londhey

MEMBERS
Shibendu Ghosh • Niteen Karnik • SV Kulkarni
Ghan Shyam Pangtey • Trupti Trivedi

EX-OFFICIO
BR Bansode • Mangesh Tiwaskar

Jt. SECRETARY
Shobha M Itolikar

Advisory Board (2017-2018)

Philip Abraham
MB Agarwal
Rakesh Aggarwal
MS Amraesan
DN Amrapurkar
S Arulraj
Smrati Bajpai
Sripad Banavali
Amar K. Banerjee
Sandeep Bawdekar
D Behera
Rakesh Bhadade
Ashit M Bhagwati
Sudhir Bhandari
Shobna Bhatia
Smita M Chakote
Sekhar Chakraborty
Anil Chaturvedi
VP Chaturvedi
MPS Chowla
M Chenniappan
RM Chhabra
AR Chogle
RR Choudhary
SN Chugh
Sidhartha Das
Alaka Deshpande
Shubhangi V Dhakde
Vithal N Dhakde
SB Ganguly
Liyakat Ali Gauri
K Ghosh
Soumitra Ghosh
Nithya Gogtay
Yojana Gokhale
SK Goyal
Virender Kr Goyal
Pramit Gupta
Vishal Gupta
Ashutosh Halder
Rohini Handa
L Harshvardhan
NK Hase
DK Hazara
Shivkumar Iyer
Charu K. Jani
Bhavin Jankharia
RV Jayakumar
SK Jindal
Kavita Joshi
Shilpa S Joshi
Mala Kaneria
SV Khadilkar
Uday Khopkar
Renuka Kulkarni
Vrinda Kulkarni
Vikram Lele
Charulata V Londhey
SV Madhu
BK Mahavarkar
Sanjiv Maheshwari
M Maiya
JK Maniar
Arvind Mathur
Girish Mathur
Kalpana Mehta
Sudhir Mehta
AP Misra
Isaac C Moses
K Mugundhan
YP Munjal
JMK Murthy
A Muruganathan
Sita Naik
Velu Nair
SN Narasingan
G Narasimolu
CL Nawal
Rajan Nerukar
JJotirmoy Pal
Jayant Kr Panda
Vijay Panikar
KK Pareek
Rajesh Patil
Deepak Patkar
Anirudha Phadke
Munish Prabhakar
Anupam Prakash
YSN Raju
C Venkata S Ram
Praveen R K Rathi
Neelam N Redkar
BB Rewari
Mrinal Kanti Roy
Banshi Saboo
Rakesh Sahay
Anjan Saikia
Santosh Salagre
SA Sangle
K Sarat Chandra
SK Sarin
RN Sarkar
Nalini Shah
Raman Sharma
SK Sharma
Ashit Sheth
NP Singh
SK Singh
Surjit Singh
Archna Sonawale
NK Soni
Uma Sundar
Avinash N Supe
Rakesh Tandon
Kamlesh Tewary
BB Thakur
Urmila Thatte
AG Unnikrishnan
V.Vahia
Prema Varthakavi
Subhash Verma
Vijay Viswanathan
Gurpreet S Wander

Subscription Information
Journal of The Association of Physicians of India is published monthly. The annual subscription is ₹ 10,000 (India) and US $ 500 (other countries). The journal is dispatched within India by surface mail and to other countries by sea mail.

Copyright and Photocopying
No part of this publication may be reproduced, or transmitted in any form or by any means, electronic or mechanical, including photocopy without written permission from the Hon. Editor.

Business Correspondence
Enquiries concerning subscription, advertisement, etc. should be addressed to Prof. Milind Y. Nadkar, Editor-in-Chief, JAPI, No. 006 & 007, Turf Estate, Dr. E. Moses Road, Opp Shakti Mill Compound, Mahalaxmi (West), Mumbai-400 011.

Printed, Published and Edited by
Prof. Milind Y. Nadkar, on behalf of The Association of Physicians of India, Journal of The Association of Physicians of India, Turf Estate, Unit No. 006 & 007, Opp. Shakti Mill Compound, Off Dr. E. Moses Road, Near Mahalaxmi Railway Station (West), Mumbai-400 011.

Advertorial Enquiry:
Prof. Milind Y. Nadkar, Editor-in-Chief, JAPI, No. 006 & 007, Turf Estate, Dr. E. Moses Road, Opp. Shakti Mill Compound, Mahalaxmi (West), Mumbai-400 011.

Printed at Shree Abhyudaya Printers, A2/210, Shah & Nahar Industrial Estate, Lower Parel (West), Mumbai 400 013.

E-mail: onlinejapi@gmail.com / api.hdo@gmail.com

JAPI App: myJAPI
www.japi.org

Printed at Shree Abhyudaya Printers, A2/210, Shah & Nahar Industrial Estate, Lower Parel (West), Mumbai 400 013.

Tel.: (022) 2494 5863 * urvi@urvi.cc

Journal of The Association of Physicians of India • Vol. 65 • September 2017
GOVERNING BODY (2017-2018)

President Elect
Pritam Gupta (New Delhi) (2018)

President
BR Bansode (Mumbai) (2018)

Past President
Gurpreet Singh Wander (Ludhiana) (2018)

Vice Presidents
Girish Mathur (Kota) (2018)

BB Rewari (New Delhi) (2019)

Hon. General Secretary
Mangesh Tiwaskar (Mumbai) (2019)

Jt. Secretary (HQ)
Ashit M Bhagwati (Mumbai) (2019)

Hon. Treasurer
Charu K Jani (Mumbai) (2020)

Members
Vijay Viswanathan (Chennai) (2018)

MPS Chawla (New Delhi) (2018)

Sekhar Chakraborty (Siliguri) (2018)

DP Singh (Bhopalpur) (2018)

Central Zone
Rajinder K Bansal (Ludhiana) (2018)

North West Zone
Prabhat Pandey (Bikaner) (2019)

West Zone
Narayan Deogaonkar (Nasik) (2020)

North Zone
RM Chhabra (New Delhi) (2020)

Mid South Zone
Naval Chandra (Hyderabad) (2020)

South Zone
K Mugundhan (Salem) (2020)

Mid East Zone
RR Choudhary (Patna) (2020)

East Zone
RN Sarkar (Kolkata) (2020)

Zonal Members

Invited Members
Editor-in-Chief, API Text Book
Sandeep Kumar (New Delhi)

Ex-Officio Members

Dean, ICP
Rohini Handa (New Delhi) (2018)

Director, PRF
YP Munjal (Gurgaon) (2018)

Co-opted Members

Jt. Secretary (President’s place)
Nihar Mehta (Mumbai)

Organising Secretary, APICON 2018
P Chandrasekhar (Bengaluru)

Organising Secretary, APICON 2017
Shashank R Joshi (Mumbai)

Indian College of Physicians

FACULTY COUNCIL (2017-2018)

Chairman
BR Bansode (Mumbai) (2018)

Dean
Rohini Handa (New Delhi) (2018)

Dean Elect
G Narasingul (Hyderabad) (2018)

Dean, ICP
Rohini Handa (New Delhi) (2018)

Hon. Gen. Secretary
Mangesh Tiwaskar (Mumbai) (2019)

Past Dean
A Muruganathan (Tirupur) (2018)

Jt. Secretary (H.Q.)
Ashit M Bhagwati (Mumbai) (2019)

Jt. Secretary (Dean’s place)
AP Mishra (New Delhi) (2019)

Hon. Treasurer
Charu K Jani (Mumbai) (2020)

Elected Members
Rakesh Gupta (New Delhi) (2018)

Anupam Prakash (New Delhi) (2019)

SB Ganguly (Kolkata) (2020)

Jayanta Kumar Panda (Cuttack) (2018)

PS Karmakar (Kolkata) (2019)

Atul Bhasin (New Delhi) (2020)

Y Satyanarayana Raju (Hyderabad) (2018)

Sudhir Mehta (Jaipur) (2019)

Vikram A Londhey (Mumbai) (2020)

Shriram V Kulkarni (Khopoli) (2018)

Jai Bhagwan (Gurgaon) (2019)

Udai Lal (Hyderabad) (2020)

Ex-Officio Members

President Elect
Pritam Gupta (New Delhi)

Editor-in-Chief, API
Milind Y Nadkar (Mumbai)

Director - PRF
YP Munjal (Gurgaon)

Editor-in-Chief, API Text Book
Sandeep Kumar (New Delhi)

Physicians Research Foundation

BOARD OF DIRECTORS (2017-2018)

Chairman
BR Bansode (Mumbai) (2018)

Dean
YP Munjal (Gurgaon) (2019)

Hon. General Secretary
Mangesh Tiwaskar (Mumbai) (2019)

Jt. Secretary (Director’s Place)
Ghan Shyam Panthay (New Delhi)

Hon. Treasurer
Charu K Jani (Mumbai) (2020)

Members
Soumitra Ghosh (Kolkata) (2018)

Ashok Kumar Das (Puducherry) (2019)

JK Mitra (Ranchi) (2020)

AK Mukherjee (Kolkata) (2018)

Suman Bhandari (New Delhi) (2019)

Shyam Sundar (Varanasi) (2020)

Invited Members
Editor-in-Chief, API
Milind Y Nadkar (Mumbai)

Editor-in-Chief, API Text Book
Sandeep Kumar (New Delhi)
Don’t let the RBCs shed out their original colour

Retain the Original Colour of RBCs

With **DEXORANGE**

Syrup/Capsules/Powderable Syrup

(Ferrous Ammonium Citrate)

The Masterpiece in Hematinics

- Pregnancy & Lactation
- General Weakness
- Anaemia
- Chemotherapy Induced Anaemia
- High Blood & Iron Dyscrasias
- Loss of Appetite
- Circulatory Disturbances
- Nutritional Anaemia
- Cirrhosis Extraordinary

[Advertisement Image]
Once-daily TRESIBA®
ULTRA-LONG
DURATION OF ACTION

GET HbA1c DOWN WITH CONTROL

- Successful reductions in HbA1c
- Lower risk of nocturnal hypoglycaemia versus glargine
- Flexibility in day-to-day dosing time when needed
...delivered in a once-daily dose.


For the use of Tresiba®, Tresiba® Auto-injector and Tresiba® Pen by registered medical practitioners or authorized healthcare professionals only.

Novo Nordisk India Private Limited
Plot No. 32, 47-50, EPIL Area,
Whitefield, Bangalore - 560 066. India
visit us at: www.novonordisk.co.in

TRESIBA®
insulin degludec [rDNA origin] injection

US FDA Approved

US FDA Approved

US FDA Approved

US FDA Approved

US FDA Approved
Fosfomycin: A Revived Antibiotic for Urinary Tract Infections

Falguni S Parikh

Urinary tract infections (UTIs) are the most commonly encountered bacterial infections. Approximately 100,000 hospitalizations occur due to UTIs mostly in susceptible population like women, elderly, diabetics, patients on indwelling catheters, patients with bladder involvement due to spinal cord diseases or multiple sclerosis etc.

Enterobacteriaceae are commonly implicated organisms. Various studies from India have shown presence of Escherichia coli (E coli) as the commonest bacteria causing UTI followed by Klebsiella.1 Multi-resistant enterobacteriaceae due to the production of extended spectrum β-lactamases (ESBL) have become very common in India.2,3

Just as in other infections there is an increasing incidence of multidrug resistant and extensively drug resistant bacteria causing UTI especially in patients with comorbidities and repeated antibiotic exposures.4,5 Easy availability of over the counter antibiotics and inappropriate antibiotic use compound the problem. Symptomatic UTIs are often treated on empiric basis for short duration without sending urine cultures causing incomplete clearance of the bacteria and development of resistance. Rapidly increasing resistance in uropathogens compels physicians to use still higher antibiotics like beta lactam beta lactamase inhibitors, carbapenems and now even colistin. The resistance spectrum of pathogens varies in different regions.

Extended spectrum beta lactamase (ESBL) are plasmid or chromosomally mediated beta lactamases with broad activity against penicillins, cephalosporins and monobactams. They inactivate the beta lactam antibiotic function by breaking amide bond of beta lactam ring. 28-84% ESBL production is reported from various Indian studies.3,6,7 Carabapenemase enzyme renders carbapenems like imipenem and meropenem useless. These are of serious concern as there are very few new antibiotics in the pipeline.

There is a worldwide concern about the MDR and XDR organisms causing UTI and Infectious Diseases Society of America recommends that the physicians obtain information on local resistance spectrum of organism causing UTIs and that ongoing surveillance be conducted to monitor changes in susceptibility of uropathogens.8

Fosfomycin, originally named phosphonomycin, was discovered in Spain in 1969.9 Fosfomycin inhibits phosphoenolpyruvate transferase, the first enzyme involved in the synthesis of peptidoglycan, inhibiting cell-wall synthesis.10

There are three forms of Fosfomycin: Fosfomycin tromethamine (a soluble salt) and Fosfomycin calcium for oral use, and Fosfomycin disodium for intravenous use. Fosfomycin, is a safe antibiotic with limited adverse events.

Oral Fosfomycin is mainly used in the treatment of urinary tract infections, particularly those caused by Escherichia coli and Enterococcus faecalis.

It remains a reliable therapeutic option for uncomplicated UTI due to its main advantages, including single dose usage and very high and sustained urinary concentrations that rapidly kill bacteria, reducing the opportunity for mutant selection.

Intravenous fosfomycin has been administered in combination with other antibiotics for the treatment of nosocomial infections due to multidrug-resistant (MDR) bacteria.11-13 Intravenous fosfomycin is available in India since 2016. The recommended dose for complicated UTI is 12-16 g in 2-3 divided doses.

The laboratory methods that have been used for the determination of in vitro susceptibility of Gram-positive and Gram-negative pathogens to Fosfomycin include agar (Mueller-Hinton agar) dilution, broth dilution, disk diffusion, and E test techniques.

In this issue of the Journal, Patel et al present their findings about Fosfomycin susceptibility using E test in urinary tract infections caused by enterobacteriaceae. Of the 72 isolates 57(79%) were susceptible, 5 were intermediate and 10 were resistant to fosfomycin. There was 92% susceptibility in ESBL producing enterobacteriaceae and 72.34% sensitivity in...
carbapenemase resistant bacteria. Number of resistant isolates was more by EUCAST as compared to CLSI breakpoint criteria.

Using more stringent criteria may help for selecting appropriate antibiotic doses with the goal of increasing treatment efficacy and reducing the risk of selecting multidrug-resistant pathogens.

Microbiological evidence of high in vitro susceptibility of the enterobacteriaceae to Fosfomycin makes it a potentially effective antimicrobial option for UTIs. It necessitates further exploration in order to determine the appropriate therapeutic regimen, whereas the possibility of monotherapy to induce resistance in vivo requires careful clinical studies.

References


Chellaram Diabetes Institute

2nd International Diabetes Summit - 2018
Pune

9th - 11th March, 2018 (Friday - Sunday)

With Faculty From
Karolinska Institute, Sweden ● Mayo Clinic, USA ● University of Manchester, UK
University of Turin, Italy ● University of London, UK ● The Best Speakers From All Over India

Highlights -
1st International Diabetes Summit - 2017

- 50 National and 12 international speakers from USA and Europe
- 1500 attendees, Oral/Poster presentations by 35 young researchers.
- The Maharashtra Medical Council awarded 7 Credit Points to the program.

REGISTRATION FORM
First Name ___________________________ Surname ___________________________ Gender M / F

MMC / Other Council No. ___________________________

Hospital / Institution ____________________________________________________________
Qualification ___________________________ Specialty ___________________________
Address for Communication _______________________________________________________

City ___________________________ Pincode ___________________________ State / Country ___________________________
Mobile Number / Contact No (with area code) ___________________________ Email Id ___________________________

PAYMENT DETAILS

<table>
<thead>
<tr>
<th>Category</th>
<th>Up to 1st Jan 2018</th>
<th>Up to 8th March 2018</th>
<th>Spot</th>
</tr>
</thead>
<tbody>
<tr>
<td>National Delegate</td>
<td>Rs. 7,000/-</td>
<td>Rs. 7,500/-</td>
<td>Rs. 9,500/-</td>
</tr>
<tr>
<td>PG Student*</td>
<td>Rs. 4,000/-</td>
<td>Rs. 4,500/-</td>
<td>Rs. 5,500/-</td>
</tr>
<tr>
<td>HCPs</td>
<td>Rs. 7,000/-</td>
<td>Rs. 7,500/-</td>
<td>Rs. 9,500/-</td>
</tr>
<tr>
<td>International Delegate</td>
<td>USD 200/-</td>
<td>USD 250/-</td>
<td>USD 300/-</td>
</tr>
</tbody>
</table>

*This includes PHFI candidates

Medvents Conferences & Events Pvt Ltd
E-mail: reachmedevents@hotmail.com
Supriya Tak: +91 7767834459

Please send the cheque/DD in favour of “Chellaram Foundation” to:
The Secretariat Address: 2nd International Diabetes Summit 2018
Chellaram Diabetes Institute, Lalani Quantum, Pune-Bangalore-Nh4
Bavdhan (Budruk) Pune - 411021 | E-mail: lds@cdi.org.in
Contact Ms. Shraddha U. Mahajan: 020 - 66839722

For regular Updates please visit:
www.cdidiabetesummit.org / www.cdi.org.in
Fosfomycin Susceptibility in Urinary Tract Enterobacteriaceae

Bhargav Patel¹, Kinjal Patel², Anjali Shetty³, Rajeev Soman⁴, Camilla Rodrigues³

Abstract

Introduction: Antibiotic treatment of Urinary Tract Infections (UTI) is becoming increasingly difficult due to emergence of multi-drug resistant (ESBLs, AmpC, CRE) uropathogens. Fosfomycin is an old antibiotic that has evoked renewed interest with unique properties of not sharing any structural similarity and lack of cross-resistance with other antimicrobial agents. Our aim is to evaluate in-vitro activity of Fosfomycin against urinary tract Enterobacteriaceae.

Material and Methods: The study period was March 2014 to September 2015. All 72 isolates were identified using conventional biochemical tests. Antimicrobial susceptibility testing was performed using the automated broth microdilution system Vitek 2 (bio- Mérieux, Inc., Durham, NC). Fosfomycin susceptibility was determined by the E-test (bioMérieux, Inc., Durham, NC) method. Interpretive criteria from the Clinical and Laboratory Standards Institute (CLSI) for fosfomycin susceptibility are not available for the Enterobacteriaceae other than Escherichia coli. Therefore, results were interpreted according to criteria for E. coli (i.e., susceptible at a MIC of ≤ 64 µg/ml), as has been reported previously.

Results: Overall, 79.16% (57/72) isolates were susceptible to fosfomycin with 92.00% (23/25) susceptibility in ESBL producing enterobacteriaceae and 72.34% (34/47) in CRE. One CRE isolate has developed resistant while on treatment. There was not much difference in number of susceptible isolates CLSI:EUCAST = 57:53, but number of resistant isolates was more with EUCAST (CLSI:EUCAST = 10:19).

Conclusion: Study demonstrate that, a considerable proportion (79.16%) of the multidrug-resistant Enterobacteriaceae with diverse resistance mechanisms, including ESBL and CRE, found susceptible to fosfomycin. Consequently, fosfomycin may currently be considered a useful antibiotic agent in the treatment armamentarium of UTIs.

Introduction

Antibiotic treatment of Urinary Tract Infections (UTI) is becoming increasingly difficult due to emergence of multi-drug resistant (ESBLs, AmpC, CRE) uropathogens. Fosfomycin is an old antibiotic that has evoked renewed interest with unique properties of not sharing any structural similarity and lack of cross-resistance with other antimicrobial agents. It inhibits cell wall formation by binding to enzyme UDP-N-acetylglucosamine and inhibits formation of the cell wall precursor N-acetylmuramic acid. It has broad antimicrobial spectrum against MDR pathogens, both Gram-negative and Gram-positive organisms. Recent reports show in vitro activity against carbapenem-resistant Klebsiella pneumoniae (CR-Kp), Pseudomonas aeruginosa, extended-spectrum β-lactamase (ESBL) producing bacteria, and vancomycin-resistant enterococci (VRE). IDSA and ESCMID recommends fosfomycin as one of the first line agent for uncomplicated cystitis and pyelonephritis. Susceptibility testing of this agent requires

Table 1: CLSI and EUCAST interpretative criteria for fosfomycin

<table>
<thead>
<tr>
<th>Disc content</th>
<th>CLSI</th>
<th>EUCAST</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zone diameter</td>
<td></td>
<td></td>
</tr>
<tr>
<td>200 µg</td>
<td>≥ 16</td>
<td>13-15</td>
</tr>
<tr>
<td>MIC</td>
<td>≤ 64</td>
<td>128</td>
</tr>
</tbody>
</table>

¹Consultant Microbiologist, HCG Hospital, Ahmedabad, Gujarat; ²Clinical Assistant, ³Consultant Microbiologist, ⁴Consultant Physician and Infectious Disease Specialist, PD Hinduja Hospital and MRC, Mumbai, Maharashtra

Received: 24.05.2016; Accepted: 29.05.2017
Intermediate - 1 - 1 - 1 - 1 - 1 5
17 11 5 8 1 10 - - - 5 57
Susceptible
Resistant 10

Intermediate 05 -
Susceptible

isolates of diffusion and agar dilution method 

1). CLSI approves only disk susceptibility are different (Table 

for interpretation of fosfomycin 

performed using the automated susceptibility testing was 

biochemical tests. Antimicrobial 

identified using conventional 

study period. All isolates were 

isolates were tested during the 

2014 to September 2015. Total 72 

Material and Methods 

in admitted patients at our tertiary 

care centre.

infections other 

organisms.

and agar dilution method 

that too only for 

Escherichia coli 

Enterococcus faecalis without 

microdilution criteria.6 EUCAST 

recommends both agar dilution 

and broth microdilution.7 Data 

from studies evaluating the role 

of fosfomycin in infections other 

than UTIs are also encouraging.3,9-11 

Given its unlinked mechanism 

of resistance, its real value may be in 

the treatment of CRE, rather than as 

an alternative for ESBL producing 

organisms.

Aim and Objectives 

We assessed the in vitro activity 

of fosfomycin against multidrug 

resistant urinary Enterobacteriaceae 
in admitted patients at our tertiary 
care centre.

Material and Methods 

The study period was March 
2014 to September 2015. Total 72 
isolates were tested during the 
study period. All isolates were 
identified using conventional 
biochemical tests. Antimicrobial 
susceptibility testing was 
performed using the automated 
broth microdilution system Vitek 
2 (bio- Mérieux, Inc., Durham, 
NC). We used CLSI guidelines to 
identify ESBL production. CRE 
were defined according to CDC 
definition used for infection control 
purpose. Fosfomycin susceptibility 
was determined by the E-test 
(bioMérieux, Inc., Durham, NC) 
method. Interpretive criteria 
from the Clinical and Laboratory 
Standards Institute (CLSI) for 
fosfomycin susceptibility are not 
available for the Enterobacteriaceae 
other than Escherichia coli.10 
Therefore, results were interpreted 
according to criteria for E. coli (i.e., 
susceptible at a MIC of ≤ 64 µg/ml), 
as has been reported previously.2,4,10 
Comparison of susceptibility using 
CLSI and EUCAST breakpoints was 
also made (Table 3).

Results 

Overall, 79.16% (57/72) isolates 
were susceptible to fosfomycin 
(Table 2) with 92.00% (23/25) 
susceptibility in ESBL producing 
enterobacteriaceae and 72.34% 
(34/47) in CRE. One CRE isolate 
has developed resistant while on 
treatment.

There was not much difference 
in number of susceptible isolates 
(Table 3) CLSI:EUCAST = 57:53, 
but number of resistant isolates 
was more with EUCAST (CLSI : 
EUCAST = 10:19).

Discussion 

This study revealed good 
susceptibility against ESBL 
producing Enterobacteriaceae 
similar to earlier observations.4 
Fosfomycin was found to be 
susceptible in 72.34% (34/47) of 
CRE isolates. These data are in 
cordance with others.12,14 

Though only one susceptible 
isoalte developed resistance 
while on treatment in our study, 
correlation between in-vitro 
susceptibility and microbiological 
cure is required. Neuner concluded 
that the rate of microbiological 
cure (59%) was lower than that of 
in-vitro susceptibility (86%).15 

Based on predictable urinary 
levels of fosfomycin, it would 
seem that EUCAST breakpoints 
are very stringent, while CLSI 
breakpoints would be more 
applicable, even to systemic 
fections. Chinnappan addressed 
the issues of interpretive criteria 
and methodology of susceptibility 
testing.16 Kaase compares 
susceptibility testing methods, 
like Etest and disk diffusion with 
agar dilution and found that Etest 
and disk diffusion showed poor 
agreement with fosfomycin agar 
dilution.14 Perdigao-Neto studied 
the activity of fosfomycin against 
MDR-Gram negative bacilli and demonstrated that with the high 
level of fosfomycin achievable in 
blood with intravenous infusion, 
the EUCAST breakpoint may 
be very stringent and the CLSI 
breakpoint may be applicable for 
systemic infections with MDR Gram 
negative bacilli and wide difference 
in susceptibility occurred between 
E-test and agar dilution method.17 

Conclusion 

In conclusion, a considerable 
proportion (79.16%) of the 
multidrug- resistant 
Enterobacteriaceae with diverse 
resistance mechanisms, including 
ESBL and CRE, found susceptible 
to fosfomycin. Consequently, 
fosfomycin may currently be 
considered a useful antibiotic agent 
in the treatment armamentarium of 
UTIs.

Table 2: Susceptibility to fosfomycin using CLSI 

<table>
<thead>
<tr>
<th>Fosfomycin</th>
<th>E. coli</th>
<th>Klebsiella spps</th>
<th>Enterobacter spps</th>
<th>Proteus spps</th>
<th>Morganella spps</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Susceptible</td>
<td>17</td>
<td>11</td>
<td>5</td>
<td>1</td>
<td>10</td>
<td>-</td>
</tr>
<tr>
<td>Intermediate</td>
<td>-</td>
<td>1</td>
<td>-</td>
<td>1</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td>Resistant</td>
<td>1</td>
<td>-</td>
<td>1</td>
<td>5</td>
<td>-</td>
<td>1</td>
</tr>
<tr>
<td>18</td>
<td>12</td>
<td>6</td>
<td>14</td>
<td>1</td>
<td>12</td>
<td>-</td>
</tr>
</tbody>
</table>

Table 3: Comparison of susceptibility using CLSI and EUCAST breakpoints 

<table>
<thead>
<tr>
<th>Fosfomycin</th>
<th>CLSI</th>
<th>EUCAST</th>
</tr>
</thead>
<tbody>
<tr>
<td>Susceptible</td>
<td>57</td>
<td>53</td>
</tr>
<tr>
<td>Intermediate</td>
<td>05</td>
<td>-</td>
</tr>
<tr>
<td>Resistant</td>
<td>10</td>
<td>19</td>
</tr>
</tbody>
</table>
References


39th CME in Internal Medicine

Conducted by Medical Education & Research Trust, Bangalore from 21st to 27th September, 2017

Morning – Guest Lecture, Workshops & Symposium.

Afternoon - Bedside Clinics & Case Discussion by Eminent Teachers

Registration Fees: Rs.3,000/- only

Last date for Registration 15th September, 2017

After 15th September - Rs.4,000/-

Pay by draft to Convener CME in Internal Medicine, Bangalore

Programme Directors

Dr. P. Chandrasekhar
poocha_sekhara@yahoo.co.in

Dr. V. Channaraya
Mobile: 9341234049 • veraya@yahoo.com

Convenor
Dr. K. Ravi - 9845128212
e-mail: ravikdoc@gmail.com

Address for Correspondence: The Convenor, Medical Education & Research Trust, API Bhavan, No.16/F, Millers Tank Bed Area, Vasanthnagar, Bangalore 560 052. Ph. No.: 080-02353525 / 9845128212 (M) e-mail: apikarnataka@gmail.com
All that shines is not Vitamin D

In Vitamin D₃ Insufficiency and Deficiency

Rx zinDee™
Cholecalciferol Granules 60,000 I.U.
Sachets

Makes Life Lightful

FRANCO-INDIAN PHARMACEUTICALS PVT. LTD.
23, Dr. E. Moses Road, Marathahalli 400 011
A Study of Endothelial Dysfunction in Patients of Non-Alcoholic Fatty Liver Disease

Vaibhav Shukla¹, Jalees Fatima¹, Saurabh Chaudhary², Mohsin Ali², Ishan Mishra²

Abstract

Introduction: The prevalence of non-alcoholic fatty liver disease (NAFLD) is increasing worldwide rapidly and is regarded as the hepatic manifestation of metabolic syndrome. The present study was undertaken to study the endothelial dysfunction by flow mediated vasodilatation in NAFLD patients.

Material and Methods: 32 cases and 16 age and sex matched controls were included in the study. Flow mediated vasodilatation of the brachial artery was studied in both cases and controls. Anthropometric, clinical and biochemical assessment was also done.

Results: It was found that NAFLD patients had a significant endothelial dysfunction as assessed by flow mediated vasodilatation as compared with controls. Percentage change in FMD among NAFLD patients (13.54±3.65%) was found to be lower than that in controls (16.84±4.61%) and difference was found to be statistically significant (p 0.010).

Conclusion: From the present study it can be concluded that NAFLD patients have significant endothelial dysfunction even in the absence of traditional risk factors of cardiovascular disease.

Introduction

Non alcoholic fatty liver disease (NAFLD) is fast attaining the status of being the most common disease throughout the world. The prevalence is as high as 20-30% of general population in western countries¹-⁴ while in India the prevalence in various studies varies from 9-32% in different studies.⁵-⁷ NAFLD is regarded by many to be the hepatic manifestation of metabolic syndrome and therefore it may be linked to cardiovascular disease. Since there are few studies on endothelial dysfunction in NAFLD we decided to undertake this study to assess endothelial function in NAFLD patients by flow mediated vasodilation.

Material and Methods

This was a case control study conducted in the department of medicine. All patients of NAFLD above 18 years of age who were diagnosed ultrasonographically were included in the study. Patients of NAFLD who had hepatitis B & C, autoimmune hepatitis, primary biliary cirrhosis, Wilson’s disease, chronic alcohol intake, diabetes, hypertension, dyslipidemia, on statin therapy and smokers were excluded from the study. Age and sex matched healthy individuals served as controls. A written informed consent was taken from all patients. The patients underwent a complete clinical examination, anthropometric measurements, laboratory tests and ultrasonography.

FMD= \frac{d_2-d_1}{d_1} \times 100

where \( d_2 \) = Brachial artery diameter at 5 min post deflation and \( d_1 \) = Base line brachial artery diameter

Editorial Viewpoint

• Non-alcoholic fatty liver disease is regarded as the hepatic manifestation of metabolic syndrome.
• This study finds NFLD patients have significant endothelial dysfunction even in the absence of traditional risk factors of cardiovascular disease.

Procedure for Measurement of Flow Mediated Vasodilatation (FMD)

A longitudinal section of the brachial artery was analysed; (Medial epicondyle was used as anatomical landmark for brachial artery). USG machine with high resolution (B) scan 7.5Hz linear accelerator was used to assess brachial artery diameter and its changes.

Flow mediated vasodilatation (FMD), which reflects endothelium dependent vasodilatation, was calculated as the percentage increase in diameter from baseline to the maximum value which is obtained after the cuff deflation using the following formula:

1Professor, 2Resident, Era Medical College, Lucknow, Uttar Pradesh
Received: 02-02-2017; Accepted: 28-04-2017
Results

The present study was conducted in the Department of Medicine of a teaching hospital to study the endothelial dysfunction by flow mediated vasodilatation in patients of Non-alcoholic Fatty Liver disease. All patients more than 18 years of age, admitted to indoor/attending the OPD in the Department of Medicine, and ultrasonographically diagnosed as non-alcoholic fatty liver disease were enrolled in the study. Of these, 32 cases fulfilling the inclusion criteria and giving consent to be included in the study were included as Cases. 16 Age and Sex matched controls were also included in the study.

Age of patients included in the study ranged from 22 to 72 years. The mean age of Cases was 45.06±10.91 years and that of Controls was 45.06±12.71 years (Table 1).

The BMI of subjects included as Cases and Controls ranged from 20-24.50 kg/m² while difference in mean BMI of Cases (22.27±1.48 kg/m²) and Controls (22.53±1.56 kg/m²) was not found to be statistically significant.

Chief complaint of majority of cases of NAFLD was abdominal pain (53.13%) followed by fullness of abdomen (37.50%) and decreased appetite (9.38%).

No statistically significant differences in above hematological and biochemical variables of Cases and Controls was found (p>0.05) (Table 2).

Though brachial artery diameter at baseline of Controls (3.81±0.16 mm) was found to be higher than that of Cases (3.78±0.17 mm) but difference in brachial artery diameter of Cases and Controls was not found to be statistically significant (p=0.533) (Table 3).

Range of Post-cuff deflation brachial artery diameter of Cases was 3.92-4.76 mm while that of Controls was 4.22-4.68 mm. Mean post-cuff deflation brachial artery diameter of Cases was 4.29±0.22 mm while that of Controls was 4.45±0.15 mm. Difference in post-cuff deflation brachial artery diameter of Cases and Controls was found to be statistically significant (p=0.013) (Table 3).

Range of change in Brachial artery in Cases was 0.2-0.90 mm while in Controls it was 0.36-0.93 mm. Mean brachial diameter change in Cases (0.51±0.14 mm) was found to be statistically significant. It was lesser than that in Controls (0.64±0.16 mm) (Table 3).

% Change in FMD among Cases (13.54±3.65%) was found to be lower than that in Controls (16.84±4.61%) and difference was found to be statistically significant (Table 4).

At baseline, statistically no significant difference was observed between two groups with respect to brachial artery diameter, however, post-cuff deflation diameter was found to be significantly lower in cases as compared to controls. On evaluating the change in brachial artery diameter too, it was found to be lower in cases as compared to controls for both absolute as well as percentage change (FMD%) (Table 5).

Discussion

Non-alcoholic fatty liver

Table 1: Demographic profile of study population

<table>
<thead>
<tr>
<th>Variables</th>
<th>Total</th>
<th>Cases (n=32)</th>
<th>Controls (n=16)</th>
<th>Statistical significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age Group</td>
<td></td>
<td>No.</td>
<td>%</td>
<td>No.</td>
</tr>
<tr>
<td>21-30</td>
<td>5</td>
<td>3</td>
<td>9.38</td>
<td>2</td>
</tr>
<tr>
<td>31-40</td>
<td>15</td>
<td>10</td>
<td>31.25</td>
<td>5</td>
</tr>
<tr>
<td>41-50</td>
<td>14</td>
<td>9</td>
<td>28.13</td>
<td>5</td>
</tr>
<tr>
<td>51-60</td>
<td>9</td>
<td>7</td>
<td>21.88</td>
<td>2</td>
</tr>
<tr>
<td>&gt;60</td>
<td>5</td>
<td>3</td>
<td>9.38</td>
<td>2</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>20</td>
<td>12</td>
<td>37.50</td>
<td>8</td>
</tr>
<tr>
<td>Male</td>
<td>28</td>
<td>20</td>
<td>62.50</td>
<td>8</td>
</tr>
</tbody>
</table>

Table 2: Comparison of hematological and biochemical variables in study population

<table>
<thead>
<tr>
<th>Variables</th>
<th>Cases (n=32)</th>
<th>Controls (n=16)</th>
<th>Statistical significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemoglobin (g/dl)</td>
<td>11.5-14.5</td>
<td>13.14 ± 0.86</td>
<td>11.5-14.5 ± 1.11 ± 0.84</td>
</tr>
<tr>
<td>S. Bilirubin (mg/dl)</td>
<td>0.4-1.1</td>
<td>0.77 ± 0.16</td>
<td>0.4-1.1 ± 0.79 ± 0.20</td>
</tr>
<tr>
<td>SGPT (IU/L)</td>
<td>20-45</td>
<td>33.66 ± 6.50</td>
<td>27-42 ± 36.25 ± 4.23</td>
</tr>
<tr>
<td>SGOT (IU/L)</td>
<td>22-48</td>
<td>34.63 ± 6.36</td>
<td>22-48 ± 30.94 ± 5.77</td>
</tr>
<tr>
<td>LDL (mg/dl)</td>
<td>60-96</td>
<td>57.16 ± 8.51</td>
<td>68-96 ± 77.31 ± 8.22</td>
</tr>
<tr>
<td>HDL (mg/dl)</td>
<td>44-58</td>
<td>50.63 ± 4.35</td>
<td>45-58 ± 51.63 ± 4.03</td>
</tr>
</tbody>
</table>

Table 3: Comparison of brachial artery diameter (in mm) at baseline, after producing ischemia (post-cuff deflation) and difference in diameter (post cuff diameter - baseline diameter)

<table>
<thead>
<tr>
<th>Total No. of subjects</th>
<th>Baseline</th>
<th>Brachial artery diameter</th>
<th>Difference after ischemia</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean ± S.D.</td>
<td>Range</td>
<td>Mean ± S.D.</td>
</tr>
<tr>
<td>Cases</td>
<td>32</td>
<td>3.78 ± 0.17</td>
<td>3.54 - 4.18</td>
</tr>
<tr>
<td>Controls</td>
<td>16</td>
<td>3.81 ± 0.16</td>
<td>3.62 - 4.15</td>
</tr>
<tr>
<td>Total</td>
<td>48</td>
<td>3.79 ± 0.16</td>
<td>3.54 - 4.18</td>
</tr>
</tbody>
</table>

* t=0.628; p=0.533; t=2.589; p=0.013
t=2.836; p=0.007
disease is a fast emerging global epidemic which is recognized as a common metabolic disorder that is closely associated with obesity and insulin resistance. With the growing epidemic of obesity, a high prevalence of NAFLD, ranging from 18 to 45%, has been reported in various ethnic groups. With the increasing evidence regarding relationship of NAFLD with obesity and insulin resistance, it has been shown to have a strong agreement with other associated risks related with obesity and insulin resistance. The increased association of NAFLD with obesity and insulin resistance has attracted the attention of researchers regarding its possible association with cardiovascular risk.

Endothelial dysfunction is a well established response to cardiovascular risk factors and precedes the development of atherosclerosis. Endothelial dysfunction is involved in lesion formation by the promotion of both the early and late mechanisms of atherosclerosis, including up-regulation of adhesion molecules, increased chemokine secretion and leukocyte adherence, increased cell permeability, enhanced low-density lipoprotein oxidation, platelet activation, cytokine elaboration, and vascular smooth muscle cell proliferation and migration. Endothelial dysfunction is a term that covers diminished production/availability of nitric oxide and/or an imbalance in the relative contribution of endothelium-derived relaxing and contracting factors. Also, when cardiovascular risk factors are treated the endothelial dysfunction is reversed and it is an independent predictor of cardiac events.

Although association between NAFLD and endothelial dysfunction as observed by flow mediated dilatation has been studied in various studies and some of these studies showed that irrespective of presence of components of metabolic syndrome (diabetes, obesity, dyslipidemia, hypertension), NAFLD itself was a strong predictor of endothelial dysfunction, thus opening a new dimension for exploration. With this background, the present study was carried out with an aim to study endothelial dysfunction by flow mediated vasodilatation in patients of Nonalcoholic Fatty Liver disease free of metabolic syndrome factors in terms of a comparative evaluation with normal healthy controls.

The age of NAFLD patients in present study ranged from 22 to 72 years. Majority of patients were above 40 years of age (59.4%). Mean age of patients was 43.06±10.91 years. In a study by Amarapurkar et al. (2007) it was reported that the prevalence of NAFLD was associated with age >40 years. However, they also found NAFLD prevalence to be associated with central obesity, elevated fasting blood sugar and raised liver functions. In the present study despite the absence of these risk factors, the age profile of patients did not show a change. However, in another study by Kim et al. (2004) mean age of patients with NAFLD was reported to be 53.2±9.8 years. However, the difference between two groups could be attributed to the difference in inclusion criteria. In present study, we included all the subjects above 18 years of age, however the inclusion criteria used by Kim et al. (2004) set the inclusion age to be 30 years. In the study of Mohammadi et al. (2011), who conducted the study in a design and patient selection criteria similar to ours, the mean age of patients was reported to be 38.7±14.952 years. In another study conducted by Colak et al. (2013) who also conducted their study in non-obese NAFLD patients reported the mean age to be 42.8±9.8 years. All these findings indicate towards a high age-related association of NAFLD, irrespective of the obesity status. With aging, the liver undergoes substantial changes in structure and function that are associated with significant impairment of many hepatic, metabolic and detoxification activities. Although NAFLD is not uncommon in children and teenagers yet in that situation it is mostly associated with obesity.

In present study, majority of patients were males (62.5%). Male to female ratio was 1.67:1. This finding is also in agreement with the observation made by Amarapurkar et al. (2007) who found NAFLD to be more prevalent in males than females. They reported a male to female ratio of 1.81:1.

In the present study, among NAFLD patients, pain abdomen (53.13%) was the most common complaint followed by fullness of abdomen (37.50%) and decreased appetite (9.38%) respectively. To the best of our knowledge none of these complaints have a known relationship with cardiovascular risk and endothelial dysfunction.

In the present study, baseline brachial artery diameter was 3.78±0.17 mm in NAFLD cases

| Table 4: Comparison of % change in FMD among study population |
|-----------------|-----------------|-----------------|-----------------|-----------------|
| Mean ± S.D.     | Range           |
|-----------------|-----------------|-----------------|-----------------|-----------------|
| Cases           | 13.54 ± 3.65    | 5.05 - 23.81    |
| Controls        | 16.84 ± 4.61    | 9.09 - 24.80    |
| Total           | 14.64 ± 4.25    | 5.05 - 24.80    |

\[ t = 2.699; \ p = 0.010 \]

| Table 5: Intergroup (cases-controls) change in brachial artery diameter from baseline and post- cuff deflation |
|-----------------|-----------------|-----------------|-----------------|-----------------|
|                 | Cases (n=32)    | Controls (n=16) | Significance of difference |
|                 | Mean ± S.D.     | Mean ± S.D.     | 't'             | 'p'             |
| Baseline diameter | 3.78 ± 0.17     | 3.81 ± 0.16     | 0.587           | 0.560           |
| Post-cuff diameter | 4.29 ± 0.22     | 4.45 ± 0.15     | 2.614           | 0.012           |
| Change diameter  | 0.51 ± 0.14     | 0.64 ± 0.16     | 2.892           | 0.006           |
| FMD (%)          | 13.54 ± 3.65    | 16.84 ± 4.61    | 2.702           | 0.010           |

\[ 't' = 20.910; \ p < 0.001 \]

et al. (2004) set the inclusion age to be 30 years. In the study of Mohammadi et al. (2011), who conducted the study in a design and patient selection criteria similar to ours, the mean age of patients was reported to be 38.7±14.952 years. In another study conducted by Colak et al. (2013) who also conducted their study in non-obese NAFLD patients reported the mean age to be 42.8±9.8 years. All these findings indicate towards a high age-related association of NAFLD, irrespective of the obesity status. With aging, the liver undergoes substantial changes in structure and function that are associated with significant impairment of many hepatic, metabolic and detoxification activities. Although NAFLD is not uncommon in children and teenagers yet in that situation it is mostly associated with obesity.

In present study, majority of patients were males (62.5%). Male to female ratio was 1.67:1. This finding is also in agreement with the observation made by Amarapurkar et al. (2007) who found NAFLD to be more prevalent in males than females. They reported a male to female ratio of 1.81:1.

In the present study, among NAFLD patients, pain abdomen (53.13%) was the most common complaint followed by fullness of abdomen (37.50%) and decreased appetite (9.38%) respectively. To the best of our knowledge none of these complaints have a known relationship with cardiovascular risk and endothelial dysfunction.

In the present study, baseline brachial artery diameter was 3.78±0.17 mm in NAFLD cases

et al. (2013) who also conducted their study in non-obese NAFLD patients reported the mean age to be 42.8±9.8 years. All these findings indicate towards a high age-related association of NAFLD, irrespective of the obesity status. With aging, the liver undergoes substantial changes in structure and function that are associated with significant impairment of many hepatic, metabolic and detoxification activities. Although NAFLD is not uncommon in children and teenagers yet in that situation it is mostly associated with obesity.

In present study, majority of patients were males (62.5%). Male to female ratio was 1.67:1. This finding is also in agreement with the observation made by Amarapurkar et al. (2007) who found NAFLD to be more prevalent in males than females. They reported a male to female ratio of 1.81:1.

In the present study, among NAFLD patients, pain abdomen (53.13%) was the most common complaint followed by fullness of abdomen (37.50%) and decreased appetite (9.38%) respectively. To the best of our knowledge none of these complaints have a known relationship with cardiovascular risk and endothelial dysfunction.

In the present study, baseline brachial artery diameter was 3.78±0.17 mm in NAFLD cases

et al. (2004) set the inclusion age to be 30 years. In the study of Mohammadi et al. (2011), who conducted the study in a design and patient selection criteria similar to ours, the mean age of patients was reported to be 38.7±14.952 years. In another study conducted by Colak et al. (2013) who also conducted their study in non-obese NAFLD patients reported the mean age to be 42.8±9.8 years. All these findings indicate towards a high age-related association of NAFLD, irrespective of the obesity status. With aging, the liver undergoes substantial changes in structure and function that are associated with significant impairment of many hepatic, metabolic and detoxification activities. Although NAFLD is not uncommon in children and teenagers yet in that situation it is mostly associated with obesity.

In present study, majority of patients were males (62.5%). Male to female ratio was 1.67:1. This finding is also in agreement with the observation made by Amarapurkar et al. (2007) who found NAFLD to be more prevalent in males than females. They reported a male to female ratio of 1.81:1.

In the present study, among NAFLD patients, pain abdomen (53.13%) was the most common complaint followed by fullness of abdomen (37.50%) and decreased appetite (9.38%) respectively. To the best of our knowledge none of these complaints have a known relationship with cardiovascular risk and endothelial dysfunction.

In the present study, baseline brachial artery diameter was 3.78±0.17 mm in NAFLD cases

et al. (2004) set the inclusion age to be 30 years. In the study of Mohammadi et al. (2011), who conducted the study in a design and patient selection criteria similar to ours, the mean age of patients was reported to be 38.7±14.952 years. In another study conducted by Colak et al. (2013) who also conducted their study in non-obese NAFLD patients reported the mean age to be 42.8±9.8 years. All these findings indicate towards a high age-related association of NAFLD, irrespective of the obesity status. With aging, the liver undergoes substantial changes in structure and function that are associated with significant impairment of many hepatic, metabolic and detoxification activities. Although NAFLD is not uncommon in children and teenagers yet in that situation it is mostly associated with obesity.

In present study, majority of patients were males (62.5%). Male to female ratio was 1.67:1. This finding is also in agreement with the observation made by Amarapurkar et al. (2007) who found NAFLD to be more prevalent in males than females. They reported a male to female ratio of 1.81:1.
and 3.81±0.16 mm in controls, thus showing no significant difference between two groups. However, post dilatation evaluation showed the mean values to be 3.92-4.76 mm in cases as compared to 4.22-4.68 mm in controls. Thus, flow mediated dilatation in NAFLD patients was 13.54±3.65% in NAFLD cases as compared to 16.84±4.61% in controls. Statistically these differences were significant too.

Reduction in endothelial function in NAFLD patients as compared to healthy controls has been observed in almost all the reviewed studies that have evaluated this relationship. Recently, a lot of data from the Western literature has suggested the increased atherosclerosis and cardiovascular risk in patients with NAFLD but it is still a matter of debate whether NAFLD per se predisposes to these abnormalities or this is all happening because of the presence of metabolic abnormalities. Mohammadi et al (2011)\(^\text{18}\) remarked that in understanding the true pathophysiologic basis of NAFLD, the chicken and egg phenomenon persists, in that some authors believe that NAFLD can produce insulin resistance\(^\text{16}\) while others claim that insulin resistance is the major determinant of development and progression of fatty liver to nonalcoholic steatohepatitis.

Endothelium is conceived to be the largest endocrine gland in the body that secretes many transmitters in order to maintain homeostasis in the circulatory system. FMD is a noninvasive ultrasonographic method which is currently recognized as a useful technique for evaluating endothelial function.\(^\text{17}\) The basic mechanism for FMD is to observe vasodilation by sonography after provoking ischemia by inflating blood pressure cuff. After brachial artery occlusion, endothelial nitric oxide is released and vascular smooth muscle relaxation occurs.\(^\text{18}\)

One of the early processes in the pathophysiology of atherosclerosis is impaired endothelial function.\(^\text{19}\) Impaired endothelial function quantified by FMD is a marker of increased cardiovascular risk, due to its correlation with impaired endothelial function in the coronary arteries.\(^\text{20}\)

The endothelium maintains normal vascular tone and blood fluidity, with no or little expression of proinflammatory factors under normal homeostatic conditions. Generally accepted cardiovascular risk factors like smoking, aging, hypercholesterolemia, hypertension, hyperglycemia, and a family history of premature atherosclerotic disease are all associated with alteration in endothelial function.\(^\text{21}\) This results in a chronic inflammatory process accompanied by a loss of antithrombotic factors and an increase in vasoconstrictor and prothrombotic products, in addition to abnormal vasoreactivity, therefore elevating risk of cardiovascular events. Studies have shown that NAFLD is also associated with chronic portal inflammation\(^\text{22}\) however this phenomenon is also shown to be increased with presence of different factors of metabolic syndrome,\(^\text{22}\) thus showing a probable inseparable relationship.

Federico et al (2016)\(^\text{23}\) have invoked the role of proinflammatory cytokines and low grade inflammation in NAFLD in causing endothelial dysfunction. Cytokine production and inflammation lead to inefficiency of mechanisms that underlie functional endothelial homeostasis. However, there is ample evidence that metabolic syndrome factors like diabetes, hypertension, dyslipidemia, obesity vis-à-vis NAFLD can both coexist as well as remain independent of each other and despite having a common risk factor profile may or may not manifest, however, all these disorders affect the metabolic activity and independently have higher odds for cardiovascular risk.

The findings of present study confirmed that NAFLD as an independent marker has an atherogenic effect that affects the FMD values. One of the limitations of present study was a small sample size, owing to which the association between severity of NAFLD and FMD could not be assessed. Moreover a correlation between different grades of NAFLD and preclinical risk for metabolic syndrome factors could not be studied. It would be of interest to carry out a larger study in a sample having both NAFLD with Metabolic Syndrome factors and without Metabolic Syndrome factors as well as controls, in order to evaluate the cumulative effect of NAFLD on FMD.

**Conclusions**

The findings of the present study show that there is significant endothelial dysfunction, independent of other cardiovascular risk factors, in patients of non alcoholic fatty liver disease in comparison to controls.

**References**


7. Duseja A. Nonalcoholic fatty liver disease in India - a lot done, yet more required! *Indian J Gastroenterol* 2010; 29:217-25.


Cardio-metabolic Risk Profile in Women with Previous History of Pre-Eclampsia

Jalees Fatma¹, Ritu Karoli², Zeba Siddiqui³, HP Gupta⁴, Ashok Chandra⁵, Mahima Pandey⁶

Abstract

Introduction: Preeclampsia is one of the leading causes of maternal and neonatal morbidity and mortality. However there is growing evidence that there are differences during the post partum period between subjects with prior preeclampsia and prior uncomplicated pregnancy and women with a history of preeclampsia are more likely to develop cardiovascular disease later in life. The aim of our study was to assess the cardio-metabolic risk profile in women with previous history of pre-eclampsia and to their counterparts who had normal pregnancy

Material and Methods: In a hospital based case-control study, 50 women aged 20-45 years who had history of preeclampsia and equal numbers of age matched women who had normal pregnancy were included. Apart from routine anthropometric and biochemical parameters, they were assessed for insulin resistance, Hs CRP (High sensitive C reactive protein) and flow mediated vasodilatation (FMD).

Results: Significant difference was noted with regard to BMI and waist circumference, systolic and diastolic blood pressures, and HOMA-IR which were higher and HDL and FMD were lower in women the previous preeclampsia than women with normal pregnancy. The prevalence of various cardio-metabolic risk factors increased in with increase in duration from index pregnancy.

Conclusion: Women with previous history of preeclampsia had adverse cardio-metabolic profile than those who had normal pregnancy. They had higher insulin resistance and endothelial dysfunction. They also have high prevalence of chronic metabolic disorders with increased duration since index pregnancy.

Introduction

Preeclampsia is a pregnancy disorder, characterized by new onset hypertension and proteinuria that occurs after 20 weeks of pregnancy and complicates 5–8% of pregnancies.¹ Preeclampsia is one of the leading causes of maternal and neonatal morbidity and mortality causing high rates of preterm delivery and intra-uterine growth restriction.² The prevalence of preeclampsia in developing countries ranges from 1.8% to 16.7%.³ Most of the pathological conditions associated with preeclampsia seem to resolve after delivery. However there is growing evidence that there are differences during the post partum period between subjects with prior preeclampsia and prior uncomplicated pregnancy and women with a history of preeclampsia are more likely to develop cardiovascular disease later in life.⁴⁻⁶

There has been a rise in cardiovascular disease death rates in women aged 35–54, which has been postulated to be secondary to the obesity epidemic.⁷ Cardiovascular disease (CVD) has gained interest in obstetrics in recent years because large observational studies revealed a remarkable increase in the long-term risk of CVD in women who experienced different types of gestational hypertensive disorders. Pre-eclampsia in pregnancy is associated with characteristic cardiovascular and biochemical alterations including vasomotor dysfunction, hypertension, endothelial damage, inflammation, and metabolic disturbances (oxidative stress, dyslipidemia, dysregulated insulin resistance, and dysglycemia).⁸⁻¹⁰

¹Professor and Head, Medicine, ²Professor, Medicine, ³Associate Professor, Medicine, ⁴Professor, Obs. and Gynae., ⁵Professor Emeritus, Medicine, ⁶Junior Resident, Medicine, Eras Lucknow Medical College Lucknow, Uttar Pradesh

Received: 12.16.2016; Accepted: 28-04-2017
and insulin resistance). These alterations are known predictors of future cardiovascular risk in life.8-10 Efforts focusing on improving awareness and preventive strategies particularly in high risk population are needed that can result in an overall decline in the number of cardiovascular deaths. Insulin resistance, and endothelial dysfunction in women with previous preeclampsia have been indicated to contribute to their increased risk of cardiovascular disease.11-13 Furthermore, given that endothelial dysfunction represents an early indicator of cardiovascular risk,14 Assessment of endothelial dysfunction by measuring flow mediated dilatation (FMD) of the brachial artery is considered as potential tool for predicting coronary atherosclerosis.15 Highly sensitive C-reactive protein (hsCRP) is also a well known surrogate marker and good predictors of subclinical atherosclerosis and future cardiovascular events.16

The aim of our study was to assess the cardio-metabolic risk profile in women with previous history of preeclampsia and in their counterparts who had normal pregnancy.

Material and Methods

We studied 50 women aged 20-45 years who had history of preeclampsia which was identified from medical records at the Department of Obstetrics and Gynecology from the Era’s Lucknow Medical College, Lucknow between January 2014 to July 2016. The diagnosis of preeclampsia was based on criteria of the International Society for the Study of Hypertension in Pregnancy (ISSHP) defined as diastolic blood pressure of 90 mm Hg or more at two consecutive measurements 6 h apart with the patient resting in the semirecumbent position, with or without proteinuria greater than 0.3 g/24 h or more than 1 g/liter (or 2+ with dipstick) in a random sample. The elevation in blood pressure was diagnosed after 20 wk gestation in a previously normotensive woman.17 They were firstly interviewed by phone. Then, they were invited to visit the endocrine clinic during the same phase of their menstrual cycles for sample collection. Exclusion criteria comprised of Diabetes mellitus, Hypertension or chronic kidney disease diagnosed before index pregnancy. Women with malignancy, end stage diseases, chronic inflammatory diseases or autoimmune disorders were also excluded.

Blood pressure in mmHg (BP) was measured by a Mercury sphygmomanometer. Anthropometric parameters such as BMI (body mass index, Kg/m²) and hip (cm) and waist circumference (WC, in cm) were recorded in all subjects and Laboratory investigations, including lipid profile, fasting blood glucose, fasting insulin, uric acid were done. Homeostasis model assessment (HOMA) index was calculated as the product of fasting glucose and insulin values divided by 22.5.18 The hsCRP concentration was determined using an immunoturbidimetric method (Randox, Mauguio, France) in mg/dl.

FMD was performed using a linear 7 MHz transducer (Vivid 7, GE Healthcare), and both groups were directed to abstain from Tea/caffeine 12 hours prior to the study. A longitudinal image was used to measure brachial artery diameter (1st baseline image), and a blood-pressure cuff was inflated on the upper arm (2–5 cm above the cubital fossa) to 50 mmHg above systolic pressure for 5 minutes and then deflated after 1 minute. A second longitudinal scan was obtained (from the same position) to calculate the brachial artery diameter (post-occlusion value). Flow-mediated dilation (FMD) was calculated as: maximum diameter during reactive hyperemia-
diameter at baseline)×100/(diameter at baseline). All measurements of the brachial artery lumen diameter were assessed at end diastole.

Fifty women of the control group of the same hospital were matched for age. All the study participants provided written informed consent and study was approved by Institutional Ethics Committee.

Statistical Analysis

The Statistical Package for the Social Sciences Version SPSS version17 (SPSS, Inc., Chicago, IL) was used for data analysis. To ensure the normal distribution of variables, Kolmogorov-Smirnov test was applied. Comparison between groups was performed using Student’s unpaired t test. Comparisons between frequencies were assessed by chi square analysis. We used Pearson’s correlation coefficient to assess the relationships. P < 0.05 was considered statistically significant.

Results

We included100 women aged 20-45 years having singleton pregnancy in our study. Out of which 50 women had history of preeclampsia defined as cases and 50 who had normal pregnancy were defined as controls. Baseline characteristics of two groups have been shown in Table 1. Women in the cases group were of similar age compared with the control but significant difference was noted with regard to body mass index and waist circumference. Systolic and diastolic blood pressures in women with the previous preeclampsia pregnancy were higher in women than with normal pregnancy.

Metabolic Characteristics

Fasting glucose levels were higher in cases but not significantly different from controls.

Fasting insulin levels and HOMA were significantly higher in women with history of preeclampsia than in control subjects (P=0.002 and
Table 1: Baseline clinical characteristics and biochemical parameters in women with h/o previous preeclampsia and control subjects

<table>
<thead>
<tr>
<th>Variables</th>
<th>H/o previous preeclampsia (N=50)</th>
<th>Controls (N=50)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>34.82 ± 3.26</td>
<td>35.7 ± 4.6</td>
<td>0.54</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>26.2 ± 4.8</td>
<td>24.7 ± 4.2</td>
<td>0.02</td>
</tr>
<tr>
<td>Waist circumference (cm)</td>
<td>90.2 ± 6.8</td>
<td>86.3 ± 6.2</td>
<td>0.01</td>
</tr>
<tr>
<td>Systolic BP (mmHg)</td>
<td>136 ± 20</td>
<td>118 ± 16</td>
<td>0.04</td>
</tr>
<tr>
<td>Diastolic BP (mmHg)</td>
<td>86.4 ± 7.2</td>
<td>70 ± 7.6</td>
<td>0.001</td>
</tr>
<tr>
<td>Fasting glucose (mg/dl)</td>
<td>86 ± 7.6</td>
<td>82.2 ± 6.0</td>
<td>0.08</td>
</tr>
<tr>
<td>Triglyceride (mg/dl)</td>
<td>122 ± 54</td>
<td>119 ± 32</td>
<td>0.12</td>
</tr>
<tr>
<td>HDL-cholesterol (mg/dl)</td>
<td>102 ± 39.2</td>
<td>96 ± 27</td>
<td>0.6</td>
</tr>
<tr>
<td>HDL-cholesterol (mg/dl)</td>
<td>40.8 ± 7.6</td>
<td>48 ± 9.7</td>
<td>0.001</td>
</tr>
<tr>
<td>Uric acid</td>
<td>4.5 ± 1.8</td>
<td>3.8 ± 1.2</td>
<td>0.05</td>
</tr>
<tr>
<td>Insulin (µu/ml)</td>
<td>10.2 ± 3.4</td>
<td>6.1 ± 1.8</td>
<td>0.002</td>
</tr>
<tr>
<td>HOMA-IR</td>
<td>2.2 ± 0.22</td>
<td>1.12 ± 0.18</td>
<td>0.01</td>
</tr>
</tbody>
</table>

Data is expressed in mean ± SD

P=0.01, Table 1). Lipid profile was normal in all study subjects except that HDL was significantly lower in cases than controls.

Hs CRP levels were also higher in cases as compared to controls as shown in Table 2. Baseline brachial artery diameter (vessel size) was similar in the two groups and FMD was significantly reduced in women with previous preeclampsia.

Correlation analysis between FMD and the various parameters examined that showed strong negative association of Hs CRP with FMD (r =-0.600; P =0.001). Negative significant correlations were also found between FMD and HOMA as well as between FMD and fasting insulin (r=-0.45; P=0.014 and r=0.38; P =0.03 respectively. Conversely, FMD exhibited positive relations with HDL cholesterol (r = 0.48; P= 0.002). A significant correlation was also found between FMD and body mass index and waist circumference (r =0.36; P = 0.046, r=0.42, P=0.01).

We studied prevalence of various comorbidities in women with previous pre-eclampsia with increasing duration from index pregnancy that revealed increased number in all diseases in women who had preeclamptic pregnancy more than 10 years (Table 3).

Discussion

CVD is a disease of preventable and treatable risk factors, and evidence shows that when guidelines are followed and risk factors appropriately addressed and treated, CVD outcomes improve.19

Previous history of preeclampsia presents as an opportunity which should be used appropriately to assess for and treat CVD risk factors early to improve a woman’s cardiovascular risk profile earlier in their health care trajectory. This study was aimed to detect presence of atherosclerotic markers in this high risk cohort.

Women diagnosed with preeclampsia are at increased risk of future cardiovascular or cerebrovascular events, with an estimated doubling of odds compared to unaffected women.20 This has implications for the follow-up of all women who experience pre-eclampsia, not just those who deliver pre-term. The theory to explain enhanced cardiovascular risk in women with a history of pre-eclampsia is that pregnancy is a ‘stress test’ and the development of hypertensive disorders during pregnancy identifies a woman destined to develop cardiovascular disease. This association may reflect shared common risk factors for both pre-eclampsia and cardiovascular and cerebrovascular disease. This is based on ample data revealing overlapping risk factors for pre-eclampsia and cardiovascular disease.21

The underlying pathophysiology of preeclampsia (PE) is not completely understood, but it is currently believed that the initiating event in PE is reduced placental perfusion, which develops from shallow cytotrophoblast migration toward the uterine spiral arterioles which leads to inappropriate vascular remodeling and a hypoperfused placenta.1 This placenta becomes ischemic as the pregnancy continues which leads to the release of factors that cause maternal vascular endothelial dysfunction.22,23

Endothelial dysfunction appears to be a central component of the pathophysiology of preeclampsia.24 In our study, endothelial function was significantly lower in women with a history of preeclampsia. This is consistent with previous reports and indicates that preeclampsia-associated endothelial dysfunction persists in later life too.25-27

Increased resistance to insulin

Table 2: Atherosclerosis markers in women with h/o preeclampsia and control subjects

<table>
<thead>
<tr>
<th>Variables</th>
<th>H/o previous preeclampsia (N=50)</th>
<th>Controls (N=50)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>HsCRP (mg/dl)</td>
<td>3.6 ± 2.12</td>
<td>3.08 ± 2.4</td>
<td>0.06</td>
</tr>
<tr>
<td>Vessel size (mm)</td>
<td>2.8 ± 0.06</td>
<td>3 ± 0.12</td>
<td>0.05</td>
</tr>
<tr>
<td>FMD (%)</td>
<td>16.6 ± 2.3</td>
<td>8.3 ± 2.23</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Data is expressed in mean ± SD

Table 3: Prevalence of cardio-metabolic risk factors in women with h/o preeclampsia according to duration from index pregnancy

<table>
<thead>
<tr>
<th>Variable</th>
<th>≤5 Years (n=20)</th>
<th>5-10 years (n=18)</th>
<th>&gt;10 years (n=12)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>10(50)</td>
<td>13(72)</td>
<td>9(75)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>5(25)</td>
<td>6(33)</td>
<td>6(50)</td>
</tr>
<tr>
<td>Dyslipidimia</td>
<td>4(20)</td>
<td>6(33)</td>
<td>5(50)</td>
</tr>
<tr>
<td>Metabolic Syndrome</td>
<td>10(50)</td>
<td>12(66)</td>
<td>9(75)</td>
</tr>
</tbody>
</table>

Data is expressed as n(%)
action is a well-established cardiovascular risk factor. The exact mechanism by which insulin resistance impairs endothelial function are not known, however, oxidative stress and inflammation may act synergistically, leading to a reduced expression of endothelial nitric oxide synthase. As previously observed, we also found increased insulin resistance in women with previous preeclampsia as both fasting insulin and HOMA-IR were significantly higher in cases along with hsCRP, though rise in hs CRP could not achieve statistical significance.

Romundstad et al. noted that women with a history of pre-eclampsia or gestational hypertension also had substantially higher body mass index and systolic and diastolic blood pressures and unfavourable lipids compared with those with normotensive pregnancies. In our study systolic and diastolic blood pressures were higher, waist circumference was greater and HDL was lower in women with previous preeclampsia than controls who had normal pregnancy.

There is not much literature addressing cardiovascular risk markers in our population so our study is unique in this respect. We tried to study prevalence of various cardio-metabolic co morbidities in our study group with increasing duration from the index pregnancy that revealed increase in all diseases with increase in duration.

Our study had certain limitations including small sample size and cross-sectional design. More prospective studies which are appropriately designed with large sample size that include follow up are needed in our population.

**Conclusion**

Women with previous history of preeclampsia had adverse cardio-metabolic profile than those who had normal pregnancy. They had higher insulin resistance and endothelial dysfunction. They also have high prevalence of chronic metabolic disorders with increased duration since index pregnancy. Primary prevention of cardiovascular disease in this group of women should be undertaken, and reproductive history needs to be considered when dealing with cardiovascular risk assessment.

**References**


---

**Workshops During CME APICON 2018, Bengaluru**

Date: 22nd February, 2018 (11.00 a.m. - 2.00 p.m.)

Workshops:

1. **A to Z of CBC (Learning CBC through case studies)**
   - Faculty: Dr Sudhir Mehta, Jaipur and Dr Swati Pai, Bengaluru
   - Slots: 50 (First come, first served)
   - Registration: mandatory, No Registration Fee.

2. **Joint & Soft tissue Injection Workshop**
   - Hands on using mannequins
   - Faculty: Dr SJ Gupta, New Delhi and other eminent rheumatologists
   - Slots: 15 (First come, first served)
   - Registration: mandatory
   - Registration Fee Rs 1000/- (Non refundable)

3. **Clinical Decision Making Workshop**
   - Faculty: Gp Capt Shankar Subramanian, Gp Capt Ajay Handa, Wg Cdr TVSVGK Tilak
   - Slots: 30 (First come, first served)
   - Registration: mandatory, No Registration Fee.

These workshops are open only to delegates registered for APICON 2018. Prior registration is mandatory. No Spot registrations are allowed. Workshops will be held at Dr. Babu Rajendra Prasad International Convention Centre, GKVK-University of Agricultural Sciences, Bengaluru, Karnataka on 22 February 2018. Timing is subject to change.

For registration contact:
**Dr. P. Chandrasekhara, Organising Secretary, APICON 2018,**
No. 16/F, A.P.I. Bhavana, Miller Tank Bed area, Vasantha Nagar, Bengaluru - 560052
Landline : +91 (80) 48535566 • E-mail: secy@apicon2018.org • Web: www.apicon2018.org
Abstract

Introduction: Acute kidney injury (AKI) is reported to occur in patients with falciparum malaria but not uncommon with vivax malaria. AKI, anemia, thrombocytopenia and jaundice is a recurrent finding in severe malaria and can mimic as thrombotic microangiopathy (TMA). Relationship of malaria with TMA is unclear till date however evidences suggest their association.

Materials and method: We reviewed our electronic database to evaluate relationship of malaria with TMA, of cases of malaria, jaundice and AKI.

Result: 4 patients found to have P. vivax malaria and histopathologically confirmed TMA. All had fever, oliguria, jaundice at presentation. The time between onset of symptoms and admission ranged from 7 to 14 days. All had parasitemia at presentation so were treated with Artesuanate. Hemodialysis and Plasmapheresis was done in all patients. On follow-up all patients recovered and asymptomatic urinary abnormality persisting in one patient.

Conclusion: High index of suspicion should be kept for TMA in a patient who has nonrecovery AKI with persistent anemia and thrombocytopenia even after clinical and laboratory evidences of recovery from malaria, as response to plasmapheresis seems excellent in this subset of malarial AKI. There could be a pathogenetic link between P.vivax and TMA though yet to be confirmed in larger studies.

Introduction

The most important species of malaria parasite are Plasmodium (P) falciparum, which causes falciparum malaria, P. malariae, which causes Quartan malaria, and P. vivax and P. ovale, which cause tertian malaria. Acute kidney injury (AKI) is seen mostly in Plasmodium falciparum infection (1-30%) but P. vivax and P. malariae can occasionally contribute for renal impairment. The pathogenetic mechanism of renal failure in malaria is still unclear. However it is thought that cytoadherence, multifactorial changes in cortical perfusion, cytokine release, and hypovolemia lead to tubular necrosis.

The association between renal failure, anemia, thrombocytopenia and jaundice is a common finding in studies on severe malaria and these finding can mimic with thrombotic microangiopathy (TMA). Although relationship of malaria with TMA is not clear till date but there is a recent case series from India and few reports exists in medical literature about their association mainly in children with P.vivax infection. So we undertook a retrospective search of our hospital record to find out cases of malaria associated acute kidney injury with clinical, laboratory and histopathological evidence of TMA.

Materials and Method

We reviewed data from electronic database of our institute, of cases of malaria, jaundice and AKI and initially admitted and treated as complicated severe malaria. We included only those cases of malaria and AKI in this study who had hemolytic anemia, thrombocytopenia and clinical and laboratory evidences, suggestive of microangiopathy (raised LDH and Schistocytes on peripheral smear).
Table 1: Characteristics of the study patients

<table>
<thead>
<tr>
<th>Variables</th>
<th>Case 1</th>
<th>Case 2</th>
<th>Case 3</th>
<th>Case 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographic characters</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age in years</td>
<td>35</td>
<td>40</td>
<td>23</td>
<td>32</td>
</tr>
<tr>
<td>Sex</td>
<td>Male</td>
<td>Female</td>
<td>Female</td>
<td>Male</td>
</tr>
<tr>
<td>Co morbidities</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Clinical features</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Renal failure at presentation</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>AKI class</td>
<td>Rifle-F</td>
<td>Rifle- F</td>
<td>Rifle-F</td>
<td>Rifle- F</td>
</tr>
<tr>
<td>Dialysis dependant at presentation</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>H/o Antimalarial (Artesuanate)</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>H/O blood transfusion</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Bleeding diathesis</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Laboratory features</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anemia with reticulocytosis</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Thrombocytopenia &lt; 100000/dl</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Schistocytes on GBP</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>S. LDH</td>
<td>Raised</td>
<td>Raised</td>
<td>Raised</td>
<td>Raised</td>
</tr>
<tr>
<td>Transaminitis</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Indirect hyperbilirubinemia</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>C3 and C4</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>H/O plasmodium vivax positivity</td>
<td>Present</td>
<td>Present</td>
<td>Present</td>
<td>Present</td>
</tr>
<tr>
<td>Proteinuria</td>
<td>1+</td>
<td>2+</td>
<td>1+</td>
<td>1+</td>
</tr>
<tr>
<td>Microhematuria</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Kidney biopsy</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Light microscopy</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Outcome</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total duration of AKI</td>
<td>3 week</td>
<td>5 week</td>
<td>8 week</td>
<td>7 week</td>
</tr>
<tr>
<td>Total number of Hemodialysis sessions</td>
<td>10</td>
<td>12</td>
<td>17</td>
<td>14</td>
</tr>
<tr>
<td>Response to Plasmapheresis</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Total number of Plasmapheresis sessions</td>
<td>7</td>
<td>5</td>
<td>7</td>
<td>8</td>
</tr>
<tr>
<td>Dialysis independency at discharge</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Serum creatinine (mg/dl) 3 months after discharge</td>
<td>2</td>
<td>1.7</td>
<td>1.9</td>
<td>1.5</td>
</tr>
</tbody>
</table>

All the patients had fever with chills, jaundice and oligouria

and in whom diagnosis of TMA was confirmed on kidney biopsy.

AKI was defined as per RIFLE definition.

Malaria was diagnosed through a thorough diagnostic evaluation. Direct visualization of the parasite in Giemsa-stained peripheral blood smears both thick and thin blood smear were done. A rapid diagnostic test for malaria antigen detection (OptiMAL test, DiaMed AG, Switzerland) which is based on detecting specific Plasmodium LDH antigen by using monoclonal antibody directed against isoforms of the enzyme was also done.

Jaundice was defined as icteric sclera and/or total bilirubin levels >2 mg/dl.

TMAs was defined as haemolytic anemia (haemoglobin level <10 g/dl, lactate dehydrogenase level greater than normal values, undetectable haptoglobin level, and schizocytes in the peripheral blood smear), thrombocytopenia (platelets typically <1, 50,000/mm3). Renal Biopsy finding of TMA were mainly affecting glomeruli and arterioles. The arterial changes were defined as swelling of the endothelium to presence of medial fibrinoid necrosis and thrombosis of the lumen. The glomerular lesions were intracapillary thrombosis, focal necrosis and mesangiolysis, and “glomerular double contour” aspect on silver stains.

Data of all patients of malaria and TMA were recorded as demographic profile, clinical presentation, laboratory finding, kidney biopsy finding, plasmapheresis and its response. Outcome were recorded as Total duration of AKI, Total number of Hemodialysis sessions required, Response to Plasmapheresis, Total number of Plasmapheresis sessions required, Dialysis independency at discharge, Serum creatinine (mg/dl) 3 months after discharge.

Results

4 patients found to have biopsy proven TMA with history of P. vivax out of 251 patients of malaria with AKI. Baseline characteristics of the study patients are shown in Table 1. All 4 patients were young (range, 23-40 years); and 2 were males. All patients were had history of being treated with Antimalarial for P. vivax malaria before admission to our hospital but none was positive for Plasmodium Falciparum parasite.

Presenting clinical features fever, oliguria anemia and jaundice, were present in all patients. All patients had detectable malaria parasite or antigen during admission from our laboratory and were treated with parental Artesuanate. All patients had undetectable malaria parasite or antigen after antimalarial. The time between onset of symptoms and admission to our hospital for AKI ranged from 7 to 14 days. All patients were dialysis dependant at presentation. There was history of blood products transfusion in form of PRBC and Random donor platelets in all patients. All patients had laboratory evidence of TMA in the form of anemia, reticulocytosis, thrombocytopenia, schistocytes in general blood picture and raised serum LDH levels. Transaminitis with hyperbilirubinemia was present in all patients. Urine findings varied with Proteinuria ranging from 1+ to 2 + on dipstick and microhematuria was present in two patients (Patient 1 and 2). All 4 patients had histopathological evidence of TMA. Findings were summarized in Figure 1. All patients received Hemodialysis (10-17 session) and plasmaphereis
(5-8 session) and became dialysis independent subsequently. On follow-up at 3 months, serum creatinine ranged from 1.5 – 2 mg/dl.

**Discussion**

Complicated malaria closely mimics TMA as hemolytic anemia, thrombocytopenia, jaundice, and renal failure can be seen in both. Therefore, high index of suspicion is necessary for diagnosis of TMA in patients of malarial AKI, especially when the patient has persistent anemia, thrombocytopenia, and non-recovering renal failure, as these patients may improve with therapeutic interventions like plasmapheresis. All our patients had malaria associated with non-recovering ARF, and TMA was suspected in view of persistent anemia and thrombocytopenia in spite of both clinical and laboratory recovery of malaria after antimalarial treatment.

Though malaria is not known to cause TMA as yet but there are evidences of its association with TMA in medical literature. Recently, a case series by Sinha et al. from India found 9 cases of TMA associated with P. vivax in 3 months of time during monsoon season. In one case report associated ADAMTS 13 deficiency was found with malaria and malaria was thought to be as precipitating factor of ADAMTS 13 deficiency. Antimalarial drugs such as quinidine and mefloquine were reported to cause TMA associated with malaria. In our case series we have not done ADAMTS levels and none of our patient had history of ingestion of Antimalarial like mefloquine and quinidine.

The unique finding in this case series is that all patients of non-recovering AKI due to malaria had history of ingestion of Antimalarial like mefloquine and quinidine. The temporal clustering of these 4 cases of P. Vivax malaria with TMA stimulated us to hypothesize possible underlying pathogenetic
mechanism for this entity or to find out possible link between P. vivax and TMA. The temporal relationship of malaria and TMA in our patient was made after exclusion of common causes of TMA, well supported by clinical course and therapeutic response to plasmapheresis in all cases. The lesion in endothelium of renal microvasculature can be inciting event in TMA associated with P. vivax and which can be explained on the basis of: (1) infected RBCs get adhere to endothelium of microvasculature via knob on RBCs membrane, and with aggregation of parasitized RBCs, causing sluggish blood flow and local tissue hypoxia. This may manifest as renal cortical disruption and failure; (2) malarial toxin just like shiga toxin can alter endothelial cell integrity and provoke sequence of events leading to extensive microvasculature which subsequently result TMA. The P. vivax had lower pyrogenic threshold than P. falciparum the level of parasitemia associated with fever but organ-specific studies have shown that the inflammatory response during P.vivax infection is greater than that seen in P. falciparum infections with a similar or greater parasite biomass. Cytokine production during P. vivax infections is higher than that in P. falciparum infections of similar parasite biomass. Lung injury seen in P. vivax malaria there is pathophysiological evidence for pulmonary vascular sequestration and post treatment alveolar capillary inflammation. Although endothelial function has not been described in vivax malaria, endothelial ‘stimulation’ has been reported at autopsy and concentrations of circulating endothelial activation markers are at least as high in uncomplicated vivax malaria as they are in falciparum malaria. P. vivax infection is found to be associated with elevated thrombomodulin, Von Willebrand factor (VWF) and procoagulant activity. These altered haemostatic pathways could result in intravascular coagulation and endothelial inflammation through increased formation of ultra-large VWF and platelet aggregates. So greater inflammatory response and cytokine production. Weibel-Palade body exocytosis, hemolysis-associated nitric oxide quenching, altered thrombostasis, platelet activation, endothelial cell injury, and the impairment of vasomotor responses and microcirculatory flow all may contribute to the pathophysiology of P. vivax induced TMA.

The occurrence of TMA and P. vivax malaria in these four patients may be coincidental or may be due to this malaria parasite per se. However there may be a common link between TMA and P.vivax parasite thru direct endothelium injury. The important question remains to be answered why only few patient of P. vivax malaria used to have TMA and why this entity is only reported from India. The ethnic susceptibility and genetic predisposition to TMA may be responsible factor.

Limitations of our study were like its retrospective nature, unavailability of work up for genetic and autoimmune causes of TMA and of course only few patients. These finding should be confirmed in larger study, especially from endemic zones of malaria.

Conclusion

We should keep high index of suspicion for TMA in a patient who has nonrecovering ARF with persistent anemia and thrombocytopenia even after clinical and laboratory evidences of recovery from malaria, as response to early institution of specific therapy like plasmapheresis is excellent in this subset of nonrecovering malarial ARF. There could be a pathogenetic link between P.vivax and TMA though yet to be confirmed in larger studies.

References

A Study of Genetic Markers in Patients of Rheumatoid Arthritis and their Co-Relation with Severity of the Disease

Gauri Liyakat Ali1, Suman Kapur2, Sai Chinmayi3, Qadir Fatima4, Harshal Pise5, Asim Khan6, Ambreen Liyakat7, V Jilova8, Urvashi Dube9

Original Article

Abstract

Introduction: Dyslipidemia has been reported to attribute to early death due to increased atherosclerosis leading to CVDs in patients with RA. Recent reports have suggested a role of adipocytokines in mediating joint damage rheumatoid arthritis (RA). RA has long been associated with increased cardiovascular risk as atherosclerosis is more prevalent in patients of RA than in the general population. Specific alleles of APOE gene have been reported to be associated with risk for atherosclerosis and LEP gene alleles have been associated with increased BMI. We evaluated the association of polymorphisms in the APOE and the LEP gene, with risk for developing RA and severity of joint damage in patients with RA.

Materials and Methods: Peripheral blood samples from age and ethnicity matched healthy controls and RA patients, recruited for the study, were collected and used for DNA isolation and allele typing for D7S1875 (LEP gene) and APOE using PCR-LP/RFLP based method reported in literature4,5 followed by data analysis using Medcalc.

Results and Conclusions: Based on the findings of this study no correlation was seen between RA and LEP gene (D7S1875) allele/genotypes. It was seen that the APOE*4 allele was more prevalent in controls than in cases indicating that this allele is probably playing a significant protective role (p=0.0002, OR=0.3336, CI:0.1856-0.5997) as opposed to the other two Apo E alleles. The Apo E*3 allele was the most prevalent allele in both cases and controls which is similar to earlier reports from several different groups. No significant association was observed between the APOE genotype and the DAS28 score. Finally, it can be concluded that while the short allele of the D7S1875 (LEP gene) marker increases the risk for developing RA (OR=1.72, p=0.038) the APOE*4 allele seems to play a protective role in RA (OR=0.3336, p=0.0002).

Introduction

Rheumatoid arthritis (RA) is a chronic, systemic inflammatory disorder that may affect many tissues and organs, but principally attacks the joints producing an inflammatory synovitis that often progresses to destruction of the articular cartilage and ankyloses of the joints. RA can also produce diffuse inflammation in the lungs, pericardium, pleura, and sclera, and also nodular lesions, most common in subcutaneous tissue under the skin. Although the cause of RA is not yet known, autoimmunity plays a pivotal role in its chronicity and progression.

The incidence of RA in Rajasthan is 3 cases out of 10,000 people in the population per annum. Onset is uncommon under the age of 15 and from then on the incidence rises with age until the age of 80. The prevalence rate is 1% with women affected 3 to 5 times more often as men. RA is 4 times more common in smokers than non-smokers. Some Native American groups

1Additional Principal and Senior Professor, Department of Medicine, S.P. Medical College, Bikaner, Rajasthan; 2Senior Professor, PhD Student, Department of Biological Sciences, BITS Pilani, Hyderabad Campus, Hyderabad, Telangana; 3Professor, Department of Pathology, 4Postgraduate, Department of Medicine, S.P. Medical College, Bikaner, Rajasthan; 5Senior Resident, Department of Ophthalmology, SMS College, Jaipur, Rajasthan; 6Consultant Radiologist, SDMH, Jaipur, Rajasthan; 7Post Graduate Student, S.P. Medical College, Bikaner, Rajasthan; 8Research Assistant, Department of Biological Sciences, BITS Pilani, Hyderabad Campus, Hyderabad, Telangana

Received: 30.10.2015; Accepted: 12.06.2017
have higher prevalence rates (5-6%) and people from the Caribbean region have lower prevalence rates. First degree relatives’ prevalence rate is 2-3% and disease genetic concordance in monozygotic twins is nearly 15-20%.9

Cardiovascular diseases (CVDs) are one of the most common comorbidities of RA. It has been reported that patients with RA have 4 fold higher risk for CVDs in comparison to the general population from the same geographical location in India.10 The APOE genotype is a known genetic risk factor for CVDs apart from dementia and Alzheimer’s disease (AD).5 APOE gene is located on chromosome 19q3.2 and has three alleles (E*2, E*3, E*4). Subjects with at least one E4 allele are at increased risk for CVD outcomes since presence of an E*4 allele is linked to higher low-density lipoprotein cholesterol levels even in a population with younger age groups.11 A study in a Norwegian cohort has shown a longitudinal linear association between APOE genotypes and radiographic joint damage in patients with RA.12 Hence studying association of alleles of APOE gene in RA population will be not only useful to identify risk for increased severity of RA but also to identify risk for CVDs.

Other gene widely studied for its association with obesity and CVDs is the LEP gene. This gene, located on chromosome 7q32.1, encodes a protein that is secreted by white adipocytes, and which plays a major role in the regulation of body weight. Apart from this it also has several endocrine functions, and is involved in the regulation of immune and inflammatory responses, hematopoiesis, angiogenesis and wound healing. Several studies have been carried out to identify association between serum leptin levels and RA. RA patients have higher levels of serum leptin than control group and show a positive correlation with BMI.13 More over leptin is known to induce IL1 antagonist, RA patients with this antagonist depict a slower process of destruction in their joints. Thus, it is envisaged that variation in LEP gene can be associated with severity of disease in RA.14

The current study was planned to delineate the genetic differences in polymorphism of the APOE and LEP genes among subjects with and without RA and estimate the distribution frequency of their prevalent alleles in clinically defined sub-groups of patients and controls recruited from North West India.

Material and Methods

Following a prospective case control study design all available patients and volunteers were recruited during 2008-2010. Peripheral blood samples of patients were collected at Rheumatology clinic and Medicine Department of S.P. Medical College, Bikaner after explaining the objective of the study and taking a written informed consent from the patients or from guardian family members. The same criteria for blood collection were followed in controls where samples were matched for age and ethnicity.

The study was done in 298 subjects involving 162 RA cases and 136 age and ethnicity matched control subjects with no known history of disease. The volunteers and patients were explained about the purpose of the research study by the resident (SR/JR) in their native language, who subsequently also obtained a written informed consent from the recruited patients/control subjects. A detailed proforma was used to gather clinical history of the recruited patients and information about their family history.

The RA cases comprised of 122 women (mean age 43.01+13.23 years) and 40 (mean age 47.4+14.9 years) men. The control group comprised of 85 unrelated healthy controls and 51 related controls.

The mean age of the unrelated control group was 35.12+14.13 while the mean age of the related control group was 50.76+16.75 years. The related controls were deliberately chosen from higher age group to minimize the chances of errors in segregation of groups due to late onset of disease.

Inclusion Criteria

All patients of RA above 16 years of age and diagnosed as per American College of Rheumatology (ACR) criteria, 1987 were included in the study.

Exclusion Criteria

Subjects below the age of 16, patients with other diseases and RA patients suffering from diseases with overlapping conditions like scleroderma, SLE, Polio have been excluded from the study.

Allele Typing

DNA from blood samples was isolated using lab established protocols.4 Extracted DNA was visualized on 0.8% agarose gel for quality check and further quantified using spectrophotometer. Isolated DNA was used for PCR amplification using primers designed for the APOE and the LEP genes. PCR amplicons were analyzed for length polymorphism in case of D7S1875 and sequenced for allele typing. APOE gene polymorphism was detected using PCR-RFLP method based on Hha1 digestion.5 The data obtained was analyzed using statistical tools for determining the association of RA with D7S1875 marker in LEP gene and APOE gene alleles 2, 3 and 4.

Results

No significant differences in clinical parameters were observed between cases and controls (Table 1). Total cholesterol was observed to be higher in cases but the difference was not statistically significant (159.22±56.92 Vs 148.85±22.98; t=-0.739 p=0.4612).

Polymorphism in Rheumatoid Arthritis

Bimodal Distribution of D7S1875 Alleles
The values in the two groups were comparable with non-significant differences.

### Table 1: Clinical profile of the cases and controls

<table>
<thead>
<tr>
<th></th>
<th>Cases</th>
<th>Related controls</th>
<th>Un-related controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>Mean±SD</td>
<td>N</td>
<td>Mean±SD</td>
</tr>
<tr>
<td>Age</td>
<td>162</td>
<td>44.35±13.79</td>
<td>41</td>
</tr>
<tr>
<td>SBP</td>
<td>146</td>
<td>130.65±9.71</td>
<td>7</td>
</tr>
<tr>
<td>DBP</td>
<td>146</td>
<td>78.43±8.53</td>
<td>7</td>
</tr>
<tr>
<td>Total cholesterol</td>
<td>104</td>
<td>159.22±56.92</td>
<td>19</td>
</tr>
<tr>
<td>TG</td>
<td>78</td>
<td>147.01±106.72</td>
<td>17</td>
</tr>
<tr>
<td>Urea</td>
<td>101</td>
<td>35.46±30.03</td>
<td>16</td>
</tr>
<tr>
<td>Total protein</td>
<td>100</td>
<td>6.50±1.77</td>
<td>19</td>
</tr>
<tr>
<td>Albumin</td>
<td>81</td>
<td>2.72±0.79</td>
<td>18</td>
</tr>
<tr>
<td>Globulin</td>
<td>89</td>
<td>0.98±1.26</td>
<td>-</td>
</tr>
<tr>
<td>A/G Ratio</td>
<td>82</td>
<td>0.66±0.19</td>
<td>-</td>
</tr>
<tr>
<td>Creatinine</td>
<td>62</td>
<td>0.68±0.75</td>
<td>17</td>
</tr>
<tr>
<td>PR</td>
<td>144</td>
<td>79.11±13.00</td>
<td>7</td>
</tr>
<tr>
<td>RR</td>
<td>144</td>
<td>18.01±8.48</td>
<td>7</td>
</tr>
</tbody>
</table>

The values in the two groups were comparable with non-significant differences.

### Table 2: Genotype and allele frequencies of leptin gene D7S1875 polymorphism in cases and controls

<table>
<thead>
<tr>
<th>Group</th>
<th>Genotype frequency</th>
<th>Allele frequency</th>
<th>Subjects having one short allele</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt;206/&lt;206</td>
<td>&lt;206/&gt;206</td>
<td>&gt;206/&gt;206</td>
</tr>
<tr>
<td>Cases</td>
<td>(132)</td>
<td>(0.42)</td>
<td>(0.35)</td>
</tr>
<tr>
<td>Controls</td>
<td>(136)</td>
<td>(0.54)</td>
<td>(0.27)</td>
</tr>
</tbody>
</table>

<206/≤206/206/>206p=0.093, OR=1.604, CI<sub>95%</sub>=0.8567-2.3038, X<sup>2</sup>=2.2
<206/>206Vs≤206p=0.038*, OR=1.7192, CI<sub>95%</sub>=1.0168-2.60107, X<sup>2</sup>=4.23
>206/>206Vs≤206p=0.48, OR=1.071, CI<sub>95%</sub>=0.543-2.1146, X<sup>2</sup>=0.047

* p<0.05, indicates statistically significant differences

### Fig. 1: Genotypic distribution and allele frequencies of the D7S1875 polymorphism in leptin gene

To study the role of genetic variants of LEP gene among RA patients we examined alleles of the Short Tandem Repeat (STR) marker, D7S1875, located in the upstream region of this gene. The alleles ranged in size from 196 to 226 bp in length and were divided into approximately two equal groups, at 206 bp, according to their natural tendency for bimodal distribution. The results obtained were analyzed for genotypes <206/>206 and >206/>206 bp distribution among 132 cases and 136 controls from the cohort (Figure 1 and Table 2).

### APOE Gene Polymorphism in Rheumatoid Arthritis

Alleles of the APOE gene were examined to study their role in RA patients. Table 3 and Figure 2 show distribution of APOE genotypes and alleles among cases and controls. Only 141 cases and 56 controls from the recruited cohort of 298 subjects could be successfully genotyped for APOE gene.

### DAS Score and APOE alleles

The DAS28 score provides a number on a scale from 0 to 10 indicating the current activity of the disease in a RA patient. A DAS28 score above 5.1 indicates high disease activity whereas a DAS28 score below 3.2 indicates low disease activity. Remission is achieved by a DAS28 lower than 2.6 (comparable to the ARA remission criteria).

The cases of RA were evaluated for their disease activity based on their DAS28 score. Association analyses for the genotype and allele frequency of APOE and LEP gene with reference to the disease activity score in RA cases was done. The transformation formula used to calculate the DAS28 is

\[0.56\sqrt{\text{tender joints}} + 0.28\sqrt{\text{swollen joints}} + 0.70*\ln (\text{ESR/CRP})\]

No association was seen with the any APOE allele (Table 4) or LEP gene polymorphism (data not shown) and DAS 28 score of the RA patients.

### Discussion

The study was carried out using a case-control design. In the present study we have assessed the relationship between LEP and APOE gene polymorphisms among subjects suffering with RA. Gender as a predictor of outcomes of RA has evoked considerable interest over the decades. Historically,
Differences between genders exist in the prevalence, age at onset, and autoantibody production of RA. It was shown in a large analysis, that disease activity measures themselves may be contaminated by gender and hence interpretations of gender differences should be done cautiously. There is no consensus whether RA is worse in females or males. Recent reports suggest that females are less likely to achieve remission and often have higher work disability rates compared with men. We also observed a female: male ratio of 2:1.

The cases when evaluated for severity based on their DAS28 score (>6) reflected a higher fraction of females (23% vs 11%). Levels of systolic blood pressure (SBP) and diastolic blood pressure (DBP) which are common risk factors of CVDs were found to be slightly higher in patients as opposed to the control subjects however; this difference was not statistically significant. Infact the increase in SBP also showed a positive correlation with age, as expected.

The present study assessed the relationship between candidate genes and RA on the basis of distribution of risk genotypes, among cases and controls. Body weight is a factor directly affecting the joints of an individual. Genetic factors are believed to play an important role in development of obesity. Adipose-derived hormone leptin is well known for its function in the control of energy homeostasis and this gene has also been shown to be associated with obesity. To study the role of genetic variants of LEP gene in RA, alleles of the upstream region of this gene,gene increases the risk of one or more short allele of the LEP gene with an increased risk for developing RA (OR=1.72, p=0.038), but insignificant effect on disease severity.

Another important gene which is implicated in dyslipidemia is APOE. Earlier reports have shown dyslipidemia in RA patients. Our study also assesses the relationship of APOE polymorphism with the disease. It was seen that the E*4 allele (p=0.0002, OR=0.3336, CI: 0.1856-0.5997) was more prevalent in controls than in cases indicating that this allele could be playing a protective role as opposed to the other two APOE alleles. E*3 allele was the most prevalent allele in both cases and controls which is similar to earlier reports. Further when controlled for the disease activity via DAS28score, no significant association was observed between the APOE genotype and the DAS28score.

In conclusion, while the short allele of LEP gene increases the risk for developing RA among Indian from North India, the APOE*4 allele seems to play a protective role in RA susceptibility. A number of twin studies have implicated the role of genetic factors in the pathogenesis of the disease and hence an understanding of the genetic profile of RA would pose great help in attaining early intervention and prevention of disease, thus reducing the disease burden on society. Needless to add the present study needs to be extended to a larger cohort of subjects from different regions and communities of India for further validation.

### Table 3: Distributions of APOE genotypes and alleles among cases and controls

<table>
<thead>
<tr>
<th>APOE genotype</th>
<th>APOE alleles</th>
</tr>
</thead>
<tbody>
<tr>
<td>E2-2</td>
<td>E2</td>
</tr>
<tr>
<td>E2-3</td>
<td>E3</td>
</tr>
<tr>
<td>E2-4</td>
<td>E4</td>
</tr>
<tr>
<td>E3-3</td>
<td>E2</td>
</tr>
<tr>
<td>E3-4</td>
<td>E3</td>
</tr>
<tr>
<td>E4-4</td>
<td>E4</td>
</tr>
<tr>
<td>E*2</td>
<td>E*3</td>
</tr>
<tr>
<td>E*4</td>
<td>E*4</td>
</tr>
<tr>
<td>Cases (141)</td>
<td></td>
</tr>
<tr>
<td>Frequency</td>
<td>(0.00)</td>
</tr>
<tr>
<td>Controls (56)</td>
<td></td>
</tr>
<tr>
<td>Frequency</td>
<td>(0.0)</td>
</tr>
</tbody>
</table>

| E*2 Vs E*3, p=0.056, OR=0.466, CI=0.21-1.02 | Presence of E*2 Vs E*3+E*4, p=0.3, OR=1.325, CI=0.6068-2.894, x²=0.5 |
| E*4 Vs E*3, p=0.0002, OR=0.3336, CI=0.1856-0.5997 | Presence of E*3 Vs E*2+E*4, p=0.2, OR=.74, CI=0.3798-1.4637 |
| E*2 Vs E*4, p=0.466, OR=1.396, CI=0.57-3.41 | Presence of E*4Vs E*2+E*3, p=0.07, OR=.297, CI=0.077-1.152 |

* p<0.05, indicates statistically significant differences

### Table 4: Genotypic and allele frequencies of the APOE gene in cases controlled for disease activity score, DAS28

<table>
<thead>
<tr>
<th>DAS28</th>
<th>APOE genotype</th>
<th>APOE alleles</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;=6</td>
<td>(0)</td>
<td>E2</td>
</tr>
<tr>
<td>(86)</td>
<td>(0.11)</td>
<td>E3</td>
</tr>
<tr>
<td></td>
<td>(0.03)</td>
<td>E4</td>
</tr>
<tr>
<td></td>
<td>(0.10)</td>
<td>E*2</td>
</tr>
<tr>
<td></td>
<td>(0.03)</td>
<td>E*3</td>
</tr>
<tr>
<td></td>
<td>(0.07)</td>
<td>E*4</td>
</tr>
<tr>
<td></td>
<td>(0.81)</td>
<td>E*2</td>
</tr>
<tr>
<td></td>
<td>(0.10)</td>
<td>E*3</td>
</tr>
<tr>
<td></td>
<td>(0.13)</td>
<td>E*4</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>DAS28</th>
<th>APOE genotype</th>
<th>APOE alleles</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;=6</td>
<td>(0.02)</td>
<td>E2</td>
</tr>
<tr>
<td>(38)</td>
<td>(0.05)</td>
<td>E3</td>
</tr>
<tr>
<td></td>
<td>(0)</td>
<td>E4</td>
</tr>
<tr>
<td></td>
<td>(0.71)</td>
<td>E*2</td>
</tr>
<tr>
<td></td>
<td>(0.18)</td>
<td>E*3</td>
</tr>
<tr>
<td></td>
<td>(0.02)</td>
<td>E*4</td>
</tr>
<tr>
<td></td>
<td>(0.05)</td>
<td>E*2</td>
</tr>
<tr>
<td></td>
<td>(0.82)</td>
<td>E*3</td>
</tr>
<tr>
<td></td>
<td>(0.13)</td>
<td>E*4</td>
</tr>
</tbody>
</table>

E*2 vs E*3 OR=1.4521, CI=0.46 to 4.6, p=0.52
E*3 vs E*4 OR=1.12, CI=0.48 to 2.63, p=0.7962
E*2 vs E*4 OR=1.6250, CI=0.41 to 6.44, p=0.4895

A DAS28 score of 6 and above is considered to be an indication of severity of the disease.
References


Referees for JAPI

API Members with minimum ten years experience of clinical practice and who are interested to contribute for JAPI as Referee may please send your details as listed below.

Name, Years of experience, Current designation and Affiliations, Area of interest, List of publications, e-mail id and Mobile number.

Kindly send above information at the earliest to: onlinejapi@gmail.com

Prof. Milind Y. Nadkar
Editor-in-Chief, JAPI
A Study of Clinical Profile of Patients presenting with Complications of Acute Febrile Illnesses During Monsoon

Kaustubh Dilip Salagre, Ravindra Nath Sahay, Amar R Pazare, Abhishek Dubey, Kunal K Marathe

Abstract

Background: The objective of this study was to describe clinico-laboratory profile and outcome of complicated acute febrile illnesses among inpatients in a tertiary care hospital during monsoon.

Methods: This was an observational, prospective study conducted in a tertiary care hospital in Mumbai, India. Between July 2016 to October 2016, adult patients admitted to the hospital with complicated acute febrile illness were included. Demographic, clinical and laboratory data were collected and analyzed for each patient. Associations were sought between death and organ specific complications.

Results: Out of 276 patients enrolled male gender 187(67.8%) and age group of below 35 years comprised the larger proportion of the cases with total 115(63.2%) dengue, 37(80.4%) leptospirosis, 25(69.4%) malaria cases. The most common symptoms reported amongst the enrolled patients included generalized body ache (85.9%), headache (77.4%), vomiting (73.4%), abdominal pain (50%), high coloured urine (34.2%), and breathlessness (32.1%), loose motion (25.1%) and altered Sensorium (8.8%). Clinical signs seen and significantly associated were pedal edema 14.5% (P=0.001), icterus 20.7%(P=0.0001) and tachypnoea 19.4%(P =0.001). Most common complication of dengue was shock (70.9%) followed by hepatic (66.5%) and haematological (65%) derangements, that of malaria was CNS involvement (29.4%), and for leptospirosis it was renal failure (45.9%) followed by respiratory distress (22.3%). Overall mortality in Dengue was 7(3.8%), malaria 2(5.6%), leptospirosis 15(32.6%), Hepatitis E 2(50%).

Conclusion: The similarity in clinical presentation and diversity of etiological agents demonstrates the complexity of diagnosis and treatment of acute febrile illness. This study of clinico-laboratory profile of complicated febrile monsoon illnesses will be helpful to reduce mortality associated with monsoon illnesses by early referral and prompt treatment. Dengue and leptospirosis remain the commonest etiologies and major killer due to respiratory and renal involvements.

Editorial Viewpoint

- Acute febrile illness during monsoon is an important health hazard in India.
- This study outlines the complexity of the diagnosis and treatment in acute febrile illness.

Introduction

Acute febrile illness (AFI) is defined as a patient with fever of 38°C or higher at presentation or history of fever that persisted for 2–7 days with no localizing source. Fever is the main clinical symptom of various tropical infectious diseases. In India, the effect of changing climate during monsoon season leads to numerous health consequences resulting from disease transmission. Like other developing nations, India with limited resources, is facing lots of health effects due to climate change, including vector borne and water borne diseases such as leptospirosis, dengue and malaria. Acute febrile illnesses in the city of Mumbai, during monsoon (July-October), rise to epidemic proportions with significant level of morbidity and mortality in the patients suffering during this period. These AFI that includes scrub typhus, dengue fever, malaria, enteric fever, and leptospirosis cause significant mortality and morbidity. A significant number includes mixed infections with the previously mentioned agents, while a few
Fig. 1: Pattern of febrile monsoon illnesses at tertiary care institution in 2016

Pattern of Monsoon Illnesses in 2016

<table>
<thead>
<tr>
<th>Year 2016</th>
<th>Percentage of Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>January</td>
<td>Leptospirosis</td>
</tr>
<tr>
<td>February</td>
<td>Dengue</td>
</tr>
<tr>
<td>March</td>
<td>Malaria</td>
</tr>
<tr>
<td>April</td>
<td>Hepatitis E</td>
</tr>
<tr>
<td>May</td>
<td></td>
</tr>
<tr>
<td>June</td>
<td></td>
</tr>
<tr>
<td>July</td>
<td></td>
</tr>
<tr>
<td>August</td>
<td></td>
</tr>
<tr>
<td>September</td>
<td></td>
</tr>
<tr>
<td>October</td>
<td></td>
</tr>
<tr>
<td>November</td>
<td></td>
</tr>
</tbody>
</table>

Others still remain unidentified. These patients of complicated acute febrile illness present a syndromic picture of jaundice, oliguria, thrombocytopenia, dyspnea, hemoptysis, myocarditis, and so on. As a first step towards the development of algorithms that could guide clinical management of complicated febrile monsoon illnesses, it is crucial to determine the epidemiology and clinico-laboratory profile of the causative pathogens.

When epidemiological data of these monsoon illnesses in last few years at our institute was analyzed we noticed similar surge of cases reported at our institution (Figure 1). More interestingly, there was significant increase in mortality secondary to end organ involvement was observed. Being tertiary referral institute there is marked increase in referral of such complicated patients to our institution. In our study we analyzed clinical and laboratory profile of patients who presented with organ specific complications such as pulmonary, renal, hepatic, hematological and neurological manifestations. Aim of our study is to determine demographic factors, symptoms, signs and laboratory parameters significantly associated with complications which will be alarming signals for clinicians before complications actually sets in. This will help to reduce mortality associated with monsoon illnesses by early referral and prompt treatment.

Methodology

Prospective observational study was conducted after approval from the Institutional Ethics Committee in a general municipal hospital in Mumbai from July 2016 till October 2016. All the patients who were admitted in the ward or intensive care unit with complications of febrile monsoon diseases, patients above 13 years of age who or their relatives willing to give consent were included in the study. Patients with associated infections when the complications cannot be attributed to febrile monsoon illness or patients with haematological malignancies, autoimmune disorders, and those on immunosuppressant were excluded from the study. Details of history and results of a thorough physical examination were entered on a standard data collection sheet. The routine baseline investigations included complete blood count analysis, serum electrolytes, liver and renal function tests. Reports of thick/thin smear performed to detect malarial parasites, enzyme-linked immunosorbent assay (ELISA) tests performed for agents believed to be endemic to the region like dengue IgM ELISA, leptospira IgM ELISA and Widal test or Leptospirosis PCR, Dengue PCR report if available were entered in case record sheet. All the reports done free of cost in the institutions or reports already done by referring physicians were entered. Outcome of disease in the form of either discharge or death was noted to measure mortality associated with disease complications.

Diagnostic Criteria

- Dengue: Clinical features of dengue with dengue IgM or dengue PCR positive and other serology and blood culture negative,
- Malaria: Malaria parasite (trophozoites of Plasmodium falciparum, Plasmodium vivax or mixed) visualized on thick/thin blood smears.
- Enteric fever: Blood culture positive for Salmonella typhi or Salmonella paratyphi or 4-fold rise in titre on the Widal test in convalescent sera.
- Leptospirosis: Leptospira IgM or PCR positive with other serology and blood culture negative.
- Hepatitis A/E: IgM Hepatitis A/E positive with other serology and blood culture negative.
- Complication: Complication can be arbitrarily defined as a secondary disease or condition that develops in the course of a primary disease or condition and arises either as a result of it or from independent causes and involving organs other than the primary organ involved in the disease. It may include organ specific complications such as pulmonary, renal, hepatic, hematological and neurological manifestations.

Statistical Analysis

Statistical analysis was done with SPSS Software (version 21.0,
Table 1: Symptoms of patients with complicated febrile monsoon illnesses (N = 276)

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Dengue (N=182)</th>
<th>Malaria (N=36)</th>
<th>Leptospirosis (N=46)</th>
<th>Mixed infection (N=8)</th>
<th>Hepatitis E (N=4)</th>
<th>Total</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>142 (79.3)</td>
<td>26 (74.3)</td>
<td>34 (75.6)</td>
<td>5 (71.4)</td>
<td>2 (50)</td>
<td>209 (74.4)</td>
<td>0.64</td>
</tr>
<tr>
<td>Body ache</td>
<td>159 (87.4)</td>
<td>28 (77.8)</td>
<td>41 (89.1)</td>
<td>6 (75)</td>
<td>3 (75)</td>
<td>237 (85.9)</td>
<td>0.43</td>
</tr>
<tr>
<td>High colored urine</td>
<td>50 (27.8)</td>
<td>13 (36.1)</td>
<td>25 (56.8)</td>
<td>2 (25)</td>
<td>3 (75)</td>
<td>93 (34.2)</td>
<td>0.002</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>90 (49.7)</td>
<td>18 (50)</td>
<td>24 (52.2)</td>
<td>3 (42.9)</td>
<td>2 (50)</td>
<td>137 (50)</td>
<td>0.98</td>
</tr>
<tr>
<td>Diarrhoea/loose stools</td>
<td>48 (26.5)</td>
<td>7 (19.4)</td>
<td>7 (15.2)</td>
<td>3 (37.5)</td>
<td>4 (100)</td>
<td>69 (25.1)</td>
<td>0.017</td>
</tr>
<tr>
<td>Rash</td>
<td>47 (26.1)</td>
<td>5 (13.9)</td>
<td>3 (6.7)</td>
<td>1 (12.5)</td>
<td>0</td>
<td>56 (20.5)</td>
<td>0.026</td>
</tr>
<tr>
<td>Bleeding from nose/mouth</td>
<td>17 (9.4)</td>
<td>2 (5.6)</td>
<td>7 (15.6)</td>
<td>2 (25)</td>
<td>0</td>
<td>28 (10.2)</td>
<td>0.32</td>
</tr>
<tr>
<td>Breathlessness</td>
<td>46 (25.4)</td>
<td>17 (47.2)</td>
<td>24 (52.2)</td>
<td>1 (14.3)</td>
<td>0</td>
<td>88 (32.1)</td>
<td>0.001</td>
</tr>
<tr>
<td>Oliguria</td>
<td>28 (15.6)</td>
<td>6 (16.7)</td>
<td>12 (26.7)</td>
<td>2 (25)</td>
<td>0</td>
<td>48 (17.6)</td>
<td>0.38</td>
</tr>
<tr>
<td>Convulsions</td>
<td>4 (2.2)</td>
<td>0</td>
<td>2 (4.4)</td>
<td>1 (14.3)</td>
<td>1 (25)</td>
<td>8 (2.9)</td>
<td>0.019</td>
</tr>
<tr>
<td>Altered Sensorium</td>
<td>8 (4.4)</td>
<td>4 (11.1)</td>
<td>8 (17.4)</td>
<td>3 (42.9)</td>
<td>1 (25)</td>
<td>24 (8.8)</td>
<td>0.009</td>
</tr>
<tr>
<td>Nausea/Vomiting</td>
<td>141 (77.9)</td>
<td>21 (58.3)</td>
<td>29 (64.4)</td>
<td>6 (75)</td>
<td>4 (100)</td>
<td>201 (73.4)</td>
<td>0.053</td>
</tr>
</tbody>
</table>

Percentages in parenthesis

Table 2: Signs of patients with complicated febrile monsoon illnesses (N = 276)

<table>
<thead>
<tr>
<th>Sign</th>
<th>Dengue (N=182)</th>
<th>Malaria (N=36)</th>
<th>Leptospirosis (N=46)</th>
<th>Mixed infection (N=8)</th>
<th>Hepatitis E (N=4)</th>
<th>Total</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ascites</td>
<td>15 (8.4)</td>
<td>4 (11.1)</td>
<td>3 (6.5)</td>
<td>0</td>
<td>0</td>
<td>22 (8.1)</td>
<td>0.79</td>
</tr>
<tr>
<td>Rapid weak pulse</td>
<td>62 (34.3)</td>
<td>9 (25)</td>
<td>14 (30.4)</td>
<td>1 (12.5)</td>
<td>2 (50)</td>
<td>88 (32)</td>
<td>0.51</td>
</tr>
<tr>
<td>Hepatomegaly</td>
<td>17 (9.4)</td>
<td>2 (5.7)</td>
<td>8 (18.2)</td>
<td>0</td>
<td>0</td>
<td>27 (10)</td>
<td>0.25</td>
</tr>
<tr>
<td>Splenomegaly</td>
<td>7 (3.9)</td>
<td>2 (5.7)</td>
<td>4 (9.1)</td>
<td>0</td>
<td>0</td>
<td>13 (4.8)</td>
<td>0.60</td>
</tr>
<tr>
<td>Pedal edema</td>
<td>16 (8.8)</td>
<td>10 (27.8)</td>
<td>13 (28.3)</td>
<td>1 (12.5)</td>
<td>0</td>
<td>40 (14.5)</td>
<td>0.001</td>
</tr>
<tr>
<td>Purpura</td>
<td>13 (7.3)</td>
<td>0</td>
<td>1 (2.2)</td>
<td>0</td>
<td>0</td>
<td>14 (5.1)</td>
<td>0.28</td>
</tr>
<tr>
<td>Coma</td>
<td>15 (8.2)</td>
<td>6 (16.7)</td>
<td>10 (21.7)</td>
<td>1 (12.5)</td>
<td>0</td>
<td>32 (11.6)</td>
<td>0.09</td>
</tr>
<tr>
<td>Icterus</td>
<td>17 (9.3)</td>
<td>6 (16.7)</td>
<td>29 (63)</td>
<td>2 (25)</td>
<td>3 (75)</td>
<td>57 (20.7)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Tachypnoea</td>
<td>23 (12.7)</td>
<td>11 (31.4)</td>
<td>17 (37.8)</td>
<td>2 (25)</td>
<td>0</td>
<td>53 (19.4)</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Percentages in parenthesis

Chicago, USA). Mean (SD) or median (range) were calculated for the continuous variables and t-test or Mann–Whitney test was used to test the significance. The categorical variables were expressed in proportion and Chi-square test or Fisher exact test was used to compare dichotomous variables. A descriptive analysis was done to characterize the participant population by sociodemographic data (e.g. age, gender, monthly income, and occupation). For all tests, a two-sided P = 0.05 or less was considered statistically significant.

**Observations**

Total number of patients who were admitted in King Edward Memorial hospital for febrile illnesses during the study period of July 2016 to October 2016 was 2417 of which diagnosed cases of the diseases under consideration were 919 (this included cases of malaria, dengue, leptospirosis, hepatitis E, and Enteric fever). In 1497 patients cause of fever was other than monsoon illnesses or not found hence were excluded from study. There were 276 cases presenting as complicated febrile monsoon illness with prevalence of complications studied was 30.03%. Of the 276 cases studied 182 were dengue, 36 malaria, 46 leptospirosis, 4 hepatitis E, and 8 mixed infections.

Males 187 (67.8%) outnumbered females 89 (32.2%) with maximum patients in the age group of below 35 years 208 (75.4 %) which was statistically significant with P value of < 0.000. However when gender distribution of diseases (P value is 0.1225) and gender distribution within different age group (P value is 0.6265) was plotted no statistical significance was observed. Mean age of presentation was 29 years with SD of ±12.52 for males and 31 years for females with SD of ±14.26. Most of the patients presenting with complications were from lower (43.8%) and middle socioeconomic class (53.6%).

Overall, the most common symptoms reported by the enrolled patients included generalized body ache (85.9%), headache (77.4%), vomiting (73.4%), abdominal pain (50%), high coloured urine (34.2%), breathlessness (32.1%), and loose motion (25.1%) and altered Sensorium (8.8%). Symptoms which were significantly associated with complications were high coloured urine (P=0.002), diarrhoea (P=0.017), rash (P=0.026), breathlessness (P=0.001), convulsions (P=0.019) and altered Sensorium (P=0.009). Others symptoms like headache, body ache, abdominal pain, bleeding from nose/mouth, Oliguria, nausea and vomiting were not significantly associated (Table1). Clinical signs seen and significantly associated were pedal edema (P=0.001), icterus (P=0.0001) and tachypnoea (P=0.001) (Table 2).

Investigations (Table 3) showed that mild to moderate anaemia was frequent but most had haemoglobin of >12 gm% (44.1%). While most had platelet count above 80,000 mm³, 20.4 % had thrombocytopenia of greater degree below 20,000 mm³. Average Serum transaminases were elevated and there was prerenal impairment with elevated blood
On application of the Pearson’s Chi-square test, complications that were significantly associated were central nervous system (CNS) involvement (P=0.026), respiratory distress (P=0.038), renal failure (P=0.0001) and shock (P=0.02). Hepatitis and haematological involvement had no significant association with complications (Table 4). Most common complication of dengue was shock (70.9%) followed by hepatic (66.5%) and haematological (65%) derangements., that of malaria was CNS involvement (29.4%), for leptospirosis it was renal failure (45.9%) followed by respiratory distress (22.3%).

Involvement of 3 organ systems was most commonly observed 118 (42.75%) followed by 2 64(23.18%) and 4 systems 56(20.28%).

(Figure 2). Overall mortality in Dengue was 7(3.8%), malaria 2(5.6%), leptospirosis 15(32.6%), Hepatitis E 2(50%), non for mixed infections and enteric fever. Main cause of mortality in dengue was hypovolemic or haemorrhagic shock, in leptospirosis, malaria was acute respiratory distress syndrome (ARDS) and acute kidney injury (AKI) and that to in Hepatitis E was fulminant hepatic failure and disseminated intravascular coagulopathy.

**Discussion**

This is prospective observational study which was conducted to study clinico-laboratory profile of complicated febrile monsoon illnesses. Each year, the number of patients, who suffer from fever increases, during monsoon. The total number of acute febrile illness patients during the study period of 4 months who got admitted to our hospital was 919 patients out of which 276 had single or multiorgan complications. These individuals were further divided into 3 age groups of <35 years (Young adults), 35 to 55 years (Middle aged) and > 55 years (Elderly individuals). Out of 276 patients enrolled male gender (67.8%) in the age group of below 35 years comprised the largest proportion of the cases with total 115(63.2%) dengue, 37(80.4%) leptospirosis, and 25 (69.4%) malaria cases. This observation was consistent with study by Abhilash KP et al where male predominance was seen in leptospirosis (87.5% vs. 12.5%), malaria (84.7% vs. 15.3%), enteric fever (70.2% vs. 29.8%), and dengue (57% vs. 43%) out of majority were younger than 40 years. In another study by Mittal G et al (65.3%) majority of acute undifferentiated febrile illness were males. This is probably explained by the fact that exposure to mosquitoes and transmission
of vector-borne diseases are more associated with the predominantly outdoor occupational exposure of males and immigration of young male population to metropolitan cities like Mumbai.6,7

With the onset of the monsoon, the number of cases of AFI increases and this trend persists through the winter months. During this period, dengue (65.9%) was the predominant cause of febrile monsoon illness followed by leptospirosis (16.7%) and malaria (13%). Our results are similar to those found in other tropical regions of the developing world, although the relative incidence of specific pathogens varies from place to place.6,9 Leptospirosis, malaria, scrub typhus, rickettsial infections, and dengue have been identified as major causes of AFI in Thailand and Nepal.9 In fact, nearly half of the global burden of dengue is borne by the Southeast Asian countries of India, Indonesia, Myanmar, and Thailand.10

The majority of the cases of dengue, leptospirosis and malaria were reported during the monsoon and post monsoon seasons, in accordance with the reported patterns of disease transmission.5,11 However, we found no significant seasonal variation in Hepatitis E and enteric fever with no complicated cases of enteric fever in our study. In contrast to our observation, an increased incidence of typhoid fever during the monsoon season was noticed by Sharma et al and Malakar in Assam, India and also by Owais et al in Pakistan.12,13 Clinical presentation of these common febrile illnesses was not only fever but it was associated in most case with symptoms of breathlessness, abdominal pain, diarrhea, rash, hemoptysis, hypotension, myalgia, and Icterus. Some had oliguria as well.14 Investigation showed that their hemoglobin level was a little low but CBC was normal in most patients, and 65% had thrombocytopenia with platelet count less than 80,000 mm³. They had a prerenal impairment and their average alanine aminotransferase and aspartate aminotransferase levels were 298 and 157.14,15 More than one serological test being positive, probably due to cross-reactivity or recent infection or dual infections was seen in 8(2.9%) of cases of mixed infections. Physicians need to be aware of the high rate of these phenomena and hence be cautious in making an etiological diagnosis purely based on serological tests. These tests are of little utility early in the course of AFI but can be useful to establish the etiology during outbreaks and for patients who present after several days of onset of illness.4

Overall mortality in complicated monsoon illnesses was 26(9.6%) with leptospirosis 15(57.7%) being responsible for more than half of deaths. This observation was comparable with study by S Bajpai in 2008 when case fatality rate of acute febrile illness during monsoon was 7.23% of the 160 patients in our institution2 and ARDS and AKI were amongst most common complications responsible for deaths. When outcome of patients in our study was studied in relation to organ system affection; involvement of respiratory system in the form of ARDS (P <0.001), excretory system in the form of AKI (P<0.001) and shock (P=0.025) were significantly associated with mortality (Table 5). Syndromic involvement in the form of ARDS with or without AKI in leptospirosis, shock with hepatic and hematological involvement in dengue was observed in most of the patients.2

Our study has certain limitations. Many potential pathogens (scrub typhus, spotted fever, hanta virus, and chikungunya virus) were not routinely tested, and samples were not subjected to a broader battery of serologic testing due to financial constraints. Being observational study reports done by treating physician were used to come to diagnosis which may lead to under diagnosis of cases.

**Conclusion**

This clinico-laboratory study of complicated febrile monsoon illnesses will be of use in the development of rational guidelines for infectious disease control and treatment and will be helpful to physician to intervene or refer patients to tertiary institutes before multiorgan involvement sets in so as to decrease mortality. Dengue and leptospirosis remain the common etiologies of acute febrile illness in adults and ARDS with or without renal involvement is a major killer syndrome with poor outcome. Symptoms like breathlessness, high coloured urine, altered sensorium, oliguria are early predictors of impending complications.
Acknowledgement

The authors would like to thank Department of preventive and social medicine, Seth GS Medical College, Parel, Mumbai and Infectious diseases surveillance program cell for providing statistical information about patients of infectious diseases for Year 2016.

References


Pharmacological Reperfusion Therapy with Tenecteplase in 7,668 Indian Patients with ST Elevation Myocardial Infarction – A Real World Indian Experience

SS Iyengar¹, Tiny Nair², Jagdish Hiremath³, Anjan Lal Dutta⁴, Uday Jadhav⁵, VK Katyal⁶, Dayanand Kumbla⁷, Immaneni Sathyamurthy⁸, RK Jain⁹, M Srinivasan¹⁰, Prasant Kr Sahoo¹¹

Abstract

Objective: This real-world, observational, prescription event monitoring study was conducted to evaluate safety and efficacy of indigenous tenecteplase (TNK-tPA) in Indian patients presenting with ST elevation myocardial infarction (STEMI).

Methods: This is a multi-centric, observational, prescription event monitoring study. Data was collected for 7,668 patients from 1,307 investigator sites across India from January 2011 to February 2016.

Results: Overall, 76.71% patients were hypertensive, 47.97% patients were diabetic, 42.01% had dyslipidemia, 24.35% had ischemic heart disease and 40.82% patients were smokers. The overall rate for achieving clinically successful thrombolysis by TNK was 93.34%. Delayed administration of tenecteplase yielded lower success rate (84.66%) as against those patients who received tenecteplase within 3 hours of symptoms (94.34%). 93.2% patients had chest pain resolution after pharmacological fibrinolysis. Overall 91.1% patients had 50% resolution of ST elevation at 90 minutes and mean time for 50% ST resolution was 72.06 minutes. Overall 53 patients died (mortality of 0.69%) before discharge. The incidence of bleeding (excluding stroke) was 1.77%, any stroke without ICH was 0.18% and any ICH was 0.38%.

Conclusion: The findings of this study further reinforce the safety and efficacy of indigenous TNK-tPA in Indian patients presenting with STEMI, including high-risk sub-groups. The study also highlights the importance of early reperfusion therapy.

Editorial Viewpoint

• Use of tenecteplase in thrombolysis is increasing in India due to its safety and efficacy.
• This study highlights early repurfusion by tenecteplase with its efficacy and safety even in high risk patients.

Introduction

Coronary artery disease (CAD) is one of the most common non-communicable diseases in India and one of its severe complications is ST-elevation myocardial infarction (STEMI). The rate of increase of coronary vascular diseases (CVD) in developing countries is almost double in comparison to developed countries. This especially applies to the younger generation. Reddy et al. reported that about 52% of deaths from CVDs in India occur before 70 years of age, compared with 23% in established-market economies. It is reported in a survey conducted in 45 rural villages in India that 32% of all deaths were due to CVD. It proves that the epidemic has reached its advanced stage even in rural India.
Moreover, as per data presented of Mumbai was 240 minutes. It showed that the median pre-presentation. It is evident successful thrombolysis, as indicated by a significant relief in chest pain by Noorani et al. showed that the time taken by Indian STEMI patients with multiple evidence-based advantages is the best suitable option in Indian STEMI patients in whom PPCI cannot be performed most of the time due to logistic reasons.

This study is a multicentric, observational, prescription event monitoring study, designed to evaluate case-records of patients presenting with chest pain and diagnosed with acute STEMI and in whom PPCI was not feasible within 120 minutes of a qualifying diagnostic electrocardiogram (ECG) (first medical contact).

Study population

Data was collected for 7,668 consecutive patients from 1,307 investigator sites across India from January 2011 to February 2016.

Pharmacological reperfusion

Tenecteplase, (Elaxim) manufactured by Gennova Pharmaceuticals Ltd, Pune, India, was administered to patients of STEMI reporting to the centers, in a weight-adjusted dosing pattern at the discretion of the treating cardiologist/physician as a part of standard clinical practice. Patients also received adjuvant medication as per the physician’s instructions.

Inclusion and exclusion criteria

Participants were eligible for inclusion in the study if they presented to the hospital with chest pain, diagnosed with STEMI by the treating physicians/cardiologists and thrombolysed with TNK as per the discretion of treating physician/cardiologist. Recording of all the parameters mentioned as study data points in the patient health record file was mandatory for inclusion of a patient in the study. Patients with incomplete health record as required by the study protocol, any contraindications for tenecteplase, PCI within the previous month, previous coronary-artery bypass surgery (CABG) were excluded.

Table 1: Study endpoints

<table>
<thead>
<tr>
<th>Efficacy endpoints</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Number of patients with chest pain resolution</td>
</tr>
<tr>
<td>2 Time for resolution of chest pain (in minutes)</td>
</tr>
<tr>
<td>3 Number of patients with 50% resolution of STE at 90 minutes</td>
</tr>
<tr>
<td>4 Time for 50% STE resolution (min)</td>
</tr>
<tr>
<td>5 Number of patients with clinically successful thrombolysis</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Safety endpoints (Time-frame – before discharge)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Any bleeding (excluding ICH)</td>
</tr>
<tr>
<td>2 Any stroke (without ICH)</td>
</tr>
<tr>
<td>3 Any ICH</td>
</tr>
<tr>
<td>4 ICH without GplIIb/IIIa inhibitors</td>
</tr>
<tr>
<td>5 ICH with GplIIb/IIIa inhibitors</td>
</tr>
<tr>
<td>6 Any other ADR</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Others endpoints (Time-frame – before discharge)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Myocardial re-infarction</td>
</tr>
<tr>
<td>2 Heart failure</td>
</tr>
<tr>
<td>3 Mortality</td>
</tr>
<tr>
<td>4 Safety – as assessed by investigator</td>
</tr>
<tr>
<td>5 Efficacy – as assessed by investigator</td>
</tr>
</tbody>
</table>

STE – ST segment elevation, ICH – intracranial hemorrhage, ADR – adverse drug reaction; *Clinically successful thrombolysis was defined as clinically evident successful thrombolysis, as indicated by a significant relief in chest pain and 50% resolution of ST-segment elevation at 90 minutes on ECG.
centers for 7668 patients treated in between January 2011 to February 2016. Baseline characteristics were as shown in table 2. Mean chest pain to door time was 116.1±46 minutes. The mean chest pain to door time was less than 3 hours in 76% patients, 3-6 hours in 22% and more than 6 hours in 2% patients.

Table 2: Baseline characteristics

<table>
<thead>
<tr>
<th>Patient demographics (n=7668)</th>
<th>Value (SD) / Number of patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (years)</td>
<td>55.80±10.34</td>
</tr>
<tr>
<td>Male : female</td>
<td>4.88 : 1</td>
</tr>
<tr>
<td>Mean weight (Kg)</td>
<td>67.5±11.50</td>
</tr>
<tr>
<td>Hypertension</td>
<td>5882 (76.71%)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>3678 (47.97%)</td>
</tr>
<tr>
<td>Smokers</td>
<td>3130 (40.82%)</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>3221 (42.01%)</td>
</tr>
<tr>
<td>History of IHD</td>
<td>1867 (24.35%)</td>
</tr>
<tr>
<td>Killip class</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>3703 (48.29%)</td>
</tr>
<tr>
<td>2</td>
<td>2970 (38.73%)</td>
</tr>
<tr>
<td>3</td>
<td>868 (11.32%)</td>
</tr>
<tr>
<td>4</td>
<td>118 (1.54%)</td>
</tr>
<tr>
<td>Infarct location</td>
<td></td>
</tr>
<tr>
<td>Anterior</td>
<td>4218 (55.01%)</td>
</tr>
<tr>
<td>Inferior</td>
<td>2725 (35.54%)</td>
</tr>
<tr>
<td>Lateral</td>
<td>62 (0.81%)</td>
</tr>
<tr>
<td>Anterolateral</td>
<td>67 (0.87%)</td>
</tr>
<tr>
<td>Anteroseptal</td>
<td>150 (1.96%)</td>
</tr>
<tr>
<td>Right Ventricle</td>
<td>29 (0.38%)</td>
</tr>
<tr>
<td>Posterior</td>
<td>165 (2.15%)</td>
</tr>
</tbody>
</table>

IHD: Ischemic heart disease

Table 3: Concomittant medication

<table>
<thead>
<tr>
<th>Concomittant medications</th>
<th>No. of pts. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin</td>
<td>7616 (99.32)</td>
</tr>
<tr>
<td>Clopidogrel</td>
<td>7588 (98.96)</td>
</tr>
<tr>
<td>Unfractionated or LMW</td>
<td>7332 (95.62)</td>
</tr>
<tr>
<td>heparins</td>
<td></td>
</tr>
<tr>
<td>Betablockers</td>
<td>5140 (67.03)</td>
</tr>
<tr>
<td>Nitroglycerine</td>
<td>1483 (19.34)</td>
</tr>
<tr>
<td>GPIIb/IIIa inhibitors</td>
<td>317 (4.13)</td>
</tr>
</tbody>
</table>

LMW: low molecular weight heparin

from the study.

Study Endpoints

The safety and efficacy end points are listed in Table 1.

Statistical analysis

We performed a descriptive analysis of the data. Continuous variables are presented in means (standard deviation) or median (inter-quartile range), when skewed in distribution. Categorical variables are presented as proportions. The statistical analysis was performed using SAS software package (version 8.1).

Results

Patients

Data was collected from 1307...
endpoints were captured. Overall, 99.14% and 98.57% investigators respectively considered TNK as safe and efficacious in the treatment of STEMI. 53 patients died (mortality of 0.69%) before discharge. Re-infarction occurred in 1.5% patients during hospital stay.

**Safety**

There was no procedural complication reported during TNK administration like hypotension. The safety parameters recorded were an overall incidence of bleeding (excluding ICH), the incidence of non-hemorrhagic stroke and ICH. Any bleeding excluding stroke occurred in 1.77% patients, any stroke without ICH in 0.18% and any ICH in 0.38% patients. Angiography was performed in 16.46% patients, while 411 (5.36%) patients underwent PTCA, and 186 (2.43%) had CABG.

**Discussion**

Our study adds to the wealth of evidence from India on real-world use of TNK as a fibrinolytic agent in STEMI patients. CREATE was a large prospective clinical registry of acute coronary syndrome (ACS) patients in 89 large hospital centers across India and Kerala ACS Registry prospectively collected data on 25,748 consecutive ACS admissions from 125 hospitals in Kerala. In CREATE registry, the median time from symptoms to hospital in STEMI patients was 300 minutes and 38.1% patients reached hospital in less than 4 hours. Whereas, in a study by Noorani F et al. in STEMI patients of Mumbai region, the median total pre-hospital delay was 240 minutes. In our study, case-scenario was observed to be improved with 76% patients presenting within 3 hours of chest pain.

The Indian Registry by Iyengar et al. analyzed efficacy and safety of tenecteplase in 15,222 patients with STEMI. Overall, 95.43% patients had CST, with higher success rate (96.54%) in patients treated within 3 hours than patients presenting more than 6 hours (85.38%), and an overall mortality of 1.69%. Also, STREAM trial demonstrated that patients presenting within 3 hours of symptom onset and fibrinolysed had significantly better outcome (composite of death, shock, congestive heart failure, or re-infarction up to 30 days) than PPCI group. Our study also demonstrated the significance of early thrombolysis, wherein most of the patients presented within 3 hours.

In this study, the overall rate for achieving CST by TNK was 93.34%. Similar observation was also made in the ‘Indian Registry’ where more than 90% CST was seen with tenecteplase, including high-risk sub-groups like elderly, diabetics, hypertensives, smokers and hyperlipidemics. The fact effectively highlights a satisfactory clinical efficacy of indigenous TNK in routine clinical practice. It has been seen in earlier studies that among patients with an acute myocardial infarction, 10% to 25% have diabetes mellitus. In the present study, this prevalence was much higher (48%). Similarly high inclusion rate of diabetic patients was mentioned in a study by Sathiyamurthy et al. (44.94%).

ST segment resolution is regarded as a marker of salvaged myocardium by post-thrombolytic reperfusion. Unlike conventional angiography, ST resolution is a useful surrogate indicator of both macro and microvascular perfusion and is therefore especially valuable in evaluating the success of myocardial reperfusion therapy. In this study, 91.10% patients had 50% resolution of STE at 90 minutes and time for 50% ST resolution was 72.06 minutes. Coronary pain is an evidence of ongoing ischemia/necrosis, and thus provides an alarm for rescue angioplasty in failed reperfusion. In our study, 93.20% patients had chest pain resolution after pharmacological fibrinolysis with TNK.

In-hospital mortality rate was lower (0.69%) compared to the CREATE registry (8.6%) and Kerala ACS registry (8.2%). Reasons for differences in outcomes are likely to be driven more by the patient presenting characteristics and early reperfusion than by differences in management, particularly given the similarities in terms of anti-platelet, heparin, beta-blocker, and statin use in all the studies. Being a registry of prescription event monitoring observational study, mortality rate is likely to be underreported.

Danchin N et al. reported mortality rates of 4.3% (3.3% in those receiving thrombolysis pre-hospital and 6.1% in those receiving thrombolysis in-hospital). By contrast, in-hospital mortality was 9.5% in patients who did not undergo reperfusion. In our study, mortality rates were less comparatively (0.69%). The overall mortality is lower than earlier reported incidence of 6.18% in the ASSENT-2 and up to 6.5% in TIMI 10B study. Indian registry reported a total mortality of 1.69%, with over three fold increase in mortality was seen in patients receiving delayed treatment. The incidences of bleeding, myocardial re-infarction and heart failure were similar to that reported in TIMI 10B and ASSENT-2 studies. Incidence of bleeding was 1.77% in our study, which is significantly less compared to that reported in the ASSENT-2 trial where-in major bleeding occurred in 4.66% in the tenecteplase group.

**Strengths and limitations**

The main strength of this study is the large sample size and broad coverage of hospitals across geographical regions of India. However, our study has certain limitations. First, the study is observational, uncontrolled, and depends on reported events. Second, data is collected from case records. Further, patient data were gathered from coronary care units due to logistic considerations,
which may have led to an underestimate in event rates, since patients who died in the casualty ward would not have been included in our analyses. Furthermore, post-fibrinolytic angiograms were not available for most of the patients for various reasons and therefore angiography findings were not analyzed.

Lessons learnt

This prescription event monitoring observational registry has shown certain strengths and weaknesses of clinical practice in these areas where there are no facilities for PPCI, but fibrinolytic therapy could be administered. Physicians practicing in these centres have exhibited their competence in the management of STEMI and fibrinolytic therapy. There is a substantial scope for improving medical records, and for instituting pharmaco-invasive strategy. The way forward is to know the distances of these centres from nearest PCI capable centres so that these could act as “spoke centres”, should identify and transfer cases to “hubs”, paving path for pharmaco-invasive strategy when PPCI is not possible. The next step of the project is to encourage the setting up of STEMI network in these areas and collect data on reperfusion strategies in STEMI.

Conclusion

Pharmacological reperfusion therapy is an evidence-based treatment for STEMI. The findings of this observational study of 7,668 patients in clinical practice further reinforce the safety and efficacy of TNK-tPA in Indian STEMI patients. Our study also reconfirms the efficacy and safety of tenecteplase in patients with co-morbidities like hypertension, diabetes and dyslipidemia. More importantly, our study reconfirms the importance of early thrombolysis for successful reperfusion rates (and consequently potentially better clinical outcome), especially in the Indian scenario where reaching a PCI center may not be immediately possible. Furthermore, administering thrombolitics proves to be an eminently suitable strategy in the Indian setting, since this study re-establishes the efficacy of a thrombolytic like TNK in prompt and effective reperfusion of the myocardium. Subsequently, the patients could be transferred to PCI centres.

Conflict of Interest

The study was supported by Emcure Pharmaceuticals Ltd. The authors are on the advisory panel of Emcure Pharmaceuticals Ltd.

Acknowledgement

We would like to thank the Medical team of Emcure Pharmaceuticals Ltd for support in manuscript writing.

References

A Randomized, Controlled, Phase III Clinical Trial to Evaluate the Efficacy and Tolerability of Risorine with Conventional Rifampicin in the Treatment of Newly Diagnosed Pulmonary Tuberculosis Patients

Naresh Patel¹, K Jagannath², Agam Vora³, Mukesh Patel⁴, Anand Patel⁵

Abstract
Background: The overall goals for treatment of Tuberculosis (TB) are to cure individual patient and to minimize the transmission of Mycobacterium tuberculosis. At the time of study conduction, the standard treatment for newly diagnosed tuberculosis patients consisted of an intensive phase for two months with four drugs (HRZE), followed by continuation phase for four months with two drugs (HR). Rifampicin, which is very effective against Mycobacterium tuberculosis, in both the phases of treatment, has certain concerns, which includes, decreased bioavailability with chronic use and hepatotoxicity. To overcome these concerns a new boosted formulation of Rifampicin (Risorine) with bio-enhancer Piperine was developed. Piperine has been found to increase bioavailability of several drugs including Amoxicillin, Cefotaxime, Theophylline and Propranolol. Risorine is a fixed dose combination that contains Rifampicin 200 mg + Isoniazid 300 mg + Piperine 10 mg.

Aim and Objective: The aim of the present study was to validate the therapeutic efficacy and tolerability of Risorine formulation containing regimen with a conventional regimen in the management of patients with newly diagnosed pulmonary tuberculosis.

Methods: Total 216 patients with sputum positive and treatment naïve pulmonary tuberculosis were enrolled in the study after fulfillment of inclusion / exclusion criteria. These patients were randomized to receive either a conventional anti-TB therapy (n = 117) or a similar regimen containing Risorine (n = 99) for 6 months. During the study period, symptomatic improvement, sputum conversion and radiological improvement were monitored at regular intervals.

Results: Of the 216 enrolled patients, 75% in the Risorine group and 79% in the control group completed the study. At 4 weeks the sputum conversion rate was significantly superior in Risorine group (93%) than

Editorial Viewpoint
• A new boosted formulation of Rifampicin (Risorine) with bio-enhancer Piperine is developed.
• Risorine is a fixed dose combination of Rifampicin 200 mg + Isoniazid 300 mg + Piperine 10 mg.
• In this study Risorine showed higher sputum conversion rate during the Intensive Phase which was maintained till the end of study.

Introduction
In India, more than 40% of population is infected with TB with very high mortality rate (2.2 lakhs compared to 1.1 million globally).¹ ² The overall goal for TB treatment is to cure the individual patient, and to minimize the transmission. Earlier (at the time of study conduction), standard treatment approach for all adults with previously untreated TB consist of a 2-month initial phase of Rifampicin (R), Isoniazid (H),
Pyrazinamide (Z), and Ethambutol (E) followed by a continuation phase with H and R for 4 months.1

Amongst all the first line anti-TB drugs; blood levels of Rifampicin are found to be most variable having evidences of sub-therapeutic serum levels too. Such sub-therapeutic serum levels lead to cases of therapeutic failure (non-conversion at 2 months of treatment) and relapse (reconversion at 6 months of treatment) as well as development of bacterial resistance. One of the pharmacokinetic study in pulmonary TB patients, after two months of daily therapy, it was found that 69% patients had $C_{\text{max}}$ below the reference range and 22% had very low $C_{\text{max}}$. Wide variation in $C_{\text{max}}$ (56%) and clearance (60%) of rifampicin was also reported by Israili ZH et al.2 The reasons for underlying decreased absorption of Rifampicin are:5–9

a. Rifampicin induces its own metabolism

b. Rifampicin is potent inducer of mixed function oxidases as well as P-glycoprotein (P-gp)

Another area of concern is side effects; mainly hepatotoxicity, gastrointestinal disturbances (38% - 53%) and tolerance of Anti-TB drugs. The risk of hepatotoxicity in patients from India is higher than those reported in west (11.5 % versus 4.3 %).10 Isolated Rifampicin-induced hepatic toxicity occurs in up to 2% patients whereas co-administered with INH and PZA, it is up to 28%.11

To overcome the limitations of conventional Rifampicin, AT – 3, Renowned formulation of Rifampicin with a bio-enhancer Piperine was developed by scientists at the Indian Institute of Integrative Medicine – IIIM, Jammu in collaboration with Cadila Pharmaceuticals Limited, Ahmedabad, which is currently marketed in India as “Risorine”. Risorine contains Rifampicin (200 mg), Piperine (10 mg) and Isoniazid (300 mg). Risorine was developed to provide more Rifampicin in blood compared to in Gastro-intestinal tract as well as maintaining the blood levels of Rifampicin on chronic therapy.

Piperine is very well studied bio-enhancer of various drugs, including Rifampicin. During the initial studies by scientist at IIIM revealed the bioavailability enhancing behavior of pepper. Various studies on active principle of peppers i.e. Piperine, revealed the bioavailability enhancing behavior of several drugs including Amoxicillin, Cefotaxime, Cycloserine A, Theophylline, Propranolol, Nevirapine etc.12–15 Zutshi et al had demonstrated significant increase in blood levels of Rifampicin when co-administered with Piperine as compared to Rifampicin 450mg alone in 14 pulmonary TB patients.16

**Piperine enhances the bioavailability of drugs by:**17,18

- Inhibiting drug metabolizing enzymes in enterocytes, including cytochrome P-450 enzymes and uridine diphosphate-glucuronyl transferase, thus decreasing first-pass metabolism of drugs
- Inhibiting P-gp in enterocytes and thus inhibiting efflux of absorbed drugs from enterocytes

During pre-clinical studies, piperine was not associated with any abnormalities related to growth, organ weight ratio or blood chemistry even at higher dose (500 mg/kg). The same were not found even during autopsy and microscopic examination. Piperine 10 mg was found optimum with rifampicin 200 mg during Phase I pharmacokinetic (PK) study. During Phase I studies, PK profile of Risorine (Rifampicin 200 mg and Piperine 10 mg) was identical with Rifampicin 450 mg alone on first day; while reduced blood levels were observed in Risorine 450mg on day 14, but not with Risorine. Pharmacokinetics of other anti TB drugs like, Isoniazid and Pyrazinamide, were also unaffected with concomitant administration of Risorine.19

In a phase II randomized, double blind, comparative clinical trial was conducted in Category I, sputum smear-positive and radiologically confirmed pulmonary TB patients, Risorine containing regimen was shown to be as efficacious as the standard WHO anti-TB regimen without any additional adverse effects. Also Rifampicin blood levels were found to be reduced over 6 month’s treatment with rifampicin 450mg but not with Risorine formulation.19

Conclusions: Risorine, a novel formulation of low dose Rifampicin (200 mg), a bio enhancer Piperine (10 mg) and standard dose Isoniazid (300 mg) when given along with Ethambutol and Pyrazinamide was comparable in efficacy with standard WHO therapy using conventional formulation. Risorine provides more Rifampicin in blood compared to Gl tract as well as maintaining higher blood levels on chronic therapy compared to conventional Rifampicin with better safety profile. Risorine gives higher sputum conversion rate during the Intensive Phase which is maintained till the end of study. Further a trend was also noticed towards better tolerability with newer formulation, Risorine.

$H = $ Isoniazid, $R = $ Rifampicin, $Z = $ Pyrazinamide and $E = $ Ethambutol
To confirm the above findings and to validate the therapeutic efficacy and tolerability of Risorine containing regimen against conventional regimen in patients with newly diagnosed pulmonary TB, this Phase III study was planned. Upon positive outcome it may result in considerable dose reduction and consequently the cost of active drug i.e. Rifampicin.

Later on, Vora et al had demonstrated efficacy of Risorine in drug susceptible pulmonary TB patients. Risorine was found highly effective and well tolerated in the treatment of drug – susceptible pulmonary TB patients who developed GI intolerance with standard WHO anti TB treatment.\(^{10}\)

**Material and Methods**

**Study Design**

The present study was a randomized, triple-blind, parallel-group, multicenter, comparative clinical trial of experimental treatment (AT-3, Ethambutol and Pyrazinamide) versus WHO standard treatment. With regard to blinding, patients, investigators, as well as other study personnel were completely blinded of treatment allocations. This study consisted of two phases – an intensive phase of 2 months followed by a continuation phase of another 4 months. The study was carried out at 3 centers in India. The detailed regarding the study design and study medication administration was described in below Figure 1.

**Patient population**

Two hundred and sixteen (216) newly diagnosed pulmonary tuberculosis patients were enrolled at 3 centers in India, namely, Jammu, Bangalore and Ahmedabad. Having read, all patients signed informed consent form, which was duly approved by Institutional Ethics Committees. Eligibility criteria for enrollment in the study included:

a. Patients of either sex
b. An age of 15 to 50 years
c. Weight not less than 30 Kg
d. Only newly diagnosed, sputum positive case (fresh case) of pulmonary tuberculosis
e. Patients with minimal to extensive severity of disease were included with confirming radiological diagnosis
f. A serum aspartate transaminase (AST or SGOT) and serum alanine transaminase (ALT or SGPT) level less than 3 times the upper limit of normal (ULN)
g. A serum total bilirubin level of less than 2 times the ULN
h. A serum creatinine of less than 3 times the ULN

Patients were retained indoor for at least one month of the initial period. Although, patients were encouraged to stay in the study throughout the initial and continuation phases, however, all withdrawals were completely voluntary.

It was confirmed that all patients included in this study were free from other diseases and disorders, such as HIV infection, seizure disorder, diabetes mellitus, congestive cardiac failure, hypertension, malignancy, chronic lung disease, abnormal hepatic, renal or hematologic functions, and retinopathy. Patients were ineligible if they had a history of MDR-TB or close contact with an MDR TB patient, >3 weeks of continuous anti-TB treatment immediately prior to enrollment, >2 months of anti-TB therapy in
the past 2 years, pregnancy, or exclusively extrapulmonary TB. Patients were also excluded if they had hypersensitivity to any of the study drugs or the excipients used in their formulation; were seriously ill; had undergone organ transplantation and/or were receiving immunosuppressive drugs; received systemic corticosteroids for more than 7 days within the past one month; had a history of alcohol or drug abuse; were non-compliant to the protocol requirements. Pregnant or lactating females or women of child bearing age not following barrier contraception or on oral contraceptives were not included in the study.

Pulmonary TB disease was classified based on intensity of disease as +1 (minimal lesions: infiltration not more than one zone, without cavity), +2 (moderate disease: total extent of disease more than one zone but less than total volume of one lung; cavity size less than 4 cm), +3 (advanced diseases: area involvement more than one lung with cavitation) and +4 (far advanced disease: bilateral involvement with cavities – size more than 4 cm).

**Study Outcome Measures**

In the initial phase, the primary outcome measure was sputum conversion. If a patient could not induce or produce sputum, then it was considered a negative sputum culture. The secondary outcome measures included sputum smear conversion, clinical response, survival, and adverse events.

In the continuous phase (the 16 weeks period after the 8 weeks of intensive phase with 4 drugs), the primary outcome of the study was treatment failure (during therapy) or relapse (within 4 months after completion of therapy). Treatment failure was defined as two or more positive *M. tuberculosis* cultures at least 1 month apart, with no intervening negative cultures, after the patient completed at least 2 months in the study and was still receiving anti-TB therapy. Relapse was defined two ways: (1) a positive *M. tuberculosis* culture (of sputum or another specimen) after the patient’s sputum culture had converted to negative and the patient had completed treatment or (2) a positive culture after the patient’s symptoms/signs of clinical pulmonary tuberculosis resolved and the patient completed treatment.

Secondary endpoints of the study included adverse events or death. Adverse events that occurred during receipt of study medication and for 8 weeks after its discontinuation were graded on a 5-point scale.

In this study, “cure” has been defined as a patient who is sputum smear-negative in the last month of treatment and on at least one previous occasion. Definition of treatment completed refers to a patient who has completed treatment but who does not meet the criteria to be classified as a cure or a failure. Treatment success is defined as the sum of patients cured and those who have completed treatment.

**Evaluation and Follow-up**

Study visits were scheduled at weeks 2, 4, 6, and 8 during the initial phase and months 1, 2, 4, 6, 8, and 10 and every 4 weeks thereafter during the continuation phase.

The Baseline (screening) visit included laboratory tests involving blood, sputum (for consecutive days) and urine, physical examination including vitals, chest X-ray (PA view), pregnancy test for female patients and medical history for the patients. Laboratory examinations [blood and sputum (for two consecutive days) analysis], physical examination including vitals, concomitant illness, concomitant illness and medications were performed for each patient for all the visits after randomization. Chest X-ray (PA view) was performed at the end of initial phase and continuous phase.

Patients were provided with a ‘Study Diary’ that contains a calendar to record medication intake, visit dates for her/his duration of the study, and names and telephone numbers of the study site personnel to report problems or adverse events.

Specific adverse events (AEs) and adverse drug reactions (ADRs) were recorded at all times throughout the study. Routine examinations for AEs and ADRs related to sensitivity reactions (including cutaneous hypersensitivity), gastrointestinal, hepatic, renal or ophthalmic systems, drug fever, breast tenderness, and any other were performed and recorded during the study.

**Withdrawal Criteria**

Patients were withdrawn in case of a serious adverse event; non-compliance with protocol specifications, including non-intake of study medication for more than 15 days during the Intensive Phase or for more than 1 month during the Continuation Phase; if diagnosed as MDR-TB; were sputum smear positive at the end of 3 months and if AST, ALT and ALP levels are more than 5 times the upper limit of normal or serum bilirubin is >2mg/dl.

**Sample Size Calculation**

A sample size of the study was calculated based on an effect size and variation experienced in previous Phase-II studies with the same experimental and control administrations. The level of significance and statistical power were fixed at 0.05 (two tailed) and 80%, respectively. The sample size was calculated to be a total of 220 patients needed to complete the study. In fact, it was decided to enroll 300 patients to account for a relatively high dropout rate.

**Statistical Methods**

Comparisons of treatment groups were made by means of the Fisher’s exact test, Student’s *t*-test, and Wilcoxon rank-sum test,
Table 1: Baseline characteristics of evaluable subjects in experimental (E) and control (C) groups

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Across all centers</th>
<th>E</th>
<th>C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients</td>
<td>74</td>
<td>92</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>29.14±9.57</td>
<td>30.05±11.44</td>
<td></td>
</tr>
<tr>
<td>Weight</td>
<td>42.07±6.03</td>
<td>42.77±6.96</td>
<td></td>
</tr>
<tr>
<td>Extent of disease</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Minimal (+)</td>
<td>4 (0.41%)</td>
<td>2 (0.27%)</td>
<td></td>
</tr>
<tr>
<td>Moderate (++)</td>
<td>42 (56.76%)</td>
<td>41 (44.57%)</td>
<td></td>
</tr>
<tr>
<td>Advanced (+++)</td>
<td>14 (18.92%)</td>
<td>18 (19.57%)</td>
<td></td>
</tr>
<tr>
<td>Far advance (++++)</td>
<td>14 (18.92%)</td>
<td>31 (33.70%)</td>
<td></td>
</tr>
</tbody>
</table>

Table 2: Change in weight (Mean ± SD) in evaluable patients in both, Experimental (E) and Control (C), groups

<table>
<thead>
<tr>
<th>Treatment duration</th>
<th>All patient</th>
<th>Experimental group (E)</th>
<th>Control group (C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>42.46±6.64</td>
<td>42.07±6.03</td>
<td>42.77±6.96</td>
</tr>
<tr>
<td>Weight gain from baseline to 4 week</td>
<td>1.84±6.59 (p = 0.0115)</td>
<td>1.99±6.1 (p = 0.0492)</td>
<td>1.72±6.98 (p = 0.0967)</td>
</tr>
<tr>
<td>8 week</td>
<td>45.70±6.59</td>
<td>45.43±6.3</td>
<td>45.91±6.84*</td>
</tr>
<tr>
<td>Weight gain from 8 week to 24 week</td>
<td>1.4±6.56 (p = 0.0534)</td>
<td>1.38±6.22 (p = 0.1803)</td>
<td>1.42±6.84 (p = 0.1627)</td>
</tr>
<tr>
<td>24 week</td>
<td>47.77±6.72</td>
<td>47.77±6.99</td>
<td>47.77±6.53*</td>
</tr>
<tr>
<td>Overall weight gain from baseline to 24 weeks</td>
<td>2.07±6.65 (p = 0.0051)</td>
<td>2.34±6.65 (p = 0.0343)</td>
<td>1.86±6.69 (p = 0.0644)</td>
</tr>
</tbody>
</table>

*Out of 92 patients, 90 patients’ data available at 8 weeks and 24 weeks in control group. Two patient’s data not available; ** Difference between Experimental Group and Control Group is statistically significant (p < 0.0001)

Results

A total of 216 patients were enrolled in the study across three centers; Jammu (n=60), Ahmedabad (n=91) and Bangalore (n=65). Of these 216 patients, 99 patients were assigned in the experimental group (AT-3), whereas 117 patients were allocated in the control group. Seventy four (74.75%) and ninety two (78.63%) patients completed the 24 week of therapy among the experimental and control group, respectively.

The reason for withdrawal were a) non-compliance with protocol or lost to follow up (48 patients); b) HIV positive patient (01 patient); and c) death (01 patient in experimental arm due to excessive hemoptysis during intensive phase).

Patients Demographics and Baseline Characteristics

Overall mean age of all participants was 29.6 (± 10.6) years and mean baseline weight was 42.5 (± 6.6) Kg. Similarly, 80.7% and 19.3% of patients were male and female among both the groups. The baseline patient characteristics of age and weight were statistically insignificant and comparable among the two treatment groups. Baseline characteristics of patients along with the extent of disease were shown in Table 1.

There was no significant difference in either the number of patients or the number of doses administered between the groups. Patient’s compliance to treatment regimen was similar for both daily and intermittent doses.

Clinical Efficacy

Experimental arm shown higher sputum conversion at 4 weeks, i.e. in 93.22% patients, while in control group sputum conversion was observed in 83.75% patients. The clinical improvement in all the patients appears almost equivalent at 4 weeks in both the treatment arms. But a striking difference was observed in experimental arm with AT – 3 at 8 weeks where 10 patients got complete cure. On other hand none of the patients in control group showed such improvement. Even at the end of 24 weeks of treatment, striking difference was maintained. The cure rate observed at the end of 24 weeks was 91.89% in the experimental group and 81.52% in the standard therapy group (Figure 2).

Effect on Weight Gain

Average weight of all patients was 42.07±6.03 in experimental group and 42.77±6.96 in control group. The difference between two groups is not statistically significant at baseline. Weight gain observed from baseline to 4 weeks of treatment and from 8 weeks of treatment to end of treatment was statistically significant in experimental group while it was non-significant in control group. At the end of 24 weeks the weight gained was 5.70±6.63 Kg in experimental group and 4.99±6.83 kg in control group which is statistically significant (Table 2).

Safety and Tolerability

Both regimens were very well tolerated during the entire study period. However, in control group, total 9 patients reported with elevated liver function tests, which include 7 patients having elevated SGOT, 1 patient having elevated
Rifampicin, while very effective against *M. tuberculosis*, in both initial and continuous phases of therapy has certain concerns. The bioavailability of Rifampicin is reduced on chronic therapy. Rifampicin clearance increases during multiple dose therapy due to its known induction of hepatic enzymes, which leads to auto-induction of its own metabolism. Another area of concern is hepatotoxicity. The treatment often produces severe hepatotoxicity and potentiates the same problem caused by Isoniazid. This may lead to discontinuation of therapy. To overcome these concerns a boosted formulation of Rifampicin with a bioenhancer Piperine was developed. Piperine has been found to increase bioavailability of several drugs including Amoxicillin, Cefotaxime, Cycloserine A, Theophylline, Propranolol, Nevirapine etc. To the best of our knowledge, there are no previous attempts of increasing the bioavailability of Rifampicin to demonstrate its utility in a reduced dose for efficacy for the treatment of new TB patients.

In previous preclinical studies, different doses of piperine ranging from 1 mg to 40 mg were experimented with Rifampicin (40 mg/kg) in rats. The plasma Rifampicin levels were determined at possible peak timings of 2 and 4 hours post-dosing. It was revealed that though the bioavailability enhancing effect of piperine commences from 1 mg dose itself but the maximum effect becomes noticeable from 3 mg onwards. It stabilizes at 5 mg and is maintained up to 20 mg dose where after a decline in its effect is observed. In yet another unpublished study in rats, it was found that addition of piperine reduces the ED$_{50}$ of Rifampicin in these animals by 50%. This was later on used to formulate AT-3 wherein only 200mg of Rifampicin was used together with 300 mg Isoniazid to replace 450 mg Rifampicin and 300 mg Isoniazid.

Risorine was underwent the various stage of development before conducting Phase III clinical trial. Pre-clinical studies demonstrated that Risorine did not cause any abnormalities in general growth, body to organ weight ratio or blood biochemistry. During clinical phase I and phase II studies, pharmacokinetic profile was found to be similar as conventional Rifampicin 450 mg on day 1 while no change was observed in serum level with Risorine as compared to reduce levels with Rifampicin 450mg on chronic therapy, while no effect on co-administered other anti TB drugs. Also during Phase II study, it was found that Risorine containing regimen was as efficacious as the standard WHO anti-TB regimen without any additional adverse effect. Based on the results of Phase II study, Phase III study was planned to confirm the findings of Phase II study.

We assessed the efficacy and safety of a regimen containing AT-3 in comparison to the standard WHO regimen among newly diagnosed pulmonary TB patients. The study treatment included initial phase of 8-week treatment with either AT-3 plus Ethambutol and Pyrazinamide in experimental group or standard WHO regimen of Rifampicin, Isoniazid, Ethambutol and Pyrazinamide in control group. This was followed by continuation phase of 16-week treatment with either AT-3 in experimental group or standard WHO regimen (Rifampicin + Isoniazid) in control group.

A total of 216 patients were enrolled in the study across three centers; 99 patients in the experimental group (AT-3), whereas 117 patients in the control group (Standard WHO dose). The proportion of patients withdrawn or missing at the end of 24-week of treatment, the corresponding rates were 25.25% and 21.37%, respectively. The observed sputum conversion rate was 92.75% in the experimental group and 85.39% in standard therapy group at four weeks. The cure rate observed at the end of 24 weeks was 91.89% in the experimental group and 81.52% in the standard therapy group. Early sputum conversion was found in Risorine group which was maintained throughout the study period. At the end of the study, cure rate was found to be higher with Risorine group.

Both regimens were well tolerated with gastrointestinal side effects being the most common. Adverse events were of mostly mild to moderate severity. Elevations in SGOT, SGPT and total bilirubin were observed among 09 patients at the end 4th week of treatments in control group which was significant when compared to 03 patients in experimental group. Also 01 patient having elevated levels of all three parameters was discontinued from the study.

Later on, role of Risorine in the treatment of drug susceptible pulmonary TB was assessed by Vora et al. In that study, 33 pulmonary TB patients who cannot tolerated the conventional treatment with Rifampicin 450mg were given Risorine treatment. Out of 27 patients who were sputum positive at beginning of treatment, 24 of them became sputum negative at two months, one at three month and remaining two became sputum negative at six month of treatment. Out of 33 patients, only two patients developed nausea which was subside spontaneously and
one HIV positive patient developed hepatitis.

**Conclusion**

Rifampicin is key drug in drug susceptible TB management, simultaneously associated with low blood levels and adverse effects. These short falls associated with non-conversion and non-compliance leads to treatment failure and development of drug resistance TB. Risorine provides more Rifampicin in blood compared to GI tract as well as maintaining higher blood levels on chronic therapy compared to conventional Rifampicin. Further Risorine does not affect the pharmacokinetics of other co-administered anti TB drugs. Risorine provided higher sputum conversion during intensive phase and better cure rate at the end of treatment than conventional Rifampicin with better safety profile. Also Risorine was found to be highly efficacious and safe even in the drug susceptible pulmonary TB patients who cannot tolerate conventional Rifampicin. In conclusion, Risorine appears to be an effective and useful alternative to Rifampicin 450mg and Isoniazid 300mg in multi-drug regimens for drug susceptible pulmonary TB treatment.

**Acknowledgement**

This study was funded by Cadila Pharmaceuticals Pvt. Ltd., Ahmedabad. The sponsor was responsible for the study design, the analysis and interpretation of the data and the writing of study report. The authors would like to thank the investigators; Laxaman Y, Kusumben Shah, RK Zutshi and Rajinder Singh, and patients at the investigative sites for their support of this study.

**Conflicts of Interest**

Laxaman Y, Shah Kusumben, Zutshi RK and Singh Rajinder all had contributed to the conduct of the study. Patel Naresh, K Jagannath, Vora Agam, Patel Mukesh and Patel Anand had contributed towards data analysis and manuscript preparation / revision and final approval of the manuscript.

**Key Highlights**

- Rifampicin, a key drug in the treatment of Tuberculosis, associated with decreased bioavailability with chronic use and associated hepatotoxicity, specifically when used with Isoniazid and Pyrazinamide
- Risorine, a Novel formulation of Rifampicin that contains Rifampicin 200mg + Isoniazid 300mg + Piperine 10mg
- **Risorine, the boosted Rifampicin**, having advantage of better tolerability, better treatment compliance and better response
- Clinical cure rate is better with Risorine treatment than conventional treatment, 91.89% Vs. 81.52%
- Only 03 patients developed liver function abnormality with Risorine, while 07 patients developed liver function abnormality with conventional treatment
- DCGI approved Rifampicin formulation undergone through regulatory trials including Pre-clinical to Phase IV

**References**

In Type 2 Diabetes with High PPHG

Choose the No. 1 brand

Glycomet® Trio 1

Umbrovia 100 mg + Glibenclamide 1 mg + Vagfum 6.6 mg

Glycomet® Trio 2

Umbrovia 300 mg + Glibenclamide 2 mg + Vagfum 16.6 mg

Uptitrate to

Glycomet® Trio 1.0/0.3

Umbrovia 100 mg + Glibenclamide 1 mg + Vagfum 6.9 mg

Glycomet® Trio 2.0/0.3

Umbrovia 300 mg + Glibenclamide 2 mg + Vagfum 17.3 mg

In Obese Type 2 Diabetes with HbA1c > 9%

Glycomet® Trio Forte 1

Umbrovia 100 mg + Glibenclamide 1 mg + Vagfum 6.2 mg

Glycomet® Trio Forte 2

Umbrovia 300 mg + Glibenclamide 2 mg + Vagfum 15.3 mg

Ref: B - MAT WOCD: Dec 2016
In Hypertension get your patients to BP goal with *newer age ARB*

Ideally suited for

- Patients uncontrolled on other ARBs

**USV Azilday**

Azilsartan 80 mg

On BP goal... All Day

Ideally suited as

- An add-on to ongoing CCB/Diuretic therapy

**USV Azilday 40**

Azilsartan 40 mg

On BP goal... All Day
In India, 8 CRORE Migraine sufferers remain untreated

Flunarizine is the MOST EFFECTIVE calcium channel blocker in Migraine

63% Reduction in attack frequency
80% Reduction in headache score
83% Reduction in MIDAS™ score

An initiative to manage Migraine better

www.mewithoutmigraine.com

References:
Executive Summary: Association of Physicians of India: Position Statement on Role of Chirally Pure Molecules in Clinical Practice

Milind Y Nadkar¹, Mangesh Tiwaskar², Sanjay Kalra³, Siddharth N Shah⁴, BR Bansode⁵, Anjanlal Dutta⁶, Sarita Bajaj⁷, Sameer Aggarwal ⁸, Yatan Pal Singh Balhara⁹, AK Das¹⁰, Puneet Dhamija¹¹, YK Gupta¹², Jubbin Jacob¹³, Sundeep Mishra¹⁴, SN Narasingan¹⁵, CK Ponde¹⁶, Ram Prabhoo¹⁷, S Balakrishnan¹⁸, Manisha Sahay¹⁹, RK Sahay²⁰, I Sathyamurthy²¹, Shilpa Tiwaskar²², Agam Vora²³

The Association of Physicians of India (API) has developed a position statement on the role of chirally pure molecules in clinical practice based on the recommendations of an expert panel that included anesthesiologists, cardiologists, endocrinologists, gastroenterologists, orthopedicians, pharmacologists, physicians, pulmonologists, nephrologists, psychiatrists, and rheumatologists across India. The position statement aims to bridge the gap in awareness on the use of chirally pure drugs in different therapeutic areas in India among regulatory bodies, clinicians (including academicians and researchers), pharmacists, and patients.

A. Chiral molecules

- Chiral molecules (derived from Greek word ‘cheir’ that stands for ‘hand’ or handedness) or enantiomers, are molecules that are non-superimposable mirror images of each other (similar to the left and right hand) and comprise a chiral center (usually a carbon, nitrogen, phosphorus or sulfur atom).¹

- They are classified as
  - rectus (R)- or sinister (S)-enantiomers based on atomic mass and number
  - levo (l) or dextro (d) based on rotation of plane polarized light and
g  - cis or trans based on the position of functional group around the double bond

The mixture of two enantiomers is known as a racemate.²

B. Advantages of chirally pure drugs

- Single enantiomers or chirally pure drugs exhibit different bioactivity and metabolism as compared with the racemate. They may exhibit better receptor affinity, higher therapeutic activity, better safety profiles, less drug-drug interactions, reduced metabolic load and different pharmacological mechanism of actions and may have their distinct hepatic and renal excretion pathways.¹³,⁴

- Chiral switching is development of single enantiomers from racemic mixtures that are previously approved and marketed.⁵

C. Regulatory considerations

- The registration process for approval of chirally pure molecules in India is...
similar to the category of new drugs as per schedule Y.

India currently follows the International Conference on Harmonization of Technical Requirements Q6A guidelines for ensuring quality of marketed chirally pure molecules similar to that of new chemical entities.7,8

D. Chirally pure drugs in therapy

Some important chirally pure molecules currently used in different areas of clinical practice include the following:

Cardiology

- **S-metoprolol** (an enantiomer of metoprolol) with a higher affinity for β1 receptor, demonstrated a 13.6% increase in responders (at day 21) at the dose of 50 mg as compared with racemate (100 mg).9

  Similar results of blood pressure reduction were observed in hypertensive patients with co-existing illnesses such as chronic obstructive pulmonary disease, angina, angina co-existent with/without diabetes mellitus, and congestive heart failure without major safety concerns.10

- **S-amlodipine** (an enantiomer of amlodipine) with a lower dose (2.5 mg) demonstrated a response rate of 92.7% as compared with 5 mg amlodipine (88%).11 The incidence of pedal edema was lower with S-amlodipine as compared with amlodipine.12

Gastroenterology

- **S-omeprazole** (or esomeprazole, an enantiomer of omeprazole), exhibited higher bioavailability and less inter-patient variability as compared to omeprazole. The odds ratio of maintaining intragastric pH >4 with esomeprazole versus omeprazole was 1.57 (confidence interval=1.04, 2.38; p=0.03).13

Neuropsychiatry

- Escitalopram (S-enantiomer of citalopram, selective serotonin reuptake inhibitor) demonstrated early onset of efficacy (within 2 weeks) and reduced the risk of relapse (over 36 weeks) of depression symptoms with less adverse events, in patients with major depressive and anxiety disorders as compared with citalopram.14 Additionally, the QTc interval prolongation of escitalopram was half as compared with citalopram.15,16

- S-zopiclone (enantiomer of zopiclone, a sedative-hypnotic) displayed efficacy in the treatment of primary chronic insomnia, without the need for dose adjustment, in patients with renal failure as compared with zopiclone17 and revealed no substantial central nervous system depression.18

Endocrinology

- **Levothyroxine** (an enantiomer of thyroxine) at lower doses (0.15 mg) demonstrated efficacy equivalent to dextrothyroxine (4 mg) for lowering of serum thyroid stimulating hormone, triglycerides, cholesterol and phospholipid levels in hypothyroid patients.19

- Myo-inositol (MI) and D-chiroinositol (DCI) (both inositol isomers), used as insulin sensitizers, demonstrate beneficial effects at metabolic, hormonal, and ovarian level as therapy for polycystic ovarian syndrome. MI is the most abundant natural isoform of inositol whereas DCI is formed by epimerization of MI to DCI. Tissue-specific ratio of both exhibit different functions of these molecules. The combined administration of MI with DCI helps correct hormonal and metabolic imbalance.20,21

Anesthesia

- As compared to its racemate, esketamine (S-enantiomer of ketamine), exhibited less disorientation, pain and fever in post-operative patients.

- **Levobupivacaine** (S-enantiomer of bupivacaine) revealed less cardiotoxic effects as compared to racemate.22,23

Rheumatology, Pain, and Inflammation

- S-etodolac (enantiomer of etodolac) demonstrated 2.6 times higher potency and bioequivalence at half the dose when compared with the racemic mixture (300 mg vs 600 mg).24,25 Dexketoprofen, (the S-enantiomer of ketoprofen) an analgesic prescribed for relief from post-surgical dental pain and dysmenorrhea, demonstrated faster onset of action and efficacy at lower doses.26,27

Pulmonology

- **R-salbutamol** (an enantiomer of salbutamol) and levocetirizine (R-enantiomer of cetirizine) displayed better safety profiles as compared to their racemates.28,31

Infectious diseases

- **Levofloxacin** (active
E. Recommendations for India

These recommendations aim to create awareness amongst regulatory bodies, clinicians, pharmacists, and patients on the use of chirally pure molecules in Indian clinical practice.

For regulatory bodies

- A different set of guidelines as compared to new chemical entities are required for the expedited approval of chirally pure molecules in India
- Providing a global perspective by generating awareness on guidelines governing the approval of chirally pure molecules in different countries

For clinicians

- General awareness of the concept of chirality and its effect on improving safety and efficacy outcomes in appropriate situations
- Awareness on the availability of chirally pure drugs with differential clinical and pharmacological profiles
- Awareness to be generated by continued medical education, concept-based panel discussions, and position statement and inclusion of clinicians in conducting clinical trials of chirally pure drugs

For pharmacists

- General awareness of the concept of chirality, particularly the key differences between racemates and enantiomers and its effect on the safety and efficacy outcomes under applicable conditions
- Understanding the sanctity of drug prescriptions
- Awareness could be increased by policy campaigns, education camps, and clinicians counselling the pharmacists on non-equivalence of drugs and discouraging substitution

For patients

- Realizing the importance of chirally pure drugs and its value in reducing the drug dosage and side-effects
- Information on safety and efficacy of chirally pure drugs to be disseminated via physician counselling, media campaigns and patient education forums
- Healthcare providers should readily share their knowledge and experience with patients on using chirally pure drugs

This executive summary will be followed by a position statement of API on chirally pure molecules in clinical practice elaborating every aspect alluded to in this summary.

Acknowledgments

Dr. Sonia Philipose (SIRO Clinpharm Pvt. Ltd.) provided writing assistance and Dr. Sangita Patil, CMPP (SIRO Clinpharm Pvt. Ltd.) provided additional editorial support for this manuscript.

Author contributions

All authors met ICMJE criteria and all those who fulfilled those criteria are listed as authors. All authors provided direction and comments on the summary, made the final decision about where to publish the summary, and approved submission to the journal.

References


Pancreatic Exocrine Insufficiency in Type 1 and 2 Diabetes: Therapeutic Implications

Rupjyoti Talukdar¹, D Nageshwar Reddy²

Abstract
The objective of the present review is to focus on pancreatic exocrine insufficiency that is associated with Type 1 and 2 diabetes, its clinical and therapeutic implications, including the utility and efficacy of pancreatin supplementation. A literature search was conducted on Pubmed / Medline to identify relevant articles using terms pancreatic exocrine insufficiency in diabetes mellitus patients, pathophysiology, prevalence, treatment and management published between 2006-2016 in English language. Meta-analysis has revealed the prevalence of PEI in patients with type-1 and type-2 diabetes mellitus to be 37.7% (CI 27.2-49.5) and 26.2% (CI 19.4-34.3) respectively. Very scanty data are available that evaluates the efficacy of pancreatin in patients with diabetes. In the available studies, pancreatin was found to reduce hypoglycemia in insulin treated patients. Pancreatic exocrine insufficiency in type 1 and 2 diabetes mellitus is not uncommon and correct use of pancreatin may have a positive effect on the glycemic status of the diabetic patients.

Introduction
The pancreas is a major organ that regulates nutrient digestion and absorption in conjunction with other organs. Digestion is mediated largely by the major pancreatic enzymes lipase, amylase and proteases.¹ Reduced secretion of these enzymes from the pancreas, rapid destruction or inadequate contact between food and pancreatic enzymes within the intestine results in nutrient maldigestion. This condition is defined as pancreatic exocrine insufficiency (PEI).² The main clinical consequence of PEI is fat maldigestion and malabsorption, resulting in steatorrhea which is characterized by frothy, foul-smelling and buoyant stools, due to their high fat content. Other non-specific symptoms may include abdominal pain, flatulence, loose bowel movements and weight loss in adults, or lack of weight gain in children.³,⁴ PEI results from several diseases such as chronic pancreatitis, pancreatic cancer, acute pancreatitis with substantial areas of parenchymal necrosis, diabetes, cystic fibrosis, Zollinger-Ellison syndrome, to name a few (Table 1).⁵-⁹

In this review, we focus on PEI that result from Type 1 and 2 diabetes, its clinical and therapeutic implications, including the utility and efficacy of pancreatin supplementation. PEI not only affects patients with type 1 diabetes mellitus (T1DM), but is also observed in patients with type 2 diabetes mellitus (T2DM). The reported prevalence of PEI varies widely from 5% to 57% ascertained by fecal elastase-1 excretion in patients with DM.¹⁰ From a recently published meta-analysis, it emerged that one in three patients with DM presented with impaired exocrine function when explored by fecal elastase-1 testing. The weighted prevalence rate of PEI was marginally higher in patients with T1DM (37.7%, CI 27.2-49.5) when compared with that registered in patients with T2DM (26.2%, CI 19.4-34.3).¹⁰ These values are in keeping with the 30-50% prevalence figures in T1DM and the 15-35% values in T2DM reported in studies using direct tests for exocrine function evaluation.¹¹ In a cross sectional study from India that included 89 T1DM and 95 T2DM patients, the prevalence of PEI was observed to be 31.4% in T1DM and 29.4% in T2DM.¹²

Table 1: Etiology of PEI⁵-⁹

<table>
<thead>
<tr>
<th>Pancreatic causes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic pancreatitis</td>
</tr>
<tr>
<td>Acute pancreatitis</td>
</tr>
<tr>
<td>Pancreatic cancer</td>
</tr>
<tr>
<td>Cystic fibrosis</td>
</tr>
<tr>
<td>Obstructions of the pancreatic duct</td>
</tr>
<tr>
<td>Diabetes mellitus type 1 and 2</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Non-pancreatic causes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Celiac disease</td>
</tr>
<tr>
<td>Crohn disease</td>
</tr>
<tr>
<td>Autoimmune pancreatitis</td>
</tr>
<tr>
<td>Zollinger-Ellison syndrome</td>
</tr>
<tr>
<td>GI and pancreatic surgical procedures</td>
</tr>
</tbody>
</table>

¹Clinical Pancreatologist (Fellowship, Mayo Clinic, USA) and Clinician Scientist (Wellcome DBT Fellow), Head Pancreas Research Group, Asian Institute of Gastroenterology/Asian Healthcare Foundation, Hyderabad, Telangana; ²DM Gastroenterology, Asian Institute of Gastroenterology, Hyderabad, Telangana

Received: 03.08.2017; Accepted: 04.08.2017
**Methods**

A literature search was performed using electronic databases such as Pubmed / Medline to identify relevant articles using relevant search terms. Criteria of the search includes – publications on pancreatic exocrine insufficiency (PEI) in diabetes mellitus patients, pathophysiology of PEI, prevalence of PEI in diabetes mellitus patients, treatment and management of PEI in diabetes mellitus patients, published between 2006-2016 in English language. Type of studies included were observational studies, randomized controlled trials, review articles, systematic reviews, meta-analyses and reports limited to human clinical data. Case reports and case series were excluded.

**Pathophysiology and Risk Factors of PEI in Diabetes Mellitus**

Pathophysiological mechanisms pertaining to PEI in diabetes mellitus are not fully elucidated. However; a number of mechanisms have been proposed by which exocrine dysfunction may occur. Figure 1 describes effect of diabetes on PEI.

Insulin stimulates pancreatic acinar cell growth via the insulin-like growth factor 1 receptor i.e. exerting trophic effects on the exocrine pancreas. These trophic and stimulatory insulin effects are lost in diabetes mellitus. In addition to this, morphological distribution of islets throughout the exocrine tissue and the specific blood flow pattern of the insulo-acinar portal system suggest functional interactions between the endocrine and exocrine tissue, i.e. regulation of pancreatic exocrine secretion by stimulatory and inhibitory islet hormones. Furthermore, evidence suggests that increased levels of inhibitory islet hormones such as glucagon and somatostatin further contribute to PEI in DM. Further, PEI may potentially be responsible for variable glycemic control in patients with diabetes. According to a study in T1DM and T2DM patients; the observed decrease in fecal elastase 1 concentrations (FEC) in diabetics was associated with poor glycemic control.

Autoimmune neuropathy is a frequent complication of long-standing diabetes and pancreatic polypeptide (PP) release has been shown to be a sensitive marker of autonomic neuropathy. Impairment of PP response to a test meal appears to be correlated to the degree of autonomic neuropathy. In a study among T1DM patients, PP plasma levels of basal, cephalic phase and gastric phase, were significantly reduced compared with healthy controls despite the fact that only a minority of patients showed clinical evidence of neuropathy. This may suggest that sub-clinical autonomic neuropathy may impair pancreatic exocrine function in diabetes patients. Apart from this, disturbances of gut hormone release which includes increased basal and post-prandial plasma motilin concentrations and increased post-prandial cholecystokinin (CCK) release marks a potential influence on pancreatic exocrine function in diabetes mellitus.

Auto antibodies originating either from lysis of acinar cells or high circulating glucose concentration are also observed in diabetic patients which might affect acinar cells leading to pancreatic insufficiency. Circulating autoantibodies against pancreatic lipase have been identified in about 75% in T1DM patients and 17% in T2DM patients. Furthermore, gene dysregulation has also been observed as one of the factors leading to PEI in DM patients. In addition, a recent study by Mohapatra S et al observed pancreatic histopathological changes that was marked by mild-to-marked interacinar fibrosis with scant inflammatory infiltrate but hyalinization of arteries and without pancreatic ductal changes, in patients with DM indicating moderate-to-severe subclinical pancreatic fibrosis.

Furthermore, T1DM which is linked to primary autoimmune process and characterized by early occurrence, severe insulin deficiency and long standing disease is more frequently associated with PEI. A large study investigating risk factors for PEI in 195 T1DM patients, demonstrated strong association of PEI and disease duration. Furthermore, in adult T1DM patients, the prevalence of severe (10-30%) and moderate (22-56%) PEI was observed to be higher than in children, possibly suggesting decrease in exocrine pancreatic function with the duration of disease and increase in insulin requirement. Early onset of T2DM,
Table 2: Diagnostic tests for PEI31,36

<table>
<thead>
<tr>
<th>Tests</th>
<th>Advantage</th>
<th>Disadvantage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Direct function tests</td>
<td></td>
<td></td>
</tr>
<tr>
<td>72 hrs fecal fat estimation/</td>
<td>Gold standard</td>
<td>72 hr stool collection, 100 g standard fat diet, no</td>
</tr>
<tr>
<td>Coefficient of fecal absorption</td>
<td></td>
<td>simultaneous PERT, not pancreatic specific</td>
</tr>
<tr>
<td>Cholecystokinin/secretin stimulation</td>
<td>Gold standard for scientific evaluation of</td>
<td>Invasive and complicated</td>
</tr>
<tr>
<td>Endoscopic pancreatic function test</td>
<td>Useful in diagnosing early CP patients, useful in</td>
<td>Time consuming (30-45 minutes of prolonged</td>
</tr>
<tr>
<td>Secretin MRCP test</td>
<td>investigation the cause of malabsorptive diarrhea,</td>
<td>endoscopy), unable to quantify fluid volume</td>
</tr>
<tr>
<td></td>
<td>requires further validation</td>
<td>preventing calculation of enzyme output,</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Indirect Function Tests</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fecal chymotrypsin activity</td>
<td>Good for compliance control, single stool sample</td>
<td>Low sensitivity, not for mild PEI, watery stools</td>
</tr>
<tr>
<td>Fecal elastase-1 concentration</td>
<td>Single stool sample, PERT can be continued</td>
<td>decrease enzyme activity, PERT must be discontinued</td>
</tr>
<tr>
<td>13C-mixed triglyceride breath test</td>
<td>Acts for mild form of PEI, detects fat maldigestion</td>
<td>Poor sensitivity in mild PEI, watery stools and</td>
</tr>
<tr>
<td></td>
<td>with a sensitivity of &gt;90%</td>
<td>small bowel disease</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Requires further validation</td>
</tr>
</tbody>
</table>

It is often difficult to detect PEI in patients with DM in routine clinical practice. Majority of these patients are usually asymptomatic in the early stage of PEI.27 The classical symptoms of steatorrhoea and weight loss only tend to occur in patients with very severe PEI.28 Therefore, there should be a high index of suspicion for PEI in diabetics. More commonly, patients present with loose bowel movements, abdominal discomfort and flatulence.71 Patients with diabetes often describe symptoms of fatigue and difficulty controlling blood glucose levels.29 Although there are many causes of diarrhea in diabetic patients, such as small bowel bacterial overgrowth and diabetic dysautonomia, PEI should be suspected in patients with long standing type 1 and type 2 DM.30 Other factors that have also been shown to increase the incidence of PEI in diabetic patients include poor glycemic control, insulin dependence, elderly age, presence of microangiopathy and autonomic neuropathy.29 However, a number of other causes such as gastroparesis, celiac disease, and side effects of blood glucose lowering medications should be excluded before considering PEI.29

There are several tests for diagnosing PEI as listed in Table 2.31-36 Unfortunately, most of these tests are not performed routinely. The 72 hrs fecal fat estimation test, which is considered the gold standard to detect steatorrhoea is seldom performed routinely in laboratories due to the unpleasant nature, and is current restricted only under research setting. The direct tests such as the CCK and secretin stimulation tests, which are highly sensitive, are complicated and require expertise. These tests are also performed under research setting.

Currently the most commonly used test for detecting PEI is the fecal elastase 1 assay. Several studies reported that the prevalence of PEI in DM varied widely from 5% to 57%.10 One in three patients with DM presented with impaired exocrine function when explored by fecal elastase-1 testing. Of all patients with DM and PEI, half had severe PEI, as identified by FEC <100 µg/g stool.10 Fecal elastase 1 testing is conducted in a few laboratories across India. The advantage of this test is that a patient need not stop taking pancreatic enzymes before conducting the test. However, one needs to be careful in interpreting the results of Fecal elastase 1 estimation in the presence of diarrheal disease as it might be falsely low.27 Moreover, sensitivity of fecal elastase has been reported to be lower in diabetes.37 The 13C-mixed triglyceride breath test is the most recent test for PEI and is a fairly accurate method to evaluate exocrine insufficiency. The additional advantage of this test is that it could also be used to monitor the effect of pancreatic enzyme therapy on fat digestion.36 This method is simpler than the standard fecal fat test to assess therapy in patients with PEI.36 Unfortunately, this test is not widely available and is restricted to a few centers in Europe and USA.38

Management of PEI in Diabetes Mellitus

The mainstay of treatment of PEI in diabetes is pancreatic enzyme replacement therapy (PERT). Since there are scant data or guidelines on PERT specifically in patients with diabetes, treatment should be based on literature pertaining to treatment of PERT in chronic pancreatitis. Several pancreatic enzyme preparations have been tested and used extensively for treating PEI associated with pancreatic diseases. Recent recommendations support the use of PERT in patients with diabetes and PEI.39 Table 3 shows various pancreatic enzyme preparations that have been approved by the US FDA.40-46
Characteristics of an Ideal Pancreatic Enzyme Preparation

For optimal digestive action, a pancreatic enzyme preparation should survive the gastric acidic milieu, get released into the duodenum along with chyme, and contain the correct dose of lipase, which is the most crucial component of the preparation. Use of enteric-coated technology to coat the enzyme preparation protects them for gastric acid mediated degradation. The HP55 coating dissolves at a pH >5.5 to release the lipase, amylase and protease in the duodenum. Use of enzymes in the minimicrowave formulation enables entry of the enzyme spheres into the duodenum along with the solid food chyme. In the stomach, solid food usually gets broken down into sizes of 2mm or less by the antral contractions before moving through the pyloric channel into the first part of the duodenum. Studies have demonstrated that the size of the particles affect the synchronous delivery of enzymes with chyme to the duodenum, with particles of size 1.0-1.2mm being associated with 25% higher efficacy. In theory, along with delivering adequate amounts of lipase to the duodenum at the same time as the ingested food, the minimicrowave technology allows more adequate mixture of enzyme with the postprandial chyme. The third crucial component of pancreatic enzyme preparation is the dose of lipase. The intestine has brush border aminopeptidases and carboxypeptidases that could aid in protein digestion, along with pancreatic enzymes. Furthermore, gastric acid itself initiates protein digestion in the stomach. Furthermore, the gastrointestinal (GI) tract contains more of salivary amylase than pancreatic amylase; and in the event of PEI the concentration of salivary amylase has been shown to increase. Therefore, strict dosage criterion may not be mandatory for amylase and protease concentrations in pancreatic enzyme preparations. On the other hand, lipase is the most vulnerable among the supplemented pancreatic enzyme, with survival of as low as 1% of the enzyme during intestinal transit in the absence of substrate, i.e. fat in the diet. Therefore, a high concentration of lipase in the pancreatic enzyme supplement is mandatory to achieve the optimal dose. The pancreas has a huge reserve of enzymes, and it has been shown that only 10% of the total daily lipase output (which is 6,00,000U) is required for fat digestion. Therefore, the daily dose of at least 20,000U per meal of lipase is mandatory for fat digestion. Thus, an ideal pancreatic enzyme supplement preparation should be an enteric-coated minimicrowave with at least 20,000U of lipase; and optimal action could be achieved by taking the preparation along with or immediately after food intake. In our experience, for Indian patient’s intake along with food provides the best compliance. Since the initial response of PEI to PERT could be erratic, supplementation should usually be started with a higher dose of 25000 to 40000U of lipase. The third crucial component of pancreatic enzyme preparation is the dose of lipase. The intestine has brush border aminopeptidases and carboxypeptidases that could aid in protein digestion, along with pancreatic enzymes. Furthermore, gastric acid itself initiates protein digestion in the stomach. Furthermore, the gastrointestinal (GI) tract contains more of salivary amylase than pancreatic amylase; and in the event of PEI the concentration of salivary amylase has been shown to increase. Therefore, strict dosage criterion may not be mandatory for amylase and protease concentrations in pancreatic enzyme preparations. On the other hand, lipase is the most vulnerable among the supplemented pancreatic enzyme, with survival of as low as 1% of the enzyme during intestinal transit in the absence of substrate, i.e. fat in the diet. Therefore, a high concentration of lipase in the pancreatic enzyme supplement is mandatory to achieve the optimal dose. The pancreas has a huge reserve of enzymes, and it has been shown that only 10% of the total daily lipase output (which is 6,00,000U) is required for fat digestion. Therefore, the daily dose of at least 20,000U per meal of lipase is mandatory for fat digestion. Thus, an ideal pancreatic enzyme supplement preparation should be an enteric-coated minimicrowave with at least 20,000U of lipase; and optimal action could be achieved by taking the preparation along with or immediately after food intake. In our experience, for Indian patient’s intake along with food provides the best compliance. Since the initial response of PEI to PERT could be erratic, supplementation should usually be started with a higher dose of 25000 to 40000U of lipase with each major meal, which could then be titrated up or down based on patient’s response. Factors such as the size of the patient, size of the meals and nutrition status could also aid in determining the starting and maintenance doses of PERT. Another important aspect in achieving the best possible response to PERT is provision of adequate nutrition. Enzymes require substrate to work. Therefore, depletion of the diet with nutrients, especially fat, will render the enzyme, especially lipase, ineffective. Furthermore, even though it is generally believed that PERT aids in micronutrient digestion, there are several micronutrients, for e.g. vitamins B1-B5, vitamin C, zinc, copper, iodine, biotin and to a certain extent folic acid, which do not require pancreatic enzymes for digestion, and therefore should be supplemented especially in the presence of features of malnutrition.

Efficacy Studies Pertaining to Pancreatin

Efficacy of PERT may be influenced by denaturation of lipase by gastric acid, improper timing of enzymes in duodenum, coexisting small-intestinal mucosal disease, rapid intestinal transit and effects of diabetes. Even though data on efficacy of pancreatic supplementation in PEI associated with CP and cystic fibrosis abound in the literature, there are very limited studies on diabetes. Table 4 shows the studies that had evaluated the
evidence of pancreatin in patients with diabetes.56-58

A double-blind, randomized placebo-controlled trial among insulin treated patients receiving either Creon or placebo observed reduction in mild to moderate hypoglycemia in Creon group.56 Furthermore, a study conducted to evaluate the effect of Creon on insulin secretion in CP with secondary DM and PEI patients observed an increase in total plasma insulin and total insulin secretion after Creon administration along with an increase in the total glucagon-like peptide-1 (GLP-1) and glucose-dependent insulino tropic polypeptide (GIP) response. These findings suggest that the secretion of GLP-1 and GIP is under influence of the digestion and absorption of nutrients in the small intestine. These incretin hormones are responsible for 70% of insulin secretion following oral ingestion of glucose. Thus, pancreatic enzyme supplementation may be associated with rise in insulin levels through increase in incretin hormone response by improving digestion of nutrients.57

A recent double-blind, randomized placebo-controlled trial of Creon in patients having PEI with or without diabetes mellitus reported Creon to improve fat and protein absorption in both the groups as compared to placebo. The mean change from baseline in coefficient of fat absorption (CFA) (36% vs. 7.5%, p<0.0001) and coefficient of nitrogen absorption (CNA) (33.4% vs. 3.7%, p=0.0002) in the DM group was significantly greater with pancrelipase than with placebo (p<0.0001).

**Safety Profile of Pancreatin Enzyme Preparation**

In general, PERT is regarded as well-tolerated with few side effects, and some adverse events are comparable to those with placebo. Supplemental enzymes act within the lumen of the intestine, and this is considered an intraluminal and not a systemic therapy. Most common side effects of pancreatic enzyme preparations are, abdominal pain, nausea, vomiting, constipation, and diarrhea.59 Table 4 depicts studies that evaluated the safety of pancreatin in patients with diabetes.

**Summary**

In this manuscript we have addressed the issue of PEI in patients with type 1 and 2 diabetes. Even though not often considered in assessment of diabetes in routine clinical practice, PEI in DM is not uncommon as evidence data from India and the west suggests. Several tests to detect PEI have been developed, of which the fecal elastase and 13C-mixed triglyceride breath tests are used in clinical practice. In India, only fecal elastase test is available in very
few select centers, while the breath test is not available. Therefore, a high index of clinical suspicion is prudent to identify diabetic patients with PEI. This is important because PEI could be managed adequately with the correct use of pancreatin and studies have shown that pancreatin supplementation could also have a positive effect on the glycemic status of the diabetic patients. Even though there are no specific guidelines for management of PEI in diabetes, the principles of treatment are the same; and guidelines meant for management of PEI in chronic pancreatitis should hold good for diabetic patients also. Table 5 presents salient points on the management of PEI, that has been taken from the Romanian, Australasian, and Spanish guidelines.49,55,60

Acknowledgement

Writing support was provided by pharmEDGE through academic research funding from Abbott India Limited.

Conflict of Interest

Rupjyoti Talukdar and D. Nageshwar Reddy declare that they have no conflict of interest.

References

32. Stevens T, Parsi MA. Update on endoscopic pancreatic function testing. World J Gastroenterol 2011; 17:3957-3961.
Clinical Gastroenterology and Hepatology 2007;5:484-488.


Presenting Research Paper: Learning the steps

Sandeep B Bavdekar¹, Varun Anand², Shruti Vyas³

Abstract
For a beginner, presenting a research paper at a conference as a podium presentation can be a daunting task. She is required to choose an appropriate conference for presentation, prepare an abstract, prepare slides and the speech that goes parallel with the slides and train oneself to answer questions posed by the audience. She has also got to overcome the fear of speaking in public and conquer the phobia of encountering a hostile audience ready to shred her paper to pieces. This communication intends to provide useful tips on how to go about preparing and presenting a research paper.

Almost every conference has at least one slot reserved for oral or podium presentation of research papers. These podium presentation sessions are important for the presenters, organizers as well as for the attending delegates (Table 1). For the beginners and the recently-initiated, the challenge of organizing all the data and ideas for presentation in less than 10 minutes, might seem overwhelming. Added to that would be the anxiety of speaking in front of a crowd consisting of experts and above all, to be prepared to answer searching questions posed by the delegates. Through this communication, we intend to provide a supporting framework for the beginners about how to go about such scientific presentations, which are so vital for one’s career and above all, for advancement of science.

Once your research project is over, findings analyzed and report written; you should be on the lookout for conferences where presenting your research would be of relevance and interest to the delegates. But even before the conference is chosen, you could start thinking about the process of presentation.

Step 1: Identify the Core Message and Decide if Podium Presentation is the Appropriate Format
The first step is to identify the core message which can be stated in one or two sentences. Then consider if the research paper’s data and analysis is too vast and complex to be presented in 8-10 minutes. If you think it is, one option is to present it as a poster. The other option is to present only a part of the data as a podium presentation.

Step 2: Choose the Most Appropriate Conference and get all the Information you need about the Conference
While choosing the conference, you should give maximum importance to relevance. The question that you should ask yourself is: Will the delegates attending this conference be interested in my research paper and its findings? Would that be relevant to their needs? Of course, your other commitments, cost of registration, expenses involved, traveling time, etc. would also influence your decision. Once selected, you would want to know greater details about the conference and the oral presentation session. To get these details, visit the conference website and read its brochure. You may even contact the organizers to get all the finer points you need to know: details about the abstract (timelines, type, word count restrictions, whether figures and graphs can be incorporated, etc.), the prospective delegates (experts, beginners, super-specialists, specialists or generalists), presentation (time allotted, technical details such as software permitted) and venue (seating capacity, whether there would be concurrent sessions, kind of audio-visual aids that would be available, type of stage and seating arrangement, etc.). This information is vital for you to plan your presentation. Many conferences provide explicit instructions or guidelines and even templates for presentation.

Step 3: Make a Plan and Stick to it
Proper planning is essential for making a successful presentation. Great thought should go into making important decisions about the presentation: What is the core
message and how to elaborate on it (content), who should present the paper (presenter) and what work should other team members carry out (support), should we stick to the conventional format or innovate a bit (style) and what precautions should I take to ensure that the last-minute glitches do not spoil the effort.

Many scientists work on a research project, but only one can present it at the conference. It is best to assign the job of presentation to the one who has led the study, participated in the study and carried out the analysis. In short, the one who is well-versed with the intricate details of the study and knows the subject inside out should be the one chosen to present the study. Decide the role everyone in the research team will play. Although the presenter will have the overall responsibility, she can be helped by others in the team. For example, one member can perform a thorough literature search looking for recently-published relevant papers, another can help her prepare presentation content and slide design and all can contribute in helping her prepare for questions that might be asked. Other team members can plan how to do this in a time-bound manner and efficiently. You need to reserve enough time for discussions with team members in deciding the key message and how to elaborate on it, for practicing the speech and handling the question-answer (Q-A) session. As several activities are undertaken concurrently and as multiple milestones need to be reached in a timely and orderly fashion, it is always better to have a workable “time table”.

**Step 4: Prepare the Abstract and Submit it**

The abstract should be prepared as per the requirements specified by the conference organizers. It is always a good idea to prepare a structured abstract consisting of introduction, objectives, methodology, results and discussion as the sub-headings. When relevant and permitted by the conference, do include graphs to explain intricate results. The abstract should convey the core message. The importance of the abstract cannot be over-emphasized. It is generally published in an abstract book and/or uploaded at the conference website and it serves as a reference material for posterity. In addition, many delegates scan through the abstract book to choose which presentations to attend and which ones to skip. Ensure that all the co-authors agree with the contents of the Abstract. Write a covering letter for the abstract emphasizing the importance of your study. If time permits, one can even think of preparing the full manuscript even before the presentation. It makes the presenter’s job simpler. She has to just select the appropriate sentences, tables and graphs from the manuscript and put them on the slides. If the paper has already been presented at another conference previously or if the study results have already been published in a journal, make sure that you explicitly declare this in the covering letter. Honesty and transparency are the best practices in the scientific field. Most organizers will allow you to present the work even if it has been presented at another conference, as the type of audience and location of the conference could be different.

**Step 5: Draft the Content for Slides and Speech**

The content of slides and speech need to match and synchronized during presentation. The number of slides that you can include will depend on time available, intricacy of data and ideas to be conveyed, the number of slides with figures and graphs and the speed of the presenter’s speech. However, the general rule is to have 1 slide per minute of presentation (may be excluding the title, competing interests and acknowledgment slides). Most conferences allow the speaker to present paper in 8 minutes and expect that about two minutes will be spent on responding to questions and comments.

Logically, the slide sequence will follow the IMRaD format (Introduction, Methods, Result and Discussion) with emphasis on providing precise objectives,
Table 2: Suggested sequence of slides for research paper presentation

<table>
<thead>
<tr>
<th>Slide title</th>
<th>No. of slides</th>
<th>Content of Slides and corresponding speech</th>
</tr>
</thead>
<tbody>
<tr>
<td>Title Slide</td>
<td>1</td>
<td>List complete title of the study. Include names of all the authors (surname and initials) with institutional affiliations</td>
</tr>
<tr>
<td>Competing Interests</td>
<td>1</td>
<td>Some conferences expect the presenter to describe competing interests (financial and other). This allows the attendees to view the results in an appropriate context</td>
</tr>
<tr>
<td>Introduction</td>
<td>1</td>
<td>Use this slide to provide relevant background information in brief. It should allow the delegates to understand the need for conducting the study. State the research question.</td>
</tr>
<tr>
<td>Objectives</td>
<td>1</td>
<td>Clearly state the primary and important secondary objectives. Include only those objectives for which relevant results will be described in the presentation. Some prefer to skip this slide as they think it lengthens the talk. They incorporate objectives in the “introduction” slide.</td>
</tr>
<tr>
<td>Methods</td>
<td>1 or 2</td>
<td>Describe methodology describing important relevant information related to study design, population studied, study procedure, statistical plan and ethical aspects (IRB approval, participant consent and assent). Desist from providing unnecessary details. Complex methodology would entail using two slides.</td>
</tr>
<tr>
<td>Results</td>
<td>1 or 2</td>
<td>Provide numeric data. Use tables and graphs where relevant</td>
</tr>
<tr>
<td>Discussion/Conclusions</td>
<td>1 or 2</td>
<td>Describe what new evidence the study has provided. Describe limitations and strengths of the study. Describe how the results should be used given the overall evidence. Directions for future research. Give a take home message.</td>
</tr>
<tr>
<td>Acknowledgement</td>
<td>1</td>
<td>Acknowledge the help and assistance of funding agencies, and individuals who provided significant intellectual inputs and other support</td>
</tr>
</tbody>
</table>

IRB: Institutional Review Board

important details of methodology and results and relevant discussion on impact of the study (Table 2). However, many presenters find it convenient to work in reverse direction while preparing the slides. They prefer to write a couple of conclusions of the study and then work backwards to include relevant results and methods. It is said that this helps eliminate unnecessary information. One can incorporate a Table or a Figure to explain complex data. The Table should be complete but not too big. You can highlight the important numbers (bold-type, different color) that you would be pointing to and discussing. Complex patient flow can be depicted using a figure. Graphs constitute one of the best ways of displaying data.

You need to follow certain general rules while making slides (Table 3). The one major rule is to always adopt a ‘minimalistic’ approach: use minimum text, minimum lines, minimum images and minimum information to deliver your presentation. You should have only that much material on each slide and only those many slides that will help you deliver the core message during the allotted time. If you have too much material on the slides, you will have to rush through the written material. Your audience will not have enough time to read it and they will lose track. Skipping slides towards the end of the presentation for want of time conveys that some of your slides are unimportant. This is the surest way of making the audience disinterested in your presentation. Never write the whole messages or paragraphs on the slides. Avoid showing complex data. There is just not enough time to explain complex long tables. In such a situation, it is often advisable to summarize the data for easy understanding. When the data is too complex, some researchers prefer to print handouts about the study and make them available to the attending delegates in the presentation room. The material on the slides should be presented in the form of short phrases in bulleted format. These should be used as props or reminders for your speech.

Once the slide set has been finalized, keep a copy of the presentation on another pen-drive or hard disk. Ensure that the pen drive does not have any other important material. There have been occasions where the entire content on the pen drive has been wiped off after attaching it to the conference computer!!! Email the presentation to self or a friend. These additional copies come in handy if the computer hard disk or the pen drive gets corrupted. If you are planning to use your own laptop for the presentation, carry HDMI (High-Definition Multimedia Interface) to USB cable convertor, as some computers have HDMI cable while the others have VGA cable (Video Graphic Array) to attach to the LCD (liquid crystal display) projector.

Write down the speech in plain simple language. Do not use jargon. It impresses no one. Use short sentences and active voice. Choose your language carefully. Use words such as “significant”, “always”, “never”, “best” or “optimal’ only if they are supported by the data. Write down your speech slide-wise. This will help you write appropriate clues on the slide. You can use the ‘notes’ window in the Microsoft PowerPoint to enter your speech. This will help you when you are rehearsing your speech. You must remember that, given the constraint of time, you will not be able to go into details. You will be able to cover only the salient essential issues. For example, it is important to inform the characteristics of the participants studied (eligibility criteria). However, you cannot afford to read out all the inclusion and exclusion criteria, but will have to mention only those that will give the audience clear idea about who the study is about. It is essential to keep this balance between sufficient disclosure and the time required for delivering the methodology.
Before discussing conclusions, explain every detail. Just talk about them. However, you do not have to spend some time explaining Figure or a Graph, you will have data. If you have included a Table, provide raw numbers and simple descriptive statistics first. Always, ensure that similar graphs have similar scales.

**Table 3: Tips for the better slides for a podium research paper presentation**

<table>
<thead>
<tr>
<th>Slide formatting</th>
</tr>
</thead>
<tbody>
<tr>
<td>• The longest dimension should be the horizontal one. It is difficult to view and read vertically oriented material.</td>
</tr>
<tr>
<td>• Choose background color that provides high contrast with text color. Black or blue colored text on a white background is one option. It is less effective when color graphics such as clinical pictures are added. The other option is dark (black or blue) background. The text could be white, orange or yellow. Avoid red or green as they do not project well and readable by persons who are color-blind.</td>
</tr>
<tr>
<td>• Do not have too many words in a line. Not more than 6</td>
</tr>
<tr>
<td>• Do not have too many lines on a slide. Not more than 6</td>
</tr>
<tr>
<td>• Leave adequate margin of at least 1 cm between the lettering and outer margin of the slide</td>
</tr>
<tr>
<td>• Make duplicate slides, if you need to refer to a slide more than once. Do not go backward and forward during a presentation. It consumes time and looks shabby.</td>
</tr>
</tbody>
</table>

**Textual Matter**

• Keep text to minimum: If there are too much material to read, the audience stops listening to the presenter; as they cannot read and listen at the same time.
• Select a good easily readable sans serif font: Arial or Helvetica cause least confusion.
• For emphasis, increase letter size or use bold-type. Use italics sparingly. Avoid underlining text.
• Never use “ALL CAPS”. Difficult to read.
• Spacing: Space letters so that areas between letters are adequate making them easily legible. The lines should appear to be distributed evenly and uniformly.
• Check for spelling and grammatical errors.

**Figures and Graphs**

• Use visuals sparingly but effectively.
• Figures, drawings and graphs should be bold, simple and contain only essential details.
• No gridlines.
• Ensure that similar graphs have similar scales.

**Content**

• Use one slide to describe one unified concept or idea. This avoids confusion
• Avoid full sentences.
• Use multiple simple slides, rather than a single complicated slide, to explain a concept.

**Other**

• Standard templates are unoriginal, over-exposed and boring. Try your own design.
• Colors are nice. Play with them. Try multiple combinations to find what you like, but try to adhere to general rules.
• Overdoing colors distracts audience and is annoying too.
• Using animation and transitions, such as text or images sliding in and out or flying in and out distracts the audience. Sounds during animations are irritating.
• Avoid using flowers, sunsets, or your children’s photos to fill space.
• Avoid fancy clip arts.

section. While formulating slide/slides for the Results section, provide raw numbers and simple descriptive statistics first. Always, describe the characteristics of the study population or those of control and target groups. Provide data regarding the main research question, before moving on to other data. If you have included a Table, Figure or a Graph, you will have to spend some time explaining them. However, you do not have to explain every detail. Just talk about the salient observations or numbers. Before discussing conclusions, point out to the data from other studies, state the strengths and limitations of your study and then base your conclusions on the totality of evidence. Once you have finished writing the speech, edit it thoroughly. Review it yourself and check that the included material is good, essential and worthy of inclusion. Also check for continuity and logical flow of thoughts. Show the text of your speech and slides to your co-authors. Incorporate their useful suggestions.

**Step 6: Practice and Time your Speech. Seek Feedback and use it Gainfully**

Practicing and timing your speech are of great importance for the beginners. Invite family members, friends, co-authors and colleagues to view the presentation and give suggestions. While family members and friends will give you suggestions regarding the readability and attractiveness of slides and style of delivering speech; peers and colleagues provide technical inputs, as well. Many practice sessions will be done in solitude, in front of a laptop screen. A few practice sessions will be conducted in front of a small audience. Hence, you may feel nervous, when you have to present it to a large audience at a conference. If you have practiced well, the nervousness soon abates as you start speaking. Practicing and rehearsing will help you not only fine tune your speech; but it will allow you remember it verbatim. This will allow you to continue with your talk even if the slides do not get projected for some time due to technical fault during the presentation.

One cannot predict what questions will be asked. Hence, you cannot prepare enough for the Q-A session. However, you can still practice for it. Request your peers and colleagues to prepare questions and practice answering them. They will tell you if you become combative, submissive or excessively defensive; or whether your mannerisms change for the worse, while answering the tough ones.

**Step 7: Familiarize with the Hall and the Audio-Visual System**

It is very essential for you to familiarize yourself with the hall, a day before or during an earlier
Table 4: Habits that may distract and annoy the audience

- Unnecessary walking the breadth of the whole platform
- Moving far away from the lectern, causing the objects like microphone to fall making noise
- Too much movement or rock back and forth
- Holding the microphone too close leading to disturbance
- Coming in the way of projection stream, causing a shadow on the slides
- Cracking a joke that reveals gender-bias or disrespect towards a community or a professional group. Using expletives
- Making long circular pointer motions around the whole text line or big areas of graphic illustrations
- Keeping the pointer on, with the spot being seen on the walls and slides; thereby causing distraction
- Habit of clicking pen-pointer repeatedly
- Flipping the slides back and forth to look for a ‘particular’ slide
- Saying “um”, “urr”, “ahem” repeatedly
- Using a particular filler repeatedly. The common fillers are “actual”, “basically” and “generally speaking”
- Drop in the voice towards the end of the sentence. This makes it difficult to listen to and the content is lost

session. You will then make mental calculations regarding where to stand, how to gaze over the whole audience, whether you can move a bit while presenting or should remain near the lectern. Try to visit the control room. Check for the compatibility and how your slides look on the computer monitor. Changes in programs could lead to differences in the way colors and symbols are seen or get projected. Check how to operate the computer, mouse and pointer. Learn and practice how to advance slides. These decrease the uncertainties in your mind and help reduce your anxiety. Drinking a glass of water or taking a few deep breaths before climbing on to the stage are other measures that some speakers employ to reduce nervousness.

Step 8: Delivering the Presentation

The way you dress is also important. Adhere to the dress code, if one is prescribed. Nick Morgan suggests that the speaker should dress well and a little better than the audience. Tight clothes hinder the speaker’s movements, while overly loose clothing or accessories can get caught in odd places, like a lectern or a flip chart stand. You should be dressed comfortably avoiding bright colors or distracting prints. The clothing should also preferably allow the speaker to carry wireless microphone with ease.

As a presenter, you are a part of the visual experience of a presentation. You should stand in place that does not hinder the attendees’ view of the projected slides. Remove objects like laptop flap, water bottle or flower vase that may be casting a shadow on the slides. Start by thanking the organizers and the moderators and greeting the audience, and state why you think the study is important. The title slide is generally flashed when you are being introduced. Hence, there is no need to read the title of the study again. Some speakers start by narrating a joke or an anecdote. There are two things to consider: do so, only if you are good at it. Secondly, remember, it cuts into the extremely limited time that you have been allotted. Move on to what you did and what you found and then discuss the importance, limitations and impact of your research. Synchronization between what you are saying and what is projected, is crucial. Avoid taking support material such as written speech or outline to the stage. During presentation, although you may look at the slides on the laptop or the screen momentarily, you should be primarily speaking to your audience. Indulging in eye contact with the audience helps them maintain their interest in the presentation and encourages them to continue reading slides. Smile a bit as you talk and move the head to involve all sections of the audience. Many conferences record all presentations and lectures for transmission to the delegates seating in another hall. Many a times, the recorded video is uploaded on the conference or society website. Do ensure that you look directly at the recording camera for some time during your presentation. Use pointer judiciously to target points on graphs, figures and charts or to direct the attention of the audience to particular numbers or text written on the slide. If you have a tremor, rest your arm on the lectern. Speak slowly and clearly. The pace of and tone of the speech should be conversational and comfortable. Most importantly, your enthusiasm and confidence should be visible throughout the presentation. Do not annoy the audience with distracting behavior (Table 4).

You should always abide by the time limit given by the moderator. Extending your time beyond the permitted limit is not only disrespectful for the speakers scheduled to speak later; but might also test the patience of the audience. In addition, the Q-A session may get cancelled and you may lose an opportunity to clarify certain concepts and doubts.

Answering questions is an art and requires concentration, discipline and tact. Usually, a moderator starts by asking a clarifying question. Presenters, who are good at predicting questions, come prepared for the session with a few slides to answer likely questions. This strategy can be used especially if you have not had the time to explain some intricate data or concept in your presentation and you are sure that delegates would need to know them. Do not make too many slides for this purpose, as then you will have to search for the relevant slide, wasting time and testing the audience’s patience. Listen to the whole question and respond appropriately and to the point, demonstrating your knowledge about the research and
the subject. Be calm and talk slowly while answering the question. Never belittle or embarrass anyone in front of the group. In fact, compliment the questioner for asking a pertinent query. If you do not understand a question, ask for clarification. If you do not know the answer of a question, say so. Consider directing the question to your co-authors who may be attending. If the questioning becomes nasty, try to begin with clarifications from the point of agreement and deftly turn the question around asking the questioner for his views on the issue.

Although some people have a natural talent for providing presentation, most scientists will have to work for delivering an effective presentation. For a successful presentation, speaker should have mastery over the subject. But the way slides are made, the way she carries herself during presentation and the way presentation is delivered also contribute to the success of the presentation. This is not the end of the story. Your journey as an effective presenter and communicator may have just begun. After the presentation, you should take note of the questions that went unanswered or were difficult to answer. You should request for the contact details of the delegates who sought more information or clarifications. You should also note down the feedback received after the session. Many researchers also request the organizers for the clip of their own presentation, so that they can view it at a later date. After returning from the conference, find answers to the questions that seemed tough to answer and contact delegates to provide the information they requested. This is the “sure-shot” way of establishing and enhancing your credibility as a sincere scientist. The suggestions received should be given due importance while preparing the research manuscript.

And view the presentation video-clip to check your own performance while presenting and answering questions. This way, every presentation will allow you to expand your network, create a better research manuscript and come up with an improved performance the next time around.

References

Principles of Interim Analysis

NJ Gogtay, UM Thatte

Introduction

A clinical trial is a prospectively conducted study that evaluates the effect of two or more interventions [drugs, devices, vaccines, diagnostic tests or even surgical procedures] in human participants under a set of pre-defined conditions. The Randomized Controlled Trials [RCTs] among all trials form the cornerstone for generating evidence and are considered the “gold standard”. The number of participants required for an RCT is calculated before beginning the study and the study continues until the estimated sample size is reached. There is only one final analysis that is planned and carried out when the requisite sample size is reached. Inferences are subsequently drawn.

There are several situations, however, where one may need to review and analyze the data before the study ends. In other words, one may need to perform an Interim Analysis, i.e., analysis of data while the study is ongoing. While these analyses can be performed for any kind of study, they are usually conducted when the condition under study is life threatening, has potentially serious outcomes or the duration of therapy is long. Interim analysis (or multiple “looks” at the data while the study is ongoing) is decided at the protocol planning stage itself. Let us understand the concept of interim analysis with two well-known examples from literature where pre-planned interim analyses led to study discontinuation, but for diverse, disparate reasons.

The AIDS Clinical Trials Group [ACTG]-076 trial was designed to evaluate the use of Zidovudine [AZT] relative to placebo for the prevention of mother to child transmission of HIV from infected women to their babies. The study was planned to be run over 5 years with a target sample size of n = 748 mothers and the outcome of interest was the number of infant infections in the two groups. The study had a total of three planned interim analyses and one final analysis. The first interim analysis was decided to be conducted at the point where a third of the projected infant infections were reached. The idea behind this was to stop the study in the event that AZT was shown to be effective. The study was indeed stopped by the Data Safety and Monitoring Committee [DSMC, see later] at the first interim analysis as AZT was clearly superior [A total of n = 477 women were enrolled at this point and neonatal infection rates were 8.3% with AZT and 25.5% with placebo at 18 months of follow up]. The DSMC also recommended that all mothers in the control group be given AZT so as to derive benefit.

The Cardiac Arrhythmia Suppression Trials [CAST I and II studies] tested the hypothesis as to whether suppressing ventricular arrhythmias in patients with a recent Myocardial Infarction [MI] reduced sudden death and mortality. The DSMC permitted the study to continue at the first interim analysis. However, it was seen in the second interim analysis that in patients treated with the anti-arrhythmic agents encainide and flecainide, there was a 3.6-fold excessive risk of death [relative to patients treated with placebo] and the studies were stopped for safety concerns.

Thus, interim analyses are an important component of clinical research in general and drug development in particular. This article discusses the historical evolution of interim analyses, the definition/s, approaches to one, available methodologies to conduct one [with their merits and demerits], the concept of the “alpha spending function”, pitfalls of doing an interim analysis and finally the role of Data Safety and Monitoring Committees [DSMC] in its conduct.

Interim Analysis – Historical Perspective and Definitions

History- As clinical trials slowly but surely became the benchmark for Evidence Based Medicine, the National Institutes of Health [NIH] in the 1960s, set up a committee chaired by Dr Bernard Greenberg, a statistician from the University of North Carolina to address the challenges associated with the design, conduct, monitoring and analysis of trials and in particular complex multi-institutional studies. The idea behind setting up the committee was three-fold: detect unexpected or unacceptable toxicity early, detect benefit early and understand the trade-offs between benefits and risks early.
so that research participants could be adequately protected. The committee released its report in 1967 and it came to be known as the Greenberg report, which laid the foundations of interim analysis. It also put forth the fundamental principle that clinical trials should not be continued for longer than necessary and should definitely not cause harm to participants. It also advocated the setting up of independent committees to monitor data as they accrue [the Data Safety and Monitoring Committees or DSMCs- see later]

Definitions - In its simplest of definitions, an interim analysis constitutes analysis of data while the study is still in progress. It can also be defined as one or more planned analyses of data before the final planned analysis that permits investigators and/or funders of the study to evaluate the probability of the study’s success [or failure] while controlling for statistical errors [see below for statistical errors].

Why an Interim Analysis is Needed and Questions that it Attempts to Answer

There are three broad reasons for doing an interim analysis

Ethics

It is an ethical imperative to stop a study for two reasons – 1) when there is adequate evidence to show that one intervention is clearly superior to the other [benefit] and 2) when there is adequate evidence to stop a study for safety [or lack thereof] and prevent further participants from being exposed to undue risk. We have already seen one example of each – the AZT versus placebo study that was stopped for benefit and the CAST studies that were stopped for safety concerns. Let us now see two more examples.

Study stopped for benefit

The Anglo-Scandinavian Cardiac Outcomes Trial- Blood Pressure Lowering Arm [ASCOT-BPLA] is an example of a study stopped for benefit. It was designed to evaluate if amlodipine – based antihypertensive regimens were superior to atenolol-based anti-hypertensive regimes. The end points of interest were non-fatal myocardial infarction [primary end point] and fatal coronary heart disease. A total of 19,257 patients were followed up for a median of 5.5 years and the trial was stopped as stroke [327 vs. 422, p = 0.0003], cardiovascular death [263 vs. 342, p = 0.001] and all cause death [738 vs. 820, p = 0.02] were all significantly lower in the amlodipine group. The trial was stopped for benefit.

Study stopped for safety concerns

The Blood Conservation Using Antifibrinolytics [BART study] was a blinded RCT that compared aprotinin, tranexamic acid, and aminocaproic acid in patients undergoing high-risk cardiac surgery. The outcomes of interest were massive postoperative bleeding and 30-day mortality. A significantly higher 30-day mortality was seen with aprotinin relative to the other two drugs [relative risk 1.53, 95% CI 1.06-2.22] leading to the study’s early termination for safety concerns.

Lack of difference

The second reason why an interim analysis is needed is that during the course of the study, the data may point to the fact that the two treatments do not differ significantly. In such a situation, it would be desirable, for reasons of both cost and ethics to discontinue the study as it would be futile to continue. The PRESENT study [trial number [NCT01479244] is one such example. This study was a multicentre randomized, double-blind controlled study that evaluated n=758 women with early-stage node positive breast cancer, who had low to intermediate HER-2 neu expression. The women were randomized either to receive a novel vaccine called Nelipepimut [the vaccine would stimulate cytotoxic T lymphocytes to destroy HER-2 neu expressing cancer cells and thus produce its effect] along with standard of care or the vaccine adjuvant along with standard of care. The study was stopped by the DSMC for futility as it was felt that continuing the study further would not have a shown a difference between the two treatment arms.

Slow accrual

When there is very slow participant enrolment for any reason, a decision can be taken to either continue with the study if the research question is truly important or stop the study for futility.

How an Interim Analysis Helps

Interim analysis helps to reduce the ‘time to market’ for an intervention by permitting key decisions to be made earlier as data accrues. It broadly helps in two ways- a) Avoid drawing a wrong conclusion b) Avoid taking too long to draw the right conclusion. These analyses, however, need to be properly designed and appropriately executed, so that the integrity of data is maintained and decision-making does not compromise either the process of drug development or that of patient safety. This decision-making process is fairly complex and an interplay of several factors is involved.

The Concept of “Distributing the Alpha Across the Interim Analyses” and Understanding the Impact of the Statistical Errors on the Analysis

When we calculate the total number of patients for a study [the sample size], we use the following four elements- alpha error [usually set at 5% and corresponds to 95% Confidence Intervals], beta error
thereby risk a false positive error. For example, “5 looks” at the data would increase the alpha error to 15% and 10 looks to almost 20%.\textsuperscript{13}

2) While adjusting the alpha at every “look”, it is also important to remember that the sample size at each look is much smaller than the final sample size (The beta error of 10 or 20% is considered for this final sample size calculation). Thus, the power at each “look”, will be lower than that considered at the point of initial sample size calculation. In other words, both errors are impacted with every “look” at the data 3) There is no reason to believe that one error is worse than the other. Rather, the choice of the interim analysis strategy [see below] will affect each of these errors.

In interim analysis, however, there is considerable importance to given to the alpha error. This is likely to stem from the fact that a false positive finding will have more serious implications. Thus, most interim analysis strategies center around it [see below].

Using the Alpha Judiciously – the O’Brien-Fleming, Pocock, Haybittle-Peto Methods\textsuperscript{14,15}

There are several ways in which the alpha can be adjusted or used judiciously over the range of interim analyses planned. These are described below along with their merits and demerits and also given in Table 1.\textsuperscript{16}

O’ Brien and Fleming approach

This popular method uses a very small amount of the alpha in the initial stages and reserves a large part of the alpha for the final analyses. For example, when one interim and one final analysis are planned, 0.0054 of the alpha is expended first and 0.0492 reserved for the final analysis. This method ensures that it is difficult to reject the null hypothesis in the early stages of the study, but relatively easy later on.

Pocock approach

This method divides the alpha error equally amongst the total number of analyses planned. For example, if there is one interim and one final analysis, the p value expended at each analysis is the same- i.e., 0.029 [Table 1].

Haybittle Peto or Peto approach

This approach uses a miniscule amount of the alpha in the initial “looks” [much lower than the O’Brien and Fleming approach], but the final analysis is always performed using the entire 5% alpha. [Table 1] This method thus makes it very easy for investigators and readers to apply as 5% at the end of the study is what they are comfortable with. The criticism of this approach is that that the extremely low alpha values are going to make it almost impossible to stop the study at the early stages.

All three approaches are called Frequentist approaches [see later]. They are all inflexible in the way that the interim analysis is planned and executed. This led statisticians to devise yet another approach; one of the Alpha Spending Function.

Lan and de Mets- the alpha spending function

This is a very flexible procedure that can accommodate unequal timing, additional looks at data beyond what was originally

---

**Table 1: Comparison of the alpha values of three Frequentist approaches for interim analysis - O’Brien Fleming, Haybittle-Peto and Pocock approach**\textsuperscript{[16]}

<table>
<thead>
<tr>
<th>Number of analyses</th>
<th>Method of analysis</th>
<th>Alpha value of 5% distributed at each analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>O’Brien Fleming</td>
<td>0.0054 0.0492 - - -</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td>0.0006 0.0151 0.0471 - - -</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td>0.00005 0.0039 0.0184 0.0412 -</td>
</tr>
<tr>
<td>4</td>
<td></td>
<td>0.000005 0.0013 0.0085 0.0228 0.0417</td>
</tr>
<tr>
<td></td>
<td>Haybittle – Peto</td>
<td>0.01 0.05 - - -</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td>0.01 0.05 - - -</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td>0.01 0.01 0.05 - - -</td>
</tr>
<tr>
<td>4</td>
<td></td>
<td>0.001 0.001 0.001 0.005 -</td>
</tr>
<tr>
<td>5</td>
<td></td>
<td>0.001 0.001 0.001 0.001 0.005</td>
</tr>
<tr>
<td></td>
<td>Pocock</td>
<td>0.0294 0.0294 - - -</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td>0.0221 0.0221 0.0221 - - -</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td>0.0158 0.0158 - - -</td>
</tr>
<tr>
<td>4</td>
<td></td>
<td>0.0158 0.0158 0.0158 0.0158 -</td>
</tr>
<tr>
<td>5</td>
<td></td>
<td>0.0158 0.0158 0.0158 0.0158 0.0158</td>
</tr>
</tbody>
</table>

[Adapted from Piantadosi S, 1997]
planned including even extending the trial. Researchers can choose to “spend” their alpha (i.e., conduct interim analyses) any way they want and the method still ensures that the total alpha “spent” is no more than 0.05 (or whatever was specified at the beginning of the study).17

**Approaches to Interim Analysis – the Frequentist, Bayesian and Mixed [Bayesian – Frequentist approach]**

The approaches to an interim analysis can be broadly divided into two – Frequentist and Bayesian. Let us first understand the philosophy behind the two approaches with an example from day to day life which will serve as a metaphor for understanding these approaches in clinical research and drug development.

All of us use cell phones and are prone to misplacing them. Let us say that Mr. X generally misplaces his phone and more so at home. There are the usual three places at home that he is likely to have left the phone – the bedroom, the television room, and the dining area. Thus, when he realizes that his cell phone is “missing”, he is likely to have left the phone – the bedroom, the television room, and the dining area. Despite finding it in the dining area on three days in succession, his initial “model” that was developed based on prior information [which stated the probability of finding it in the three places would be equal], does not change. This is the “Frequentist” approach.

On the other hand, when the cell phone is found in the dining area on three consecutive days, the Bayesian approach would “change the model” to now state that the probability of finding the phone in the dining room is higher than the other two places. In other words, the results have changed the model [Bayesian thinking].

The Frequentist and Bayesian approaches thus represent two philosophies about quantifying this uncertainty that exists in the clinical research and drug development process. Let us now understand that actual processes followed in the two approaches.

**Frequentist approach**- Here, information from existing/available data also called prior information [previous studies, literature] is used at the protocol development stage. At the point of data analysis, prior information is considered as a complement to, but not part of, the formal analysis19 and the initial model remains unchanged. This approach presents results using p values, standard error of mean and the 95% confidence intervals and is also called the “traditional” or “classical” approach. Interim analyses in literature have been largely dominated by the Frequentist approach. An example of the use of the Frequentist philosophy can be found in the study by Schwartz [2001]19 who evaluated the effect of atorvastatin vs placebo on early recurrent ischemic events in acute coronary syndromes. The study protocol pre-specified 3 interim analyses that would each use an alpha value of 0.001 and the final analysis had an alpha value of 0.049 allocated to it.

[O’Brien Fleming approach]. The study showed the utility of 80mg/d of atorvastatin in reducing ischemic events over a 16-week treatment period at the final analysis. The results of the study did not change the initial model the investigators began with.

**Bayesian approach** – This approach uses and learns from evidence as it accumulates.18 Here, while we do use prior information similar to the Frequentist approach; also called prior belief and we now combine it with new information that accumulates as the study continues. The combination of old information coupled with new evidence goes beyond protocol development; can be applied to the conduct of the trial and also at the analysis stage. In this approach, prior information and the accruing results are considered seamless and inferences are drawn and updated each time that new data becomes available. The Bayesian approach thus directly address the question of how new evidence should change what we currently believe.20 These are also called as “learn as you go” approaches.

Bayesian analyses are computationally intense and thus less used compared to the Frequentist approaches. Recent advances in the past decade, in particular the development of computational algorithms, hardware and high computing speed have made it possible to use Bayesian approaches much more and these are now seen fairly frequently in literature. An example of a protocol that uses a Bayesian approach can be seen in the study planned by Carlson21 on the use of Docosahexaenoic acid (DHA) supplementation [relative to soybean + corn oil] for reducing the frequency of early pre-term births. The rationale for the study is that DHA has been associated with longer gestation, higher birth weight and less pre-term births [prior information]. A total of n = 1200 women are planned to be
enrolled. The first interim analysis is slated once n=150 women have been enrolled in each group. The data accrued will be analyzed in a blinded manner. Subsequently, more patients will be assigned to the more promising group. In other words, the data gathered will change the conduct of the study.

Studies can also use a combination of the two approaches.

**Study Designs and Interim Analyses**

RCTs can incorporate interim analysis in one of several ways. 1) A Traditional Design RCT, one that has a fixed sample size, but no interim analysis. 2) A Traditional Design RCT with interim analysis using one of the Frequentist approaches. 3) Interim analysis that actually “modifies one or more aspects of the study design, or even the hypothesis based on analysis of accumulating data” This constitutes an Adaptive Design.

**Data Safety and Monitoring Committees [DSMC]**

A clinical trial DSMC is a group of individuals [independent of the study and appointed by the sponsor] with pertinent expertise who review accruing data on a regular basis from one or more ongoing clinical trial and take decisions independent of the funder of the study. These committees are also called Independent Data Safety Monitoring Committees [IDSMC]. Like Interim Analyses, historically, the establishment of DSMCs can also be traced to the Greenberg report who recommended the establishment of independent committees based on the recognition that looking at accumulating study data was essential to ensure the ongoing safety of trial participants. Another reason stated by the Greenberg report was that those closely involved with the study design and conduct may not be objective enough to review interim data for any emerging concerns and address them.

The primary role of the DSMC is to ensure that the safety of participants in the study is protected. This is done by them in one of three ways: 1) terminate the study early either for safety concerns and thereby prevent further harm or when there is overwhelming evidence of efficacy. The latter ensures that all participants then receive the better intervention. 2) terminate the study when there is adequate evidence pointing towards futility in continuation. 3) Permit study continuation in anticipation of benefit after a due assessment of risk – benefit based on data accrued thus far.

The committee usually has 3–5 individuals with extensive clinical experience both in the disease under study, and in the management of large complex clinical trials. A DSMC has two clearly designated positions – that of the Chair and the statistician. The decision-making meetings are “closed door” and the chair communicates the minutes to the sponsor. It is important that the DSMC consider the “totality of evidence” before any recommendation and in particular when they recommend that trials be stopped early. Apart from the statistical analyses, the amount of data accrued, the nature of the results seen up to that point, their implications, cost of gathering more data and the benefit-risk assessment of what subsequent patients will be exposed to, all must be considered in tandem for decision-making.

**Conclusions**

The process of interim analysis or reviewing data before it is fully collected helps in decision making in both drug development and clinical research. Regardless of the approach used for an interim analysis, it is important to remember that statistical analysis is simply a part of the whole picture. Beyond statistical significance, any treatment difference seen needs to be clinically meaningful — that is, large enough to actually matter when the intervention is used finally in clinical practice. The decision regarding termination [for benefit, safety concerns or futility] or continuation of a study, thus, must also be driven by other aspects such as cost of the drug, ease of administration, nature of the toxicity seen, and benefit-risk assessment for the subsequent patients.

**Acknowledgements**

The authors are grateful to Dr Jaideep Gogtay [Cipla Ltd, Mumbai], Dr L. Jeyaseelan [Christian Medical College, Vellore], Dr Sudeep Gupta [Advanced Centre for Training Research and Education [ACTREC], Navi Mumbai] and Dr Manju Sengar [Tata Memorial Hospital, Mumbai] for their critical inputs that helped refine the manuscript.

**References**

6. Heart Special Project Committee. Organization, review, and administration of cooperative studies [Greenberg Report]: a report from the Heart Special Project Committee to the National Advisory Heart.
Mets Here, Mets There, Mets Everywhere....

Amey Beedkar¹, Rohan Parikh¹, Pradeep Deshmukh³

A 40 years old male, smoker, presented with shortness of breath, cough, hemoptysis and chest pain since 4 days. He had blood pressure of 100/70 mmHg, tachypnea and tachycardia. Normal S1, S2. No murmurs. Air entry was decreased on right basal area. There were no added sounds. Well’s Criteria To Assess Clinical Likelihood Of Pulmonary Embolism was 5.5. ECG showed sinus tachycardia. Chest Xay showed cannon ball opacities in right upper and mid zones. Cotton fluffy opacities involving right lower, left mid and lower zones. Obliteration of right costophrenic angle. 2D echo shoed extensive metastasis in left atrium, left ventricle.

CTPA + CT Thorax and CT Abdomen showed Right Pulmonary Artery Embolism. Bilateral pulmonary parenchymal metastasis. Right Renal cell Carcinoma. Pretracheal, prevascular, subcarinal, precardinal and aortopulmonary window lymph node mets, vertebral mets at L5

Uncommon presentation of Malignancy are common. In our case RCC presented as pulmonary embolism. Secondary or metastatic cardiac tumors are 30 times more frequent than primary. “Surprises are bound to happen”. Treatment for cardiac metastasis should be done along with that of primary malignancy. In carefully selected patients resection of cardiac metastasis provide symptom relief, improved quality of life and prolong survival. Multispeciality approach is the key in management of such patients.

References


¹Registrar, ²Associate Professor, Department of Cardiology, Super Speciality Hospital, Nagpur, Maharashtra
Received: 11-04-2016; Revised: 13-01-2017; Accepted: 31.01.2017
We invite Heads of Research Institutions, Universities, Medical and Pharmaceutical Colleges of India to nominate eligible candidates for:

(a) **Sun Pharma Research Awards-2016** and
(b) **Sun Pharma Science Scholar Awards-2017**

**a) The Sun Pharma Research Awards** are for excellence in original research in Medical and Pharmaceutical Sciences. There are four Awards of Rs. 2 lakh each; three in Medical Sciences – (Basic Research, Medical Research and Clinical Research), and one award in Pharmaceutical Science.

The sponsored work of Indian Scientists, both in India and abroad, together with their bio-data, photograph, research achievements, awards received in the past and papers published, along with justification for nomination and citation on the research work by the nominator, may be submitted online on Sun Pharma Science Foundation's website: www.sunpharmasciencefoundation.net. The nominations may be submitted online from **September 1, 2017** to **October 16, 2017**. Also required to send a print copy of the nomination, to the office of the Foundation by **October 20, 2017**.

**b) Sun Pharma Science Scholar Awards**: There are four awards—two each in Biomedical Sciences and Pharmaceutical Sciences for Rs. 50,000/- each.

Indian nationals under the age of thirty (as on October 16, 2017), who have completed at least 1st year of MD or PhD in Biomedical or Pharmaceutical Sciences are eligible to apply. Those who have completed their MD, or PhD and above the age of thirty, as on date October 16, 2017 are not eligible to apply. The applicant should have completed a Research Project and should be willing to present his/her research work in front of knowledgeable assessors.

The applicant should submit:- (1) detailed CV with photograph (2) copy of their detailed research work (3) letter from the supervisor certifying that the research work under reference has actually been done by the applicant (4) a citation (brief summary) on his/her research work. (5) forwarding letter from the Head of the Department or Institution, giving justification for nominating the applicant (6) A voluntary declaration from the applicant that they would work in the public or private funded academic/research based organizations for a minimum period of two years after completion of his/her studies. The applicant should also submit the following testimonials.

- Aggregate marks obtained in PCB/PCM in Class XII and Bachelor’s/ Master’s Degree.
- Proof of age
- Copies of the publications, if any
- Merits/Awards/Scholarships received, if any
- A letter stating that the project submitted for the award has received ethical clearance,
- A statement duly signed by the nominee and the supervisor/co-author that the thesis has no-conflict of interest academically or financially.

The applicants should submit their nominations online at Sun Pharma Science Foundation’s website: www.sunpharmasciencefoundation.net from **September 1, 2017** to **October 16, 2017**. Also required to send a print copy of the nomination, to the office of the Foundation by **October 20, 2017**.

Detailed nomination Procedure is available on Sun Pharma Science Foundation's website.

For further information please contact:
The Office of Sun Pharma Science Foundation
Sarhaul, Sector-18, Gurgaon – 122015, Haryana (India)
Tel. (91-124) 2341477; 4194342
E-mail: sunpharma.sciencefoundation@sunpharma.com
Website: www.sunpharmasciencefoundation.net
Termination of Ventricular Tachycardia by Anti Tachycardia Pacing-An Uncommon Diagnosis on 12 Lead Surface ECG

Vaibhav M Dedhia

A 56 years old male had undergone implantation of Dual chamber Automated Implantable Cardioverter Defibrillator (AICD) in November 2011 for documented sustained monomorphic ventricular tachycardia. He was a known case of Ischaemic heart disease (IHD) and had undergone angioplasty with a medicated stent to the mid left anterior descending coronary artery in September 2011. 2 D Echocardiography revealed left ventricular (LV) systolic dysfunction with LV ejection fraction of 35%. There was mild concentric left ventricular hypertrophy with normal chamber dimensions and normal right ventricular function. He had hypertension since four years, which was under control on therapy and was recently detected to have Diabetes mellitus which was controlled with Metformin and diet. He had followed up for symptoms of per rectal bleeding in January 2012 and colonoscopy revealed carcinoma at the junction of rectum and anal canal. This was proven on biopsy. After consultation with an oncosurgeon, it was diagnosed to be in an operable stage and posted for surgery (abdomino –perineal repair) after high risk informed consent in view of recent angioplasty with a medicated stent and ventricular dysfunction.

The intraoperative course was uneventful. On postoperative day 2 the patient received two shocks from the AICD device within three hours interval. On investigation there was hypokalemia (K+ 2.8meq/L) and anemia (Hb 8.0 gm%). These were corrected with potassium supplementation and blood transfusion respectively. Intravenous magnesium was also administered. Serial ECG monitoring during this period picked up several runs of non sustained monomorphic ventricular tachycardia (NSVT). As the patient was already on maintenance amiodarone, further intravenous amiodarone was not administered. The runs of non sustained tachycardia subsided completely after correction of hypokalemia. Interestingly one of the serial ECGs picked up the termination of an episode of NSVT by pacing (Anti Tachycardia Pacing –ATP). This case is extremely successful in decreasing the number of shocks.

The use of ICD and CRT-D (Cardiac Resynchronization Therapy-Defibrillator) devices, have been extremely successful in decreasing mortality rates for patients with ventricular dysfunction and mild to moderate heart failure. However, high-voltage shock therapy is painful and not always necessary. Quality-of-life scores in the ICD population are poor and are significantly affected by the occurrence of shocks. Shock pain, anticipation of the next shock, antiarrhythmic drugs, and hospitalizations due to shocks are all contributors. A recent trial demonstrated that the principle cause (26%) of all hospitalizations for ICD patients in a 12-month span was due to appropriately detected VT/VF and consequent shocks from their ICD.1

The PROVE trial showed that the use of antitachycardia pacing (ATP) programming in patients implanted with ICD or CRT-D devices was successful in terminating 89% of ventricular tachycardia (VT) episodes, potentially avoiding painful or unnecessary shocks in those patients.2 The clinical implications are that ICD patients may be spared the majority of painful shocks if ATP is programmed as the first therapy for VT. Also the longevity of ICDs may be improved by fewer capacitor charges.3

References

In the treatment of Tuberculosis

An Innovation with patented novel drug delivery process

Risorine CAP
Rifampicin 200mg + Isoniazid 300mg + Piperine 10mg Capsule

Rifampicin powered by Bio-enhancer Piperine

Clinical efficacy at par with standard regimen
• 93% sputum conversion at the end of 4 weeks
• 92% Cure rates after 24 weeks

Improved GI tolerance during 6 months treatment
• Reduced risk of drug induced hepatotoxicity
• Improved patient compliance – Reduced risk of relapse

Ensures Better Bioavailability of Rifampicin

In Intensive Phase

Risorine KIT
Rifampicin Powered by Bioenhancer Piperine

Trusted Partners in TB treatment

P-Zide
Pyrinamide 500/750/1000 mg
The (2) category power

Mycobutol
Ethambutol 450/600/850/1000 mg
The Trusted Ethambutol

Mycocox
(PhRH)

*[Read more](URL)
CASE OF THE MONTH

An Interesting Case of Recurrent Pyelonephritis

Achintya Dinesh Singh¹, Siddharth Jain¹, Agrima Mian¹, Surabhi Vyas², Neeraj Nischal³, Pankaj Jorwal³

Abstract
A 35-year-old male presented with repeated episodes of fever and abdominal pain of 3-month duration. He had been hospitalized twice with similar complaints in the past 3-month. He was diagnosed as pyelonephritis and managed with intravenous antibiotics. However, fever recurred after ten days of discharge from the hospital. With these complaints, he was referred to the Department of Medicine, AIIMS, New Delhi.

After evaluation, he was diagnosed as pyelonephritis with right sided consolidation and was started on broad spectrum antibiotics. After a transient initial improvement, his dyspnea worsened, fever recurred and he developed a tender submandibular abscess. Further evaluation for the actual focus of infection, revealed a small mass attached to the right coronary aortic cusp on transthoracic ECHO. Diagnosis of native Aortic valve endocarditis was made and suitably treated. The patient became afebrile on the 8th day of therapy and was discharged after 20-day. He is doing well on subsequent follow-up.

Introduction
There are myriad ways through which any disease can present itself. This ever-expanding conundrum of clinical presentations when further complicated by iatrogenic addendums and previous inadequate therapies further confound the diagnosis. Such perplexing case scenarios are not only intriguing but also highly informative and sharpen clinical acumen for early detection of similar conditions in the future. We describe the elusive case of a young male presenting with recurrent fever with dysuria and shortness of breath.

Case Presentation
A 35-year-old male shopkeeper without any co-morbidities presented with complaints of high-grade fever with associated chills and rigor since the last 3-month. It was associated with burning in micturition along with urgency and frequency and abdominal pain. The pain was constant and dull aching in the left middle and lower abdomen and had increased acutely in the last 5-day. He had noticed painless, gradually progressive swelling over both the lower limbs over the last one month. Over the past 2-day, he had developed acute onset shortness of breath, present even at rest and had difficulty in completing full sentences. He had also noticed decreased frequency of micturition and had not passed urine over the last 12-hour. For similar complaints, he had been evaluated at a local hospital near his hometown about 2-month back. He was diagnosed with bilateral pyelonephritis based on urine analysis and radiological investigations. He received 1-week of intravenous antibiotics (IV). After discharge, he was prescribed oral antibiotics for 5-day. Though compliant with medications, the fever spikes recurred after 2-week of discharge along with similar complaints of dysuria. He was readmitted to the hospital and was started on IV antibiotics. Ureteral stents were inserted (double-J stents) on the suspicion of ureteral obstruction (Figure 1). After 2-week of in-hospital care and medications, the patient became afebrile and asymptomatic. Ureteral stents were removed before discharge. However, after about 10-day of discharge, the patient developed fever again. This was also associated with pedal edema. The patient used over the counter medications for fever but due to worsening of symptoms presented to Medicine out-patient department (OPD) at All India Institute of Medical Sciences (AIIMS) New Delhi. There was no history of evening rise of fever, jaundice, insect bite, recent travel, visit to a forest or scrub, skin rash or photosensitivity, oral ulcers, alopecia, arthralgia, recurrent urinary tract infections or respiratory tract infections in childhood.

On examination, the patient was febrile (101°F), tachycardic (110/minute) and tachypnoeic (24/minute). There was pallor...
and bilateral pitting pedal edema extending up to the knees but no signs of icterus, clubbing or lymphadenopathy or elevated jugular venous pressure. He had bilaterally decreased breath sounds in the infra-axillary and infrascapular regions. It was associated with diffuse coarse crackles more on the right side than the left. The abdomen was distended with flank fullness. Shifting dullness was present and left renal angle was tender. Rest of his systemic examination was unremarkable.

Laboratory investigations (Table 1) revealed leucocytosis with neutrophil predominance along with mild anaemia. erythrocyte sedimentation rate (ESR) was elevated. Renal functions were deranged and associated severe hypoalbuminemia was also present. Urinalysis (Table 2) showed pyuria with proteinuria along with white blood cell (WBC) casts. Pleural fluid analysis revealed exudative effusion with leucocyte count of

<table>
<thead>
<tr>
<th>Parameter</th>
<th>At admission</th>
<th>Fourth day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemoglobin (g/DL)</td>
<td>9.1</td>
<td>9.5</td>
</tr>
<tr>
<td>HCT %</td>
<td>28.3</td>
<td>28.3</td>
</tr>
<tr>
<td>Platelet count (cells/mm³)</td>
<td>194000</td>
<td>194000</td>
</tr>
<tr>
<td>Total leucocyte count (cells/mm³)</td>
<td>31800</td>
<td>12,800</td>
</tr>
<tr>
<td>Differential leucocyte count (%)</td>
<td>P81L7M2E10</td>
<td>P69L27M4E8</td>
</tr>
<tr>
<td>S. urea (mg%)</td>
<td>97</td>
<td>23</td>
</tr>
<tr>
<td>S. creatinine (mg%)</td>
<td>4.2</td>
<td>0.6</td>
</tr>
<tr>
<td>Bilirubin (mg/dL)</td>
<td>0.5</td>
<td>0.5</td>
</tr>
<tr>
<td>Total proteins/ albumin (g/dL)</td>
<td>6.5/2.7</td>
<td>6.0/2.5</td>
</tr>
<tr>
<td>AST/ALT/ALP (IU/L)</td>
<td>13/13/514</td>
<td>31/30/114</td>
</tr>
<tr>
<td>ESR (mm in 1st hour)</td>
<td>80</td>
<td>40</td>
</tr>
</tbody>
</table>

AST- Aspartate transaminase levels, ALT-Alanine transaminase levels, ALP- alkaline phosphatase level, ESR-erythocyte sedimentation rate. mm-millimeter. IU-international units g/dL-gram per decilitre, mg/dL- milligram/decilitre

Table 1: Blood investigations at various time-points

Table 2: Urine investigations of the patient

<table>
<thead>
<tr>
<th>Urine levels</th>
<th>At admission</th>
<th>Fourth day</th>
<th>Discharge</th>
</tr>
</thead>
<tbody>
<tr>
<td>Protein</td>
<td>2+</td>
<td>2+</td>
<td>Nil</td>
</tr>
<tr>
<td>RBC/hpf</td>
<td>15-20</td>
<td>10-15</td>
<td>Nil</td>
</tr>
<tr>
<td>WBC/hpf</td>
<td>Full field</td>
<td>Full field</td>
<td>3-5</td>
</tr>
<tr>
<td>24 hr urine albumin</td>
<td>549 mg</td>
<td>450 mg</td>
<td>24</td>
</tr>
</tbody>
</table>

Hpf-High power field. Protein as per dipstick method

300 cells/mm² with neutrophil predominance and a pH of 7.25, adenosine deaminase (ADA) was 4 International Unit (IU)/Litre (L) and Xpert Mtb Rif test was negative. Ascitic fluid was transudate. Ultrasound revealed normal sized kidneys with raised echogenicity and maintained cortico-medullary differentiation. Blood and urine cultures were sent. His blood glucose was normal and HbA1c levels was 5.5%. Vasculitis and immunodeficiency workup including HIV and Hepatitis B infections was negative. Fundus was normal and he had associated anaemia of chronic disease. Emergency room bedside echocardiography revealed moderate pericardial effusion with normal left ventricular function. Chest X-ray (Figure 2) and computerised tomography (CT) scan revealed a right sided lobar consolidation with associated parapneumonic effusion and right subdiaphragmatic fluid collection.
Our likely diagnosis was complicated urinary tract infection i.e. complicated pyelonephritis with urosepsis with septic embolization leading to pneumonia and sepsis-related acute kidney injury (AKI). Disseminated tuberculosis (TB) was our second differential, however, response to antibiotics, low ADA levels in pleural fluid made TB less likely. Infective endocarditis (IE) leading to septic embolization and bacteremia was our third differential. However, lack of any underlying predisposing condition, no other embolic phenomenon and only pericardial effusion on bedside echocardiography were against it.

With the most likely diagnosis of pyelonephritis with urosepsis, the patient was started on intravenous (I.V.) Piperacillin and Tazobactam and oral linezolid. The patient became afebrile after 3-day and his renal function tests also improved. His blood culture was sterile. On urgent CT pulmonary angiography revealed no evidence suggestive of pulmonary embolism. Ultrasound imaging of the submandibular swelling was suggestive of an abscess. Appearance of a new onset abscess lead us to relook foci of actual infection. So, keeping in mind a strong suspicion of IE Trans-oesophageal echocardiography was ordered which demonstrated a firm mobile mass attached to the right aortic leaflet (Figure 3). There was a resolution in the pericardial effusion. With the diagnosis of infective endocarditis likely due to enterococci, the patient was started on IV gentamicin with vancomycin and ceftriaxone. His fever responded in about one week. Vancomycin and sensitive to vancomycin and ceftriaxone. His fever responded in about one week. He was discharged after a week of therapy. He also showed radiological resolution (Figure 4). He was discharged after 2-week of IV antibiotics as he wished to complete the remaining course from his regional clinic. He is in medicine OPD follow-up over the past one year and has been symptom-free.

### Discussion

The patient presented with recurrent episodes of pyelonephritis since 3-month. This time it was associated with acute kidney injury and pneumonia. On presentation, there was associated acute kidney injury which was likely related to sepsis or pyelonephritis. Proteinuria is uncommonly seen with pyelonephritis. Though all the organs involved could be due to separate entities as per the Hickam’s dictum, however following Occam’s razor we tried to make the least assumptions for the underlying cause of ailments. One of the diseases with such disparate manifestations is infective endocarditis. The therapeutic response of the patient after starting combination therapy for enterococcal endocarditis further supports the diagnosis.

The echocardiographic presence of mass lesion along with fever, the initial blood culture positive for enterococci and the manifestations suggestive of associated glomerulonephritis fulfill one major and three minor criteria of the Duke’s criteria. These criteria are highly specific and sensitive for the diagnosis of Infective endocarditis. Though the association of IE and pyelonephritis is not very well known, increasing number of case reports have shown correlation. In report by Loulergue et al. Recurrent episodes of pyelonephritis was found to be associated with underlying prosthetic valve infective endocarditis by Hafnia Alvei. The combined antibiotic therapy for six weeks was effective in treating the condition and there was no further relapse. These findings were further underscored by Micol et al whose study found E.coli bacteremia to be significantly associated with native valve endocarditis. The initial episode of pyelonephritis and the resultant enterococcal bacteremia is the most likely cause of the patient’s subacute IE. This led to recurrent episodes of pyelonephritis in the patient. The history of previous hospitalizations, the invasive

---

**Fig. 3:** Trans-oesophageal echocardiography showing nodular lesion in right aortic cusp (arrow)

**Fig. 4:** Follow-up chest radiograph at two weeks, showing resolution of the bilateral pleural effusion and right basal consolidation
procedure (DJ stenting) also makes hospital acquired infection a likely possibility. The exact indication for DJ stenting was not clear from previous records, however this invasive procedure could have led to the enterococci bacteremia and subsequent IE.

Enterococcal IE is a leading cause of infective endocarditis specially in hospital acquired infective endocarditis. In a recent study by Francischetto et al, E. faecalis was responsible for 19% of hospital-acquired IE, and 57% of all hospital-acquired IE were in the native valve. Similar results were found in a study by Damasco et al, where E. faecalis attributed for 27.2% of hospital-acquired IE cases seconded only by S. aureus (32.5%). In this study, intravascular catheter was found to be the most likely source of infection. In a recent study by Dahl et al, similar values were seen. However, univariate analysis revealed that male sex, community-acquired bacteremia, unknown site of origin of infection and mono bacterial bacteremia were significantly associated with risk of IE. β-lactam antibiotics in combination with gentamicin are the cornerstone of therapy of enterococcal IE. In native valve endocarditis, 4-week of therapy is advised, however in the case of suspected penicillin resistance or long-standing IE (> 3 months) treatment is extended up to 6-week. Recent studies have advocated the short term (2-week) use of gentamicin to be as effective as prolonged therapy. Vancomycin based therapy is used only in cases of ampicillin intolerance. As our case had previously received penicillin group of antibiotics we started him on the vancomycin based regimen. Dramatic response to therapy in our case is likely attributable to the synergistic action of the vancomycin and gentamicin. The prolonged course of therapy led to the successful treatment of the patient.

Despite being a colonizer in the respiratory system, pneumonia is an infrequent manifestation of enterococcal bacteremia. Though the reason is not well understood, decreased isolation of the bacteria due to the widespread use of β-lactam antibiotics may be the reason. Bacteraemia is the most likely cause of bilateral pneumonia in our case. Right sided infective endocarditis was not seen despite repeated investigations. The prompt response to therapy supports infection with similar bacteria.

To conclude, we had an atypical presentation of recurrent pyelonephritis with significant proteinuria and bilateral pneumonia. These resulted from native valve subacute enterococcal endocarditis. Upon initiation of therapy, the myriad manifestations resolved in almost 1-week and the patient is asymptomatic since. A high index of suspicion and knowledge of such conditions can guide reach a prompt clinical diagnosis. Importance of avoiding unnecessary medical interventions cannot be over emphasized. It also paves way for future research to assess the role of bacteria and association of these two distinct clinical diseases.

References
CMV Pneumonitis following Bendamustine containing Chemotherapy

Sumeet Vimal Kishor Singhaniya, Pujan Parikhb, Sandeep Goyleb

Abstract

Bendamustine has been increasingly used for treatment of indolent lymphoma in low grade lymphoma due to its comparable efficacy and side effect profile. As the drug is getting used more, specific adverse effects related to its use are also emerging particularly prolonged lymphopenia. Here we present a case of CMV reactivation following bendamustine containing chemotherapy.

Case Report

A 72-year lady was referred to our pulmonary clinic with complaints of fever of 2 weeks duration and dry cough along with shortness of breath for last two days. She had been diagnosed with low grade B cell non Hodgkin lymphoma 6 months ago and was treated with 6 cycles of Rituximab (600 mg on day 1), Bendamustine (100 mg on day 1,2) and dexamethasone (8 mg daily for 3 days post each chemotherapy cycle). She had completed her last (6th) cycle just over 4 weeks ago. Patient developed fever 2 weeks after completion of 6th cycle of chemotherapy. Her other history included hypertension, osteoarthritis, hyperthyroidism and an episode of pneumonia one year ago. She was not known to have any other cardio respiratory illnesses in the past. Her complete blood counts showed grade 3 lymphopenia. Renal and liver profiles were normal. Dengue and Malaria screens were negative. She had already received 5 day course of oral amoxicillin and clavulanic acid and despite that the fever was persistent.

On arrival to chest clinic, her room air oxygen saturation was 92% at rest and dipped down to 84% on walking 50 meters. Chest was clear on auscultation. She had undergone a PET scan 2 days earlier for response assessment following completion of chemotherapy. It showed diffuse ground glass opacities in both lungs with no evidence of metabolically active disease within the body. Bronchoscopy and lavage was done the next day. Bronchoscopy findings were normal. BAL aerobic culture, AFB stain, AFB gene Xpert and PCP-PCR were all negative. Bronchial lavage showed presence of inclusion bodies and BAL qualitative CMV PCR was positive. Blood CMV PCR showed 6680 copies/ml. She was treated for CMV pneumonitis with Inj Ganciclovir 5mg/kg twice a day for 2 weeks. The fever resolved and hypoxia settled. The patient became completely asymptomatic within 7 days of treatment and on completion of antiviral treatment her repeat Blood CMV PCR was <1000 copies/ml. The patient remained asymptomatic and was discharged from chest clinic a month later.

Discussion

Bendamustine has shown a favourable risk profile and comparable efficacy as compared to standard R CHOP regimen for indolent lymphoma in particular there is decrease incidence of alopecia. However bendamustine is known to cause more severe CD4 lymphopenia which can predispose patients to opportunistic infections like CMV. Our patient had grade 3 lymphopenia at the time of clinical presentation. Isono et al conducted a prospective study on reactivation of CMV following bendamustine chemotherapy and showed median CD4+ lymphocyte count prior to treatment of 218/µL which fell down to 75/µL by the end of treatment. The incidence of CMV reactivation in this study was approximately 15% of patients. However the actual risk of symptomatic CMV disease, which would require medical intervention was not much clear. This is in contrast to various earlier studies showed the incidences of CMV infection ranged from 0 to 5.0% and 0 to 1.5% in Bendamustine alone or in combination with Rituximab respectively. Ken Ohmachi et al found an incidence of 10.2% in their multicenter trial and recommended that the lowest threshold for CMV antigenemia assay needs to be examined in patients who develop a fever of unknown origin without neutropenia, and preemptive therapy with ganciclovir should be initiated in CMV-positive patients. A more recent study from Japan shows the risk of symptomatic CMV antigenemia as high as 20% and predominantly involving patients who were on long

1Consultant, Pulmonary Medicine, 2Clinical Assistant, Pulmonary Medicine, 3Consultant, Medical oncology, Kokilaben Dhirubhai Ambani Hospital and Medical Research Institute, Mumbai, Maharashtra

Received: 29.06.2016; Accepted: 03.06.2017
Eosinophilic Gastroenteritis
Iqbal Bagasarawala, JK Maniar, Abizer Manked, Hozefa Runderawala

Abstract
Eosinophilic gastroenteritis (EGE) is an uncommon disease of unknown etiology reported in both adult and pediatric age group. Here we report a case of a 46-year-old HIV positive female who presented to us with ascites and abdominal distension with peripheral eosinophilia and diagnosed as EGE.

Introduction
Eosinophilic gastroenteritis (EGE) is a rare disease with very few cases which have been reported. EGE can affect the entire gastrointestinal tract from esophagus to colon, most commonly affecting gastric antrum and proximal intestine. It is characterized by tissue and peripheral eosinophilia without any obvious cause. EGE can present with wide spectrum of symptoms depending on the part and layer of gastrointestinal tract involvement. Eosinophilic ascites is manifested when subserosal layer of gastrointestinal tract is involved.

Case Report
46-year-old female, married, HIV positive, diabetic and hypothyroid was admitted with complaints of gross abdominal distension, loss of appetite and nausea since 2-3 days.

Patient gives no h/o fever, loose motion, hematemesis or melena.

She was admitted 20 days back for severe vomiting; CT abdomen was done s/o sub-acute intestinal obstruction secondary to ileal stricture. Colonoscopy was normal, biopsy report was suggestive of mild terminal ileitis.

On examination, she was afebrile, pulse 82/min, regular, BP- 112/74 mm Hg, mild pallor, no icterus or pedal edema.

On per abdominal examination, her abdomen was distended, umbilicus everted, shifting dullness was present suggestive of moderate ascites. Rest of the systemic examination was normal.

On investigation, Hemoglobin- 10 gm%, total leucocytes- 16290/cmm, (Neutrophils- 30%, Lymphocytes- 22%, Eosinophils- 38%). Liver function test, serum electrolytes were normal, Stool for parasitic infestation was negative, and Serum IgE was within normal range.

USG guided peritoneal tapping was done, peritoneal fluid was slightly hazy in appearance, with total protein- 4.53 gm/dl, albumin- 2.62 gm/dl, ADA- 8.4 U/L, WBC counts- 13010 with 85% eosinophils. Aerobic culture showed no growth. "The organism and no acid fast bacilli seen, cytopathology of the peritoneal fluid showed predominant eosinophils with

References
no malignant cells (Figure 1).

**Discussion**

Eosinophilic gastroenteritis (EGE) can affect entire gastrointestinal tract from esophagus to colon, commonly affecting distal antrum and proximal small intestine, characterized by eosinophilic infiltration of bowel with or without associated peripheral eosinophilia. Data regarding its prevalence and demographic distribution is scarce. It affects adult as well as pediatric age group with female preponderance. Approximately half of the patients give history of allergic diseases like asthma, food sensitivities, eczema or rhinitis. The clinical manifestation of EGE depends on the location, extent and layer of bowel with eosinophilic infiltration.

The exact cause of eosinophilic gastroenteritis is unknown. Some cases of this disease may be caused by a hypersensitivity to certain foods or other unknown allergens. Often, a family history of allergy is present. A case was reported from India of a 40-year male with eosinophilic ascites with eosinophilic gastroenteritis.

Till date no study has been done or case reported of association between HIV and EGE.

Eosinophilic infiltration of the mucosal layer (mucosal disease) gives rise to non specific symptoms like abdominal pain, nausea, vomiting, early satiety and diarrhea. These patients can develop malabsorption, protein losing enteropathy, and failure to thrive.

Eosinophilic infiltration of the muscle layer of gastrointestinal tract (muscular layer disease) results in wall thickening and impaired motility. Patients may present with nausea, vomiting, and abdominal distension suggestive of intestinal obstruction. It sometime may result in perforation or obstruction of gastric outlet.

Patients with subserosal EGE present with ascites or ascites with other symptoms of mucosal or muscular EGE.

The pathogenesis of eosinophilic gastroenteritis is not well understood. Although food allergy role has not been clearly defined in EGE, but extensive investigation provides insight of role of food allergen, eosinophils and Th-helper 2 (Th2) cells. Food exposure activates interleukin 5 (IL-5) + Th2 cells leads to gut eosinophilia. The eotaxin family of chemokines appears to play central role in the recruitment of eosinophils in gut in response to food allergen. Eosinophils can also cause local inflammation by release of eosinophil major basic protein, a cytotoxic cationic protein.

The diagnosis of eosinophilic gastroenteritis (EGE) is based on exclusion criteria. The unexplained ascites with tissue eosinophilia may point towards EGE, when all other causes are ruled out. There is no single diagnostic criterion of EGE; it is based on clinical features, laboratory tests, and/or biopsies of the gastrointestinal tract. The other causes of hypereosinophilia such as intestinal parasite infestation with Ankylostoma, Strongyloids; malignancies like lymphoma, gastric carcinoma, colon cancer; Inflammatory bowel disease, Hypereosinophilic syndrome, Polyarteritis nodosa, drug reaction to be ruled out.

The diagnosis of EGE should include complete blood count with differential counts, erythrocyte sedimentation rate, liver function test, amylase and lipase level, stool routine and microscopic examination for ova and parasites, upper and lower gastrointestinal endoscopies with tissue biopsies, serum IgE level. In the presence of ascites, peritoneal fluid tapping should be done and fluid should be sent for routine examination, cytology, culture for tuberculosis. The peripheral smear may show eosinophils with tissue biopsy or ascitic fluid showing eosinophilic infiltration. The radiological imaging like ultrasound or computed tomography for intestinal wall thickness or stricture should be done.

The mainstay treatment of EGE is steroids. The glucocorticoids in the dose of 20-40 mg/day for first few weeks show dramatic response and then slowly tapering off. Most patients quickly respond to steroid therapy as in our case too. Elemental diet with avoidance of food allergen may also help. Other therapies like antihistaminic, mast cell stabilizer, leukotriene antagonist or IgE monoclonal antibody can also be tried.

**Conclusion**

EGE is a rare disorder that can affect any patient age group and may present with unexplained ascites. Absence of malignancy and ruling out other causes of eosinophilia, with presence of peritoneal fluid eosinophilia and significant response to steroid therapy confirms our diagnosis of Eosinophilic Ascites (EA), a rare presentation of Eosinophilic Gastroenteritis (EGE).

**References**

NovoMix™ 30 FlexPen®
(biphasic insulin aspart)

The ‘Start Insulin’ for type 2 diabetes

Superior efficacy

Improved safety

Better quality of life

Simplicity

Say YES to...


Abridged Prescribing Information: NovoMix™ 30 (biphasic insulin aspart) NovoMix™ 30 FlexPen®. Contains biphasic insulin aspart 100 units/ml. Indications: Treatment of diabetes mellitus. Dosage: Individualised by subcutaneous injection. NovoMix™ 30 has a faster onset of action than biphasic human insulin and should generally be given immediately before a meal. When necessary, NovoMix™ 30 can be given soon after a meal. No studies in children and adolescents under the age of 18 years. Contraindications: Hypoglycaemia, hyperinsulinaemia. Warnings and precautions for use: Inadequate dosing or discontinuation of treatment may lead to hypoglycaemia and diabetic ketoacidosis, which are potentially lethal. Change in usual warning symptoms of hypoglycaemia may be seen upon tightening control. The onset of action should be considered in patients where a delayed absorption of food might be expected. Transferring to a new type or brand of insulin should be done under strict medical supervision and may cause a need of change in dose. Compared with biphasic human insulin, NovoMix™ 30 significantly lowers postprandial glycaemia up to 6 hours after injection. This may need to be compensated for through adjustment of dose and/or food intake. Hypoglycaemia may constitute a risk when driving or operating machinery. Pregnancy and lactation: Limited clinical experience in pregnancy. No restrictions on use during lactation. Undesirable effects: Hypoglycaemia, oedema and infusion anaphylaxis on initiating therapy, local hypersensitivity reactions; generalised hypersensitivity reactions are rare but potentially life threatening; lipodystrophy.

For the use of a registered medical practitioner or a hospital or a laboratory only NovoMix™ 30 FlexPen®, Penfill®, Changing Diabetes® and the Apis bull logo are registered trademarks owned by Novo Nordisk A/S and registered in Denmark.
Hereditary Haemorrhagic Telangiectasia with Severe Anemia and Recurrent CNS Infections

Nrushen Peesapati¹, PBPR Naidu¹, S Sunitha², PV Sivaram³

Abstract

Hereditary Haemorrhagic Telangiectasia, also known as Osler-Rendu-Weber disease is a rare autosomal dominant disorder affecting small vessels of multiple systems whose main pathological change is the presence of abnormal arteriovenous communications. Usually presents as skin and mucosal telangiectasias, epistaxis, gastrointestinal bleeding and visceral arteriovenous malformations. Although the epistaxis and gastrointestinal blood loss can result in anaemia, patients with hereditary haemorrhagic telangiectasia rarely presents as severe anaemia or CNS infections. Herein, we report the case of a 57 year-old man who presented with severe anaemia resulting in congestive cardiac failure with history of recurrent blood transfusions and recurrent CNS infections which ultimately was diagnosed as hereditary haemorrhagic telangiectasia.

Introduction

Hereditary haemorrhagic telangiectasia (HHT) described first in 1865 is an autosomal dominant disorder causing abnormal capillary dilatations or connections called telangiectasia between arterioles and venules. Vascular lesions in HHT may also present as arteriovenous malformations (AVM), or aneurysms especially found in brain, lungs, liver and gastrointestinal system (visceral A-V malformations). Such connections remain usually asymptomatic and can be life threatening ruptured. HHT is usually not considered early in the differential diagnosis of severe anaemia, and careful history with careful examination is required to diagnose the disease.

The clinical profile of HHT, a rare disease with a classic presentation, quite rarely includes severe anaemia and recurrent central nervous system infections. Patients with HHT present normal haemostasis and platelet function, and the recurrent bleeding is therefore related to the telangiectasia. The anaemia can be due to one or both of two factors: recurrent epistaxis and gastrointestinal bleeding and recurrent CNS infections are due to septic emboli from pulmonary arteriovenous malformations.

Case Report

A 57 year old male with history of recurrent blood transfusions was admitted with complaints of dyspnoea on exertion, easy fatiguability and pedal oedema since 1 month. He also had history of recurrent spontaneous epistaxis since childhood around 3-4 episodes per month. Patient gave history of surgical intervention for left parieto-temporal cerebral abcess in 1994 evidenced by giosis on recent imaging. He was diagnosed as having Pott’s spine in 2005 and underwent surgery.

At present he is on antituberculous therapy since December 2015 for suspected tuberculoma in cerebral parenchyma.

On probing, patient admitted that some of his family members also had recurrent epistaxis and telengectasias over fingers and tongue. Neither the patient nor his family members were labelled with any specific diagnosis before this presentation. Detailed family history was taken to document mode of inheritance (Pedigree chart of patient Figure 3).

The family history clearly revealed the epistaxis had occurred in generation in a pattern indicative of autosomal dominant inheritance. Physical examination revealed marked pallor, bilateral pitting type of pedal oedema, raised jugular venous pressure. On careful observation capillary telangiectasias were present on dorsum of tongue and finger tips.

On auscultation, there was a continuous murmur of grade 5/6 heard over the left interscapular region which is suggestive of AV malformation and confirmed by colour doppler imaging.

So in view of recurrent epistaxis, autosomal dominant nature of inheritance from pedigree, mucocutaneous and visceral telangiectasias diagnosis of HHT was made (Curacao criteria)

Investigations was suggestive of severe anemia which was microcytic and hypochromic with normal thrombocytes and normal coagulation profile. Upper

Fig. 1: Telengectasias over dorsum of tongue
Fig. 2: Telengectasias on fingers

Fig. 3: Pedigree chart

¹Resident, ²Assistant Professor, ³Professor, Tirumala Hospital, Vizianagaram, Andhra Pradesh
Received: 10.04.2016, Accepted: 03.06.2017
gastrointestinal endoscopy revealed multiple telangiectatic lesions in duodenum suggestive of visceral arteriovenous malformations.

Discussion

Hereditary haemorrhagic telangiectasia (HHT) is a rare disorder with prevalence of 1 in 5,000 to 10000 with autosomal dominant transmission, despite the fact that about 20% of the cases may not have a family history.\(^3\) It is thought that the abnormal vessels in HHT develop because of aberrant TGF signaling at some stage during vascular development and mutations of HHT-associated genes.\(^4\) HHT is divided in to 4 types on genetic basis.\(^4\) It has been proposed that in the case of HHT, disease severity is more pronounced in HHT1 compared to HHT2, with an earlier age of onset for epistaxis, the appearance of telangiectasia of the skin, lip or mouth. These usually do not cause serious illness; but patients may have a variety of serious complications due to vascular involvement of internal organs, such as the gastrointestinal tract 15%, the lungs 30%, hepatic AVMs < 30%; and the central nervous system 10%, spinal AVMs 1%.

Patients need thorough investigations and close follow up for visceral AV malformations because each may contain clinically silent lesions that can result in sudden morbidity or death. Pulmonary AVM may present with dyspnoea, cyanosis, massivehaemoptysis, and haemothorax. For clinical relevance, the diameter of the artery of the PAVM must be ≥ 3 mm. Pulmonary AVMs cause right-to-left shunts resulting in hypoxaemia.

The diagnosis is based on Curacao criterion\(^2\) established in 1999\(^*-2000\) which include
1. Spontaneous, recurrent epistaxis, nocturnal nosebleeds heighten concern for HHT.
2. Mucocutaneous telangiectases, especially on lips, tongue, oral cavity, fingers and nose.
3. Internal AVM(s) (pulmonary, cerebral, hepatic, gastrointestinal, spinal).
4. First-degree relative with HHT.

Definite diagnosis: 3 or more criteria present
Possible diagnosis: 2 criteria present
Unlikely diagnosis: < 2 criteria present

Our patient had history of recurrent CNS infections which can be due to absence of a filtering capillary bed allowing emboli to reach the systemic circulation.\(^5\)

Cerebral AVMs can lead to headaches, seizures, strokes, transient ischaemic attacks, and both intracerebral and subarachnoid haemorrhage.

Gastrointestinal bleeding (common from stomach and duodenum) can result in iron deficiency anaemia or acute gastrointestinal haemorrhage.

No definitive treatment available. Appropriate management depends on clinical manifestations, site of the disease and remains largely symptomatic. Management options for cutaneous lesions include electrocauterisation with diathermy, sclerotherapy or laser therapy. AV malformations need intervention either as coiling or by clipping; treatment for bleeding is symptomatic and can require iron therapy and blood transfusions. Aspirin and other medicaments that impair haemostasis are contraindicated in such cases.

Bivacizumab\(^6\) is a humanised...
Paraneoplastic Inverse Myasthenic Syndrome as a Presentation of Bronchogenic Carcinoma

GS Chowdhary¹, Malav Jhala²

Abstract
Tumours may produce growth factors and cytokines responsible for signs and symptoms distant to the primary or metastatic site. This may be the first sign of a malignancy and its recognition may be critical for early cancer detection. Moreover, proper diagnosis spares the patient of extensive and expensive search for an alternate cause of the neurological dysfunction. In neurological paraneoplastic syndromes like Lambert Eaton Myasthenic syndrome associated with small cell lung cancer, evidence of autoimmunity against presynaptic neuro-muscular junction by anti voltage gated calcium channel anti bodies is well documented. 60% of patients with LEMS are associated with an underlying cancer, usually SCLC.

We report a 49 year old male, with over thirty pack years of smoking, who presented with dysautonomia, constitutional symptoms and weakness of all four limbs. Investigations confirmed axonal motor neuropathy with limited stage SCLC with fibro nodular lesions right upper lobe and mediastinal lymphadenopathy. He improved dramatically following chemotherapy and radiotherapy.

Introduction
The proportion of lung cancers presenting as small cell histology are between 10-20 % in men and 10-30 % in women, the predominant risk factor being tobacco exposure in over 90% of cases diagnosed.¹² Usually SCLC presents with respiratory symptoms, only a few patients are asymptomatic at diagnosis. The Paraneoplastic spectrum of SCLC differs from that of NSCLC. Neurological Paraneoplastic syndromes include sensory, sensorimotor and autoimmune neuropathies and encephalomyelitis.³⁴ Symptoms may precede the diagnosis by many months and are often the presenting complaint. These neurological symptoms are unrelated to tumour bulk and may not improve despite anti-cancer therapies. LEMS is manifested by proximal muscle weakness which improves with continued use, hypo reflexia and dysautonomia.⁵⁶ This article reports a case of a patient who presented with dysautonomia followed by proximal muscle weakness more than six months ago. He was subsequently diagnosed to have SCLC and improved following Cisplatin and Etoposide based chemotherapy.

Case Report
A 49 year old male, heavy smoker, presented in Oct 2011 with 3 months history of dryness of mouth and eyes. Soon he developed weakness of all four limbs and anorexia. He had lost 10 kgs weight over the preceding 6 months. He also had scanty productive cough off and on. The patient’s height was 171 cm and he weighed 62 kg. General examination revealed body temperature of 98.4°F, Pulse 88/min and BP 130/90 mm Hg. He had xerostomia and xeropthalmia. There was no pallor, peripheral adenopathy, clubbing or edema, nor any features of SVCO. Neurologically he had normal higher mental functions and no cranial nerve deficit. He had proximal weakness of both upper and lower limbs with Gl:IV/V power, hand grip of 70-80% and flexor plantar response bilaterally. He had hyporeflexia in all four limbs but there was no sensory loss. Other systemic

References
examination was unremarkable.

**Investigations**

Baseline haemogram revealed normal CBC, ESR, RFT, LFT, Blood Sugars and ECG. Chest X-ray showed ill defined homogenous opacity in right mid zone with superior mediastinal widening suggestive of paraatracheal adenopathy. USG Abdomen—Normal. Neostigmine test was negative. Electrodiagnostic studies confirmed low amplitude muscle action potential on single stimulus of a nerve (in contrast to myasthenia gravis where it is normal) and incremental response on fast rates of stimulation and with strong voluntary contraction. Single fibre EMG showed a jitter response which is classic of LEMS. Upper GI Endoscopy revealed antral gastritis and colonoscopy seen upto terminal ileum was normal. Biopsy revealed—non specific inflammation.

CECT Thorax showed fibro nodular lesions in right upper lobe with fluid in the horizontal fissure with mediastinal nodes (pretracheal, paratracheal, precarinal, subcarinal, right hilar) and SVC thrombosis. CECT Abdomen was normal. Nerve conduction studies showed decreased amplitude in motor nerves with normal sensory conduction suggestive of axonal neuropathy. Electromyography was normal. Whole Body FDG PET Scan revealed FDG-avid Mediastinal lymph nodes in pretracheal, prevascular, left paratrachael, Right paratracheal (SUV 6.9) and multiple discrete non-FDG avid bilateral axillary nodes. MRI Brain was normal. Bone scan was normal.

Mediastinoscopy was done and biopsy of mediastinal nodes confirmed Metastatic small cell carcinoma. Immunohistochemistry was immunoreactive for keratin and epithelial membrane antigen.

The patient received 6 cycles chemotherapy (IV Etoposide 100 mg/m2 D1 to D3 + IV Cisplatin 80 mg/m2 D1 only) along with 4500 cGy thoracic radiotherapy and later prophylactic cranial irradiation. The patient received oral prednisone 1 mg per kg along with oral pyridostigmine 60 mg. 3 times a day. He also received capsule Fluoxetine 20 mg per day for depression. The patient responded well and is symptom free on follow up. He regained normal power in all limbs but had persistence of xerophthalmia and xerostomia. He is independent for activities of daily living.

**Discussion**

SCLC presenting with neurological paraneoplastic syndromes i.e. with remote effects of tumour products is a rare manifestation. 5-15% of lung cancer patients are identified when they are asymptomatic. Most however present with loco-regional obstructive respiratory symptoms or site specific metastatic symptoms or constitutional symptoms. A small percentage may present with Paraneoplastic manifestations. In many cases their pathophysiology is related to tumour protein or cytokine release with biological effects. Neurological paraneoplastic syndromes portend a poor prognosis to lung cancer patients.

Anti-VGCC antibodies directed against pre-synaptic neuro muscular junction in LEMS is responsible for inverse Myasthenic syndrome manifesting with dysautonomia and proximal muscle weakness, as in our patient.10

Definitive therapy for SCLC limited stage usually includes 6 cycles of etoposide with Cisplatin for every three weeks. 40 Gy of radiotherapy to the chest wall mass is added for symptomatic or progressive regions. If neuro imaging does not reveal brain metastasis, PCI may be added with the aim of lengthening survival, since brain metastasis are found in 65% of patients at post mortem. PCI is recommended 2 weeks after completion of all chemotherapy to complete and very good partial responders. The role of surgery in limited disease SCLC is reserved for select patients. e.g. with a solitary pulmonary nodule.10

**Conclusion**

This case highlights the rare presentation as dysautonomia and proximal weakness in a case of paraneoplastic inverse myaesthenic syndrome.

**References**


Role of Clarithromycin in Acute Exacerbations of Chronic Obstructive Pulmonary Disease

Agam Vora

Abstract

The prevalence of chronic obstructive pulmonary disease (COPD) is increasing in under-developing and developing countries. As per current estimations, COPD will become the third leading cause of death globally, by 2030. Long-acting anti-cholinergic agents, β₂-agonists, inhaled corticosteroids, antibiotics and mucolytics are some of the agents currently used in the treatment of COPD, which improve the symptoms and overall quality of life. Several of the important classes of antibiotics are used in the management of COPD including penicillins, cephalosporins, tetracyclines, fluoroquinolones, sulphonamides, aminoglycosides and macrolides. Macrolide antibiotics such as erythromycin, clarithromycin and azithromycin have a variety of physiological activities other than their antimicrobial effects, ultimately helping in preventing exacerbations and reducing mortality rates. Clinical studies indicate that long term use of clarithromycin is effective in the treatment of COPD exacerbations with lower incidence of adverse effects. This descriptive review on the role of the clarithromycin in treatment of COPD exacerbations will highlight these properties of clarithromycin in detail.

Background

The increasing prevalence of chronic obstructive pulmonary disease (COPD) is a major concern in under-developing and developing countries, as these countries contribute to almost 90% of COPD deaths. As per current estimates, COPD will become the third leading cause of death globally, by 2030. Although the prevalence of COPD is not well-established presently in India, a series of researches performed by some scientists have suggested that it may be around 5% in the adult population, with higher prevalence reported in smokers, men and subjects from rural area, depending on the socio-economic status, use of domestic fuel (type) etc.¹

Long-acting anti-cholinergic agents, β₂-agonists, inhaled corticosteroids, antibiotics and mucolytics are some of the agents currently used in the treatment of COPD, to improve symptoms and overall quality of life. Macrolide antibiotics such as erythromycin, clarithromycin and azithromycin have a variety of physiological activities other than their antimicrobial effects, eventually helping in preventing exacerbations and reducing mortality rates.² Clarithromycin, a macrolide antibiotic, has been found to be effective in treatment of COPD exacerbations due to its antibacterial and immune modulator properties.

COPD Exacerbations

The Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines define an exacerbation as ‘an event in the natural course of the disease characterized by a change in the patient’s baseline dyspnoea, cough, and/or sputum that is beyond normal day-to-day variations, is acute in onset, and may warrant a change in regular medication in a patient with underlying COPD.’ Generally, COPD is classified into three types; type I, type II and type III (Table 1).³

The COPD exacerbations are caused by a variety of risk factors such as environmental irritants, heart failure or medication noncompliance. However, most often, exacerbations are the outcome of bacterial or viral infections (Table 2).⁴

Management of COPD Exacerbations

Clinically, COPD exacerbations are described by enhanced airway inflammation, oedema and systemic inflammation. The morbidity and mortality caused by exacerbations can be minimized with early treatment initiation. The ‘ABC approach’, the pharmacological treatment approach for COPD exacerbations, is an acronym which reflects the three classes of drugs i.e antibiotics, bronchodilators and corticosteroids (Tables 3 and 4).⁵
The concentration of bacteria is high in lower airways in patients with COPD exacerbations. Antibiotics have a significant effect on peak expiratory flow rate (PEFR) and cause an earlier resolution of all three of the cardinal symptoms, viz: increased dyspnoea, increased sputum volume and increased sputum purulence. A study performed to evaluate the relationship between sputum purulence and the presence of bacteria suggested that patients should be treated with antibiotics if they also have at least one of the other two symptoms (dyspnoea or increased sputum volume) along with sputum purulence.5

As antibiotic therapies have shown positive effects on clinical recovery and treatment outcome in patients with acute exacerbation of chronic obstructive pulmonary disease (AECOPD), the use of antibiotics is recommended from the initial treatment stage itself. Regular use of antibiotics may reduce severity and duration of AECOPD episodes.4

Further, the mortality and incidence of secondary nosocomial pneumonia may increase, if COPD patients who require mechanical ventilator are not treated with antibiotics. It is recommended that antibiotic selection should be focused against Streptococcus pneumoniae, Moraxella catarrhalis and Haemophilus influenzae. Further, the Pseudomonas aeruginosa infection should be treated with broader antibiotic exposure.7 Some classes of antibiotics used in the management of COPD includes penicillins, cephalosporins, tetracyclines, fluoroquinolones, sulphonamides, aminoglycosides and macrolides. The commonly used antibiotics are elucidated in Table 5.4

Orally administered doxycycline, trimethoprim-sulfamethoxazole or amoxicillin-clavulanate potassium are usually considered in the initial outpatient management. It is recommended that hospitalized patients should get intravenous treatment with an antipseudomonal penicillin, a third-generation cephalosporin, a newer macrolide or a fluoroquinolone, depending on local bacterial resistance patterns.4 Penicillin corresponds to a group of beta (β) -lactam antibiotics. Hypersensitivity reaction is major problem in the use of penicillin. If a patient has symptoms of allergic reactions, re-exposure to penicillin can trigger life-threatening anaphylaxis. It has been estimated that up to 60% of penicillin-allergic patients will experience another allergic incident if dose of the drug is repeated.8

Amoxicillin–clavulanic acid combination is available in a range of doses like 250/125 mg (2:1), 500/125 mg (4:1), 875/125 mg (7:1), 1000/125 mg (8:1), and 2000/125 mg (16:1). However, insufficient doses and inappropriate use of the combination may result in drug resistance.9 Although, previously conducted trials such as TACTIC (Acute Exacerbations of Chronic Bronchitis), GLOBE (Gemifloxacin Long-term Outcomes in Bronchitis Exacerbations) and MOSAIC (Moxifloxacin to Standard oral antibiotic regimen) have revealed better results with newer generation fluoroquinolones as a first line

### Table 1: Classification of acute exacerbations of COPD (AECOPD)

<table>
<thead>
<tr>
<th>Type I (most severe)</th>
<th>Type II</th>
<th>Type III</th>
</tr>
</thead>
<tbody>
<tr>
<td>All three symptoms i.e., increased sputum volume, increased sputum purulence and increased dyspnoea.</td>
<td>Any two symptoms present</td>
<td>One symptom present plus at least one of the following:</td>
</tr>
<tr>
<td>• An upper respiratory tract infection in the past 5 days</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Increased wheezing</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Increased cough</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Fever without an obvious source</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• A 20% increase in respiratory rate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Heart rate above baseline</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Table 2: Most common infectious causes of COPD exacerbations

<table>
<thead>
<tr>
<th>Mild to moderate exacerbations</th>
<th>Severe exacerbations</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Streptococcus pneumoniae</em></td>
<td><em>Pseudomonas species</em></td>
</tr>
<tr>
<td><em>Haemophilus influenzae</em></td>
<td><em>Other gram-negative enteric bacilli</em></td>
</tr>
<tr>
<td><em>Moraxella catarrhalis</em></td>
<td><em>Haemophilus influenzae</em></td>
</tr>
<tr>
<td><em>Chlamydia pneumoniae</em></td>
<td><em>Streptococcus pneumoniae</em></td>
</tr>
<tr>
<td><em>Mycoplasma pneumoniae</em></td>
<td><em>Chlamydia pneumoniae</em></td>
</tr>
<tr>
<td><em>Viruses</em></td>
<td><em>Mycoplasma pneumoniae</em></td>
</tr>
</tbody>
</table>

### Table 3: Advantages and disadvantages of pharmacological treatment

<table>
<thead>
<tr>
<th>Bronchodilators</th>
<th>Improve symptoms and forced expiratory volume-one second (FEV1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No differences between different classes</td>
<td></td>
</tr>
<tr>
<td>No differences between metered-dose inhaler (MDI) and nebulizer use</td>
<td></td>
</tr>
<tr>
<td>Discrete effects on symptoms and lung function</td>
<td></td>
</tr>
<tr>
<td>Numerous side effects</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Systemic corticosteroids</th>
<th>Improve symptoms, FEV1, and PaO2 in moderate to severe exacerbations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reduce treatment failure, relapse and length of hospital stay</td>
<td></td>
</tr>
<tr>
<td>Induce more side effects (such as hyperglycaemia)</td>
<td></td>
</tr>
</tbody>
</table>

### Table 4: GOLD 2017 recommendations for antibiotics use

COPD exacerbation rates may be reduced with the regular use of macrolide antibiotics

Antibiotics when indicated, can shorten recovery time, reduce the risk of early relapse, treatment failure and hospitalization duration. (Duration of therapy should be 5-7 days).

Antibiotics should be given to patients with exacerbations of COPD:

- Who have three cardinal symptoms, i.e: increase in dyspnoea, sputum volume and sputum purulence
- Have two of the cardinal symptoms, if increased purulence of sputum is one of the two symptoms
- Require mechanical ventilation (invasive or non-invasive)
Table 5: Commonly used antibiotics for treatment of COPD exacerbations*

<table>
<thead>
<tr>
<th>Mild to moderate exacerbations*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Macrolides</strong></td>
</tr>
<tr>
<td>Clarithromycin, 500 mg twice daily</td>
</tr>
<tr>
<td>Azithromycin, 500 mg initially, then 250 mg daily</td>
</tr>
<tr>
<td>Amoxicillin-clavulanate potassium</td>
</tr>
<tr>
<td>500 mg/125 mg tablet three times daily</td>
</tr>
<tr>
<td>875 mg/125 mg tablet twice daily</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Fluoroquinolones</th>
</tr>
</thead>
<tbody>
<tr>
<td>Levofloxacin, 500 mg daily</td>
</tr>
<tr>
<td>Gatifloxacin, 400 mg daily</td>
</tr>
<tr>
<td>Moxifloxacin, 400 mg daily</td>
</tr>
<tr>
<td>Doxycycline (100 mg twice daily)</td>
</tr>
<tr>
<td>Trimethoprim-sulfamethoxazole (one tablet twice daily)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Moderate to severe exacerbations**</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cephalosporins</strong></td>
</tr>
<tr>
<td>Ceftriaxone, 1 to 2 g IV daily</td>
</tr>
<tr>
<td>Cefotaxime, 1 g IV every 8 to 12 hours</td>
</tr>
<tr>
<td>Cefazidime, 1 to 2 g IV every 8 to 12 hours</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Antipseudomonal penicillins</th>
</tr>
</thead>
<tbody>
<tr>
<td>Piperacillin-tazobactam, 3.375 g IV every 6 hours</td>
</tr>
<tr>
<td>Ticarcillin-clavulanate potassium, 3.1 g IV every 4 to 6 hours</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Fluoroquinolones</th>
</tr>
</thead>
<tbody>
<tr>
<td>Levofloxacin, 500 mg IV daily</td>
</tr>
<tr>
<td>Gatifloxacin, 400 mg IV daily</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Aminoglycoside</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tobramycin, 1 mg per kg IV every 8 to 12 hours, or 5 mg per kg IV daily</td>
</tr>
</tbody>
</table>

| IV: Intravenous; * For orally administered antibiotics, the usual duration of therapy is five to 10 days; ** Drugs are often used in combination for synergy; IV therapy is usually employed. |

therapy, guidelines recommend that fluoroquinolones should be reserved for treatment failures and those with risk factors for poor outcome.7

The use of amoxicillin, doxycycline or cotrimoxazole is recommended as a first line agent if the risk factors for poor outcome (comorbid illness, severe COPD, frequent i.e. >3 years’ exacerbations) and the antimicrobial use in the last 6 months is absent. Antibiotics like cefuroxime axetil, amoxicillin-clavulanic acid, and macrolides such as azithromycin/clarithromycin are suggested in case of failure of first line agents.7 Macrolides have excellent tissue penetration and antimicrobial activity, mainly against gram-positive cocci and atypical pathogens. The varied biological activities and ability to modify inflammation has led to their use in the treatment of asthma, bronchiectasis and COPD.10

<table>
<thead>
<tr>
<th>Macrolide antibiotcis</th>
</tr>
</thead>
</table>
| Macrolides usually have macrocyclic lactone ring of 12 or more elements. They comprise of bioactive agents, antibiotics, antifungal drugs, prokinetics, and immunosuppressants. The widely used antibiotics family of drugs are 14-, 15-, and 16-membered macrolides.10 The first macrolide antibiotic, erythromycin, was used in the treatment of upper respiratory tract, skin and soft tissue infections previously, in patients who are allergic to penicillin. However, numerous adverse effects such as frequent gastrointestinal intolerance and short serum half-life have limited the use of erythromycin.11

The macrolides, azithromycin, clarithromycin, roxithromycin, ketolide and telithromycin, are the advanced structural analogues of erythromycin.11,12 They exhibit broader activity, more favourable pharmacokinetics and pharmacodynamics, and better tolerability when compared to erythromycin. Clarithromycin and azithromycin are widely used in the management of respiratory tract infections.11 Evidences have shown that the long term treatment with azithromycin and clarithromycin in patients with COPD is effective and tolerable, with subsequent decrease in exacerbations and associated hospitalizations.12

Further, the studies have confirmed that the effects of clarithromycin and roxithromycin in the inhibition of inflammatory cytokine production by COPD sputum cells were more effective than that of azithromycin.13 However, clarithromycin exhibited less adverse events in the treatment of respiratory tract infections when compared to roxithromycin.14

Role of Clarithromycin in COPD Exacerbations

Clarithromycin, 6-O-methylerthyromycin, is produced when C-6 hydroxyl (–OH) group of erythromycin is replaced with methoxy (–CH3) group. This substitution results into a more acid stable antimicrobial agent which inhibits the degradation of erythromycin base to the hemiketal intermediate. The improvement in oral bioavailability and reduction in gastrointestinal intolerance was observed in clarithromycin due to increased acid stability.15

The 14-hydroxylclarithromycin is an active metabolite of clarithromycin. Higher doses of clarithromycin results in nonlinear increase in the serum half-life and in the area under the plasma concentration curve (AUC) of clarithromycin. Administration of 500 mg clarithromycin (every 8 to 12 hours) resulted in a steady state peak plasma concentrations of 3 to 4 mg/L within 3 days, with elimination half-life increasing up to 5 to 7 hours.15

Mechanism: Clarithromycin mediated prevention of COPD exacerbation

Anti-inflammatory effect

Macrolides suppress mRNA levels and release of IL-8 by activating nuclear factor-kB and activator protein-1. Studies have reported that macrolide mediates anti-inflammatory effects in the sputum of patients with COPD, resulting in decreased total cell counts, neutrophil chemotaxis and IL-8 and tumour necrosis factor (TNF)-α levels.2 Clarithromycin reduces the release of viruses and cytokines into supernatant fluids in humans infected with seasonal type A influenza. Anti-inflammatory effects of macrolides may be associated with the inhibition of viral infection induced COPD exacerbations.2
Antibiotic effect

Clarithromycin reduces the production of pneumolysin, a vital virulence factor in the infection of *S. pneumoniae*. It also inhibits the twitching motility of *P. aeruginosa* and alters the structure and architecture of the biofilm. The production of pro-inflammatory cytokines, soluble intercellular adhesion molecule (ICAM)-1 and mucin is decreased by macrolides in cells such as airway epithelial cells, in response to endotoxin and extract of *H. influenzae*.2

Immunomodulatory effect

The long term treatment with clarithromycin decreases sputum production and volume in patients. A study conducted in rats reported that clarithromycin inhibited ovalbumin (OVA) and lipopolysaccharide (LPS)-induced mucus production activated by the intranasal instillation of OVA in OVA-sensitised rats and intranasal LPS instillation. Some of the *in vitro* studies also showed that clarithromycin inhibits mucin or MUC5AC production or secretion after stimulation with TNF-α, RV infection or extract of *H. influenzae* in airway epithelial cells.2

The preclinical study performed in mice infected with a lethal dose of influenza virus suggested that clarithromycin increases the survival rate. The study also reported that clarithromycin induced mechanisms such as the reduced production of nitric oxide, reactive oxygen species and interferon (IFN)-γ; elevated IL-12 levels are associated with the reduction in lung injury and the severity of pneumonia.3

Clinical evidences

The use of clarithromycin in acute exacerbation of COPD had been studied in a few clinical trials. Shmelev El *et al.* studied the effect of clarithromycin in the treatment of moderate and severe exacerbations of stage II COPD. The study compared clinical efficacy of clarithromycin with beta-lactams and respiratory fluoroquinolones. The results from the study suggested that clarithromycin has equal clinical efficacy and minor side effects when compared with the controlled drugs. Thus, study concluded that clarithromycin can be used as the initial therapy for exacerbations of COPD in a daily practice.16

Léophonte and colleagues performed study to evaluate the effect of routine use of clarithromycin tablet in the treatment of acute exacerbations of non-severe COPD. It was an open label, pharmacoepidemiological, clinical study in community practice which was performed with 180 practitioners. Seven hundred and nineteen adult patients with acute exacerbation of mild or moderately severe COPD participated in the study. About 92.5% of subjects showed a favourable clinical course of exacerbations and 99% of cases showed resolution of frankly purulent sputum, which was associated with good tolerance. The study confirmed the use of clarithromycin as a first line therapy in bacterial exacerbation of mild or moderately severe, stable COPD.17

Basyigit I *et al.* evaluated the anti-inflammatory effect of clarithromycin on serum and sputum interleukin-8 (IL-8), tumour necrosis factor-α (TNF-α), and leukotriene B4 levels in patients with COPD. It was a prospective, single-center, double-blind, placebo-controlled study which included thirty men with mild to moderate COPD. Patients received either clarithromycin or placebo for 14 days. The levels of IL-8, TNF-α and the induced sputum total cell counts decreased significantly in the clarithromycin group post-treatment compared to the pre-treatment levels (Figure 1). Likewise, significant decrease in levels of serum inflammatory markers was observed in the clarithromycin group compared to placebo group. The study suggested that the reduction in the levels of IL-8 and TNF-α might be related to the anti-inflammatory effect of clarithromycin. Thus, clarithromycin can be used to treat infection or help control the inflammation in patients with COPD.18

Banerjee D *et al.* studied the effect of oral clarithromycin on bronchial airway inflammation in moderate to severe stable COPD. It was a prospective, double blind, controlled trial in patients with moderate to severe stable COPD. Patients received therapy with oral modified-release clarithromycin 500 mg/day or placebo for 3 months. Thirty-one patients were treated with clarithromycin and thirty-six with placebo, out of total 67 patients. Although, clarithromycin had insignificant effect on sputum total cell count, neutrophil count, IL-8, Leukotriene B4, TNF-α levels or neutrophil elastase, it did cause a small reduction in the neutrophil differential (*p* = 0.04 relative to placebo) and neutrophil chemotaxis (*p* = 0.058 relative to placebo).19

Safety profile of clarithromycin

The safety profile of clarithromycin has been well documented. Clarithromycin is well-tolerated in most of the studies.15 A research study conducted in COPD patients suggested that gastrointestinal intolerability and taste perversion are common side effects with clarithromycin therapy.18 The other common adverse reactions (nausea [3.8%], diarrhoea [3%], abdominal pain [1.9%], and headache [1.7%]) reported with clarithromycin are similar to other macrolides. Overall, the results from the studies suggested that fewer than 3% of patients receiving clarithromycin withdrew from studies because of adverse effects. Laboratory abnormalities which included abnormal liver function tests and decreased white blood cell counts were also rare.15
Clarithromycin and placebo groups before and after treatment. (AT = after treatment; BT = before treatment; IL-8 = interleukin-8; LTB4 = leukotriene B4; TNF-α = tumour necrosis factor-α. *p < 0.05 before versus after treatment)

Fig. 1: Levels of induced-sputum inflammatory markers in the clarithromycin and placebo groups before and after treatment. (AT = after treatment; BT = before treatment; IL-8 = interleukin-8; LTB4 = leukotriene B4; TNF-α = tumour necrosis factor-α. *p < 0.05 before versus after treatment)

Place in Therapy

COPD is one of the leading causes of morbidity, mortality and hospitalization, worldwide. The immunomodulatory properties of clarithromycin reduce exacerbation, morbidity and mortality in patients with COPD. Clinical studies indicated that long term use of clarithromycin is efficacious in the treatment of COPD exacerbations with lower incidence of adverse effects. The present review suggests that clarithromycin can be used as a first line therapy in the management of mild or moderate COPD exacerbations.

Acknowledgment

Alpha MD provided writing assistance during the development of this review article.

Disclosure

Dr. Agam Vora have declared and confirmed that there is no conflict of interest with respect to this authored publication.

References

1st time in India

Volibo
(Voglibose 0.2/0.3 mg + Metformin 500 mg)

Boost
PPHG Control

Preserve
β-cell function

Control
65% β-cell

T2DM
48% β-cell
Sneezing – Physiological Facts and Beliefs

Geeta Gore¹, Aparna Verma²

Sneeze is an abrupt, convulsive and audible expulsion of air from lungs through the nose and mouth. It is semi-autonomous in nature, usually caused by foreign particles irritating the nasal mucosa (sternutation). Many do not realize that during sneeze one automatically close the eyes. It may first come to their notice while driving a car and rarely may even cause an accident at high speed.

The function of sneezing is to expel mucus containing foreign particles or irritants and cleanse nasal cavity. During sneeze, the soft palate and palatine uvula depress while the back of the tongue elevates to partially close the mouth passage so that ejected air may be expelled through nose, but considerable amount of air is usually expelled from mouth. Sneeze does not occur during REM sleep because of accompanied atonia. Many persons wake up from their sleep for the purpose of sneezing with a partially awake state at minimum.

Sneezing typically occurs when sufficient foreign particles or stimuli like light (photic reflex), cold air, large meal, infection etc. stimulate nasal mucosa. They trigger the release of histamines which irritates nerve cells in nose. Signals are then sent to the brain through trigeminal nerve network which in turn activate pharyngeal and tracheal muscles, resulting in powerful release of air with bio-particles at a speed of 156 Kms. Sneeze reflex centers are located in brain stem along ventro-medial part of the spinal trigeminal nucleus, lateral reticular formation. The sneeze reflex involves contraction of number of different muscle group through the body. Other than irritating foreign particles, allergens, sinus nerve stimulation and photic sneeze reflex (exposure to bright light) may stimulate sneezing. Photic sneeze reflex is an Autosomal dominant trait, affecting 18-35% of human population.

Rarer triggers are full stomach sneeze reflex (snatiation) and rarely initial stage of sexual arousal; reason being that nose, like genitals contain erectile tissue. The phenomena may arise due to cross connections in the autonomic nervous system regulating a number of functions including genital erection during arousal.

Snuff is ground tobacco leaf stalk perfumed and taken by sniffing up the nose- a form of tobacco addiction, introduced on the continent in 16th Century. Its popularity quickly spread after the monarchs and snuff boxes became a status symbol.

While sneezing is generally harmless in healthy individuals, the infectious aerosol can produce 40,000 droplets. Their spread can be limited by holding the forearm or inside of the elbow in front of mouth during sneezing. Presently this practice is considered inappropriate since it promotes spreading viruses such as H1N1 through human contact and commonly touched objects.

Various beliefs have survived through centuries. Today if someone is asserting something and the listener sneezes promptly, the person responds with “Very true” or “God bless you”. In some cultures it is perceived as a sign that someone was remembering the sneezer at that very moment. Preventive measures to be tried are: The deep exhalation of air in the lungs, holding the breath while counting ten or gently pinching the bridge of the nose for several seconds. Some people find sneezes to be pleasurable and do not wish to prevent them.

Stamps courtesy Dr. J.V. Pai-Dhungat, Former Professor of Medicine, BYL Nair Ch. Hospital, Mumbai, Maharashtra.

¹Former Head of Dept. of Audiology & Speech Therapy, BYL Nair Ch. Hospital, Mumbai, Maharashtra; ²Medical Officer, Dr. Sunny Medical Centre, Bengaluru, Karnataka.
Drug Interaction between Acenocoumarol and Linezolid

Kinjalka Ghosh1, Kanjaksha Ghosh2

1Assistant Professor of Biochemistry, KEM Hospital, Mumbai, Maharashtra; 2Director, Surat Rachidan Kendra & Research Centre, Surat, Gujarat

Sir,

We read with interest the submission by Sarkar et al in one of the current issue of the journal on the subject of our title. Any significant drug interaction particularly with a relatively new drug is worth reporting and a number of such cases strengthen the suspicion. As majority of the patients hardly takes a single drug hence a large number of similar adverse reaction with the drug combinations where the suspected drug is also prescribed helps one to dissect out cause and effect relationship.

Vitamin K antagonists are now increasingly prescribed in our country and it is one of the few drugs notorious for its innumerable drug interactions.1 It is one of the few drugs notoriously increasing prescribed in our country and it is one of the few drugs notorious for increasing prescribed in our country and it is one of the few drugs notorious for

oral vitamin K antagonists we should be sure that the particular drug has no important interaction and if it has significant interaction and unavoidable then tight follow up with very frequent INR determination is warranted. Many such patients often take supplementary alternative forms of medicine and needs to be enquired into as they may not be forthcoming with that history.

References

Rising Levels of Antibiotic Resistance in Bacteria: A cause for Concern

Rathindranath Sarkar, Rudrajit Paul, Debadipta Roy, Indranil Thakur, Jayanti Ray, Tanmay Jyoti Sau, Kunal Haldar, Jayati Mondal

Sir,

Antibiotic resistance of common pathogenic bacteria is a very serious trend in modern era all over the world. This is the reason for increased morbidity and mortality in hospital as well as the community settings. Published data from different parts of India show a similar ominous trend.

We here want to bring to your notice a recent series of antibiotic sensitivity reports of bacteria as obtained from patients admitted in our institution (a tertiary care centre of Eastern India). The patients hailed from both rural and urban areas.

As the above table shows, age range of the patients was from 43 to 77 years. While some (3 out of 7) patients were diabetic, the rest were without any apparent immunosuppressive condition.

All the organisms were gram negative bacteria. The only antimicrobials they were sensitive to (in most cases) were the polymyxins. This is the last line of treatment against bacteria in present times. We had to use Polymyxin B or colistin (Polymyxin E) in all the above cases for prolonged periods. The average stay in hospital for these patients was 16.1±3.5 days. There was no mortality.

Acinetobacter has been known to develop resistance to antibiotics extremely rapidly.2 In early 1970, the bacterium was sensitive to almost all available antibiotics.2 But by 1975, resistance to cephalosporins started to emerge. By 2000, the documented resistance to imipenem was extremely high.2 Thus, tigecycline and polymyxins are the only useful agents available against this bacteria. But recently, some reports have shown an emerging resistance to colistin.

We here want to bring to your notice a recent series of antibiotic sensitivity reports of bacteria as obtained from patients admitted in our institution (a tertiary care centre of Eastern India). The patients hailed from both rural and urban areas.

As the above table shows, age range of the patients was from 43 to 77 years. While some (3 out of 7) patients were diabetic, the rest were without any apparent immunosuppressive condition.

All the organisms were gram negative bacteria. The only antimicrobials they were sensitive to (in most cases) were the polymyxins. This is the last line of treatment against bacteria in present times. We had to use Polymyxin B or colistin (Polymyxin E) in all the above cases for prolonged periods. The average stay in hospital for these patients was 16.1±3.5 days. There was no mortality.

Acinetobacter has been known to develop resistance to antibiotics extremely rapidly.2 In early 1970, the bacterium was sensitive to almost all available antibiotics.2 But by 1975, resistance to cephalosporins started to emerge. By 2000, the documented resistance to imipenem was extremely high.2 Thus, tigecycline and polymyxins are the only useful agents available against this bacteria. But recently, some reports have shown an emerging resistance to colistin.

Table 1: Organisms isolated from patients with different clinical conditions and their drug sensitivity

<table>
<thead>
<tr>
<th>Patient Clinical condition</th>
<th>Clinical sample</th>
<th>Organism obtained</th>
<th>Sensitive to</th>
</tr>
</thead>
<tbody>
<tr>
<td>48, F</td>
<td>Urinary tract infection (UTI) in diabetics</td>
<td>Urine</td>
<td>Klebsiella sp.</td>
</tr>
<tr>
<td>50, M</td>
<td>Critical care induced pneumonia</td>
<td>Tracheal aspirate</td>
<td>Acinetobacter--do--sp.</td>
</tr>
<tr>
<td>43, F</td>
<td>UTI</td>
<td>Urine</td>
<td>E. coli</td>
</tr>
<tr>
<td>70, F</td>
<td>Diabetic foot ulcer</td>
<td>Wound swab</td>
<td>Acinetobacter Tigecycline, Polymyxin B and E baumannii</td>
</tr>
<tr>
<td>50, F</td>
<td>Diabetic with leg infection</td>
<td>Pus</td>
<td>Acinetobacter Tigecycline, Polymyxin B and E baumannii</td>
</tr>
<tr>
<td>38, M</td>
<td>UTI</td>
<td>Urine</td>
<td>E.coli</td>
</tr>
<tr>
<td>77, M</td>
<td>UTI</td>
<td>Catheter tip</td>
<td>Pseudomonas Polymyxin B, Colistin aeruginosa</td>
</tr>
</tbody>
</table>
A Patient with Dilated Cardiomyopathy and Portal Hypertension: Which Beta-Blocker to Use?

Rathindranath Sarkar1, Rudrajit Paul2, Debaditya Roy3, Asim Saha4, Tanmay Jyoti Sau5, Jayati Mondal6

1. Professor, 2. Assistant Professor, 3. Resident, 4. Professor, 5. Professor and HOD, 6. Professor, Dept of Medicine, Medical College, Kolkata, West Bengal; RMNO, Chittaranjan Seva Sadan, Kolkata, West Bengal

Sir,

Beta-blockers (BB) are group of drugs which are used for a variety of indications in medicine, starting from cardiac arrhythmia to chronic liver disease and glaucoma. There are various types of BB and the different diseases require different types. However, sometimes, the same patient may have two or more of these diseases simultaneously and then, the choice of a single beta blocker becomes a contentious issue. We here describe cases where the same patient had two diseases, both of which necessitated the use of beta blockers, albeit of different classes. Recently, we had two male patients presenting with gradually progressive dyspnoea. Both of them were alcoholic for the last eight to ten years. On examination, they were found to have massive ascites with raised jugular venous pressure. Both of them had orthopnoea and bi-basal fine crepitations in both lungs. Ultrasonography of abdomen revealed shrunken liver and dilated portal vein; upper GI endoscopy revealed grade II-III varices in the esophagus. After initial stabilization, echocardiography was done for both patients. It revealed dilated cardiomyopathy with ejection fractions of 28% and 35% respectively. In absence of other aetiologies, the cardiomyopathy was assumed to be due to prolonged alcohol exposure (serum iron profiles were done to rule out hemochromatosis). Since both the patients needed beta blockers for cardiac and hepatic pathologies, the respective super-specialty departments were consulted. Finally, they were started on carvedilol orally at 3.125 mg/day over one month. At 6 months’ follow up, symptomatically the patients were better and there was no progression of the varices.

BBs have been shown to be beneficial in portal hypertension1. The non-selective one, propranolol, has been studied extensively and has been proven to reduce hepatic venous pressure gradient.2 Breakdown of both beta-1 and beta-2 receptors are needed to have maximum benefit by reducing both splanchnic blood flow and splanchnic vasoconstriction.3 Other BB are also used in portal hypertension.

Beta-blockers are also an essential group of drugs for heart failure, especially heart failure with reduced ejection fraction, as in our patients. These beta blockers are recommended by the AHA for heart failure: bisoprolol, carvedilol and extended release metoprolol succinate (class I indication).4 Only these BBs have been shown to positively reduce mortality and hospitalization risk. However, the evidence for other beta-blockers is not strong. For example, propranolol has been studied in heart failure. It has been shown to improve left ventricular function significantly.5 But the effect on mortality is not documented. Similarly, a study from Brazil was done where carvedilol was replaced with propranolol in heart failure patients.6 This did not show any deterioration of cardiac function after the switch in the short term. However, the dose of propranolol required to maintain the adrenergic blockade level similar to carvedilol was 104±34 mg/day. At this dose, other side effects are likely.

Carvedilol, on the other hand, has been studied in portal hypertension and has been shown to be beneficial.3 Another advantage is that the dose of carvedilol for portal hypertension is similar to the heart failure dose.1,3 Different studies have shown that carvedilol reduces Hepatic venous pressure gradient to a similar degree or even greater degree than propranolol.3 The other BB like metoprolol has not shown such benefit.

Thus, in cases with portal hypertension and severe heart failure, carvedilol is a sound option.

References

15th INTERNATIONAL CONFERENCE
CARDEIOLOGY, DIABETOLOGY, ELECTROCARDIOLOGY, ECHOCARDIOGRAPHY & CRITICAL CARE
CDEE & CC CON-2017

BHOPAL

Theme: "Overcoming the Barriers in New Therapeutic Innovations"

Deliberations on focused topics you have never heard before!

- The new brave world of dyslipidemia: Marching ahead further to target ASCVD.
- Inclisiran: Will this emerging block buster win the battle of lipid management in future?
- A new revolution of improving CV outcomes with new antidiabetic medications.
- The global battle against obesity Tsunami: Can science deliver a solution?
- Is FFR ready to assume the crown jewels of invasive FFR?
- ARNI: A new revolution in chronic heart failure with reduced ejection fraction.
- The exciting world of NOACs: A new era has begun in VTE after AF.
- Reversal agents for NOACs are here: When and how to use.
- Focus on Cardio-oncology: Cancers that hurt the heart. What cardiologist needs to know?
- New devices knocking at the door: Leadless Pacemaker, SC ICD, Wearable Defibrillator.
- The nuances of difficult to treat asthma: Current approaches.
- ICU radiology for intensivist: CXR, Ultrasound, CT and MRI.
- War against Sepsis: The ongoing progress.
- Ultrasound guided decisions in the shocked patient.
- Multimodality imaging in myocardial diseases: The state of art approach.

AWARD SESSION FOR POSTGRADUATE FREE PAPERS

<table>
<thead>
<tr>
<th>Prize</th>
<th>Oral</th>
<th>Poster</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st</td>
<td>Rs. 10,000/-</td>
<td>Rs. 5,000/-</td>
</tr>
<tr>
<td>2nd</td>
<td>Rs. 5,000/-</td>
<td>Rs. 3,000/-</td>
</tr>
<tr>
<td>3rd</td>
<td>Rs. 3,000/-</td>
<td>Rs. 2,000/-</td>
</tr>
</tbody>
</table>

For any information contact

CONFERENCE SECRETARIAT
Dr. P.C. Manoria
E-5/103, Arera Colony, Bhopal 462016, M.P., Mob. No.: 98930 42229, E-mail: pmanoria@rediffmail.com
Venue: Hotel Jehan Numa Palace, Bhopal (M.P.)
BP control... every hour, 24 hours

Rosuvastatin 10 / 20 mg + Aspirin 75 mg + Clopidogrel 75 mg

The Nex... for Cardio Renal Protection

Etizolam 0.25 / 0.5 / 1 mg

Shorter action... Lesser side effects
Z Protection at 50% reduced price

Start 'EARLY' in Hypertension

ZILARTA 80

4x4 tablets

ZILARTA 80

4x4 tablets

24 hours & persistent BP control