e www.ejaypee.com, for detailed information on medicine books, visit our website www.ejaypee.com, for detailed information on medicine books, visit our website www.ejaypee.com

API Textbook of MEDICINE

Emeritus Editor
KK Pareek

Editor-in-Chief
Shashank R Joshi

Chief Editors
Jyotirmoy pal
Kamlesh Tewary
Girish Mathur
A Muruganathan
G Narsimulu

Associate Editors
Puneet Saxena
Gurpreet S Wander
Sekhar Chakraborty
Ashok K Taneja
Devendra Prasad Singh
Jimit Vadgama

Volume 2

site www.ejaypee.com, for detailed information on medicine books, visit our website www.ejaypee.com, for detailed information on medicine books, visit our website www.ejaypee.com

API Textbook of MEDICINE

Emeritus Editor
KK Pareek

Editor-in-Chief
Shashank R Joshi

Chief Editors
Jyotirmoy pal
Kamlesh Tewary
Girish Mathur
A Muruganathan
G Narsimulu

Associate Editors
Puneet Saxena
Gurpreet S Wander
Sekhar Chakraborty
Ashok K Taneja
Devendra Prasad Singh
Jimit Vadgama

Forewords
Jyotirmoy Pal
Jitendra Singh

Volume 1

13th Edition

JAYPEE

Contents

VOLUME 1

SECTION 1: ART OF MEDICINE

Section Editor: RK Singal

1. **Art and Science of Medicine** 3
   Amit K Ghosh
2. **Medical Ethics** 9
   SM Sapatnekar
3. **Emerging Scenarios and Challenges in Healthcare in Near Future** 15
   RK Singal, Atul Bhasin

SECTION 2: CLINICAL MEDICINE (SYMPTOMS, SYNDROMES, CLINICAL APPROACH)

Section Editor: Rakesh Bhadade

1. **Approach to a Patient with Fever** 25
   Dileep B Kadam, Neha R Suryawanshi
2. **Symptom-oriented Pain Management** 32
   DK Baheti
3. **Approach to Chest Pain** 41
   Priyank Mody, Mausam Mody
4. **Dyspnea** 50
   Udai Lal
5. **Cough** 56
   Agam Vora
6. **Palpitations** 65
   Jayant Arvind Antani, Vithalrao Gururao Nadagouda
7. **Abdominal Pain** 82
   Prasanna S Shah

8. Evaluation of a Patient with Newly Discovered Mass **90**
Aditya K Ghosh, Amit K Ghosh

9. Edema and Anasarca **94**
Sekhar Chakraborty

10. Ascites **101**
Raju Kanakia

11. Jaundice **107**
Aniruddha Y Phadke, Ankita Singh

12. Diarrhea and Constipation **112**
Hem Shanker Sharma

13. Weight Loss and Cachexia **120**
A Muruganathan

14. Altered Sensorium **127**
Mrinal Kanti Roy, Devlina Roy

15. Practical Approach to Syncope **132**
Amit A Saraf, Bitukaur Sodhi

16. Dizziness and Vertigo **135**
Sanjiv Maheshwari

17. Approach to Ataxia **140**
Amit Aggarwal, MPS Chawla

18. Motor Weakness **149**
Uma Sundar, Pramod Darole

19. Approach to Sensory Loss **153**
Rajinder K Bansal

20. Clinical Approach to Fever with Rash **164**
Ameya T Medhekar

21. Fever of Unknown Origin **176**
Anchin Kalia, Krunal H Patel

22. Tongue as Mirror of Clinical Medicine **183**
Dwijen Das, Sweekriti Adhikari

23. Eye in Systemic Diseases **190**
Jay Sheth, Akruti Desai, Jenil Sheth, Mekhla Naik, Nandini Banad, Sayali Karande, Supriya Sharma, Somasheila Murthy

24. Headache **207**
PK Maheshwari, Sanjay Prakash

SECTION 3: INFECTIOUS DISEASES

Section Editor: R Chandni

1. **Antimicrobial Resistance and Stewardship in India: Principles, Practice, and the Path Forward** 219
   Hemant P Thacker, Kunal Srivastava

2. **Infection in Immunocompromised Host** 234
   Niveditha Niranjan, Subramanian Swaminathan

3. **Hospital-acquired Infections** 243
   Vasant Nagvekar, Anusha Bubna

4. **Staphylococcal Infections** 254
   Ashutosh Chaturvedi, Girish Mathur, Adya Chaturvedi

5. **Streptococcal Infections** 261
   Anil Kumar kulshrestha, Bhagirath B Solanki

6. **Pneumococcal Infections** 269
   Sangram S Biradar

7. **Enterococcal Infections** 275
   Sangram S Biradar

8. **Clostridial Infections** 279
   GD Ramchandani

9. **Meningococcal and Gonococcal Infections** 287
   Swati Srivastava

10. **Enteric Fever** 296
    Saikat Datta

11. **Bacillary Dysentery** 300
    Tanu Singhal

12. **Cholera** 305
    Ravi Kant, Balachandra R

13. **Enterobacteriaceae** 314
    SS Dariya, Swati Srivastava, Princi Jain

14. ***Haemophilus influenzae* Infections** 320
    Pramod Kumar Sinha

15. ***Pseudomonas aeruginosa* Infections** 326
    Anup R Warrier

16. **Syphilis** 330
    SV Ramanamurty

17. Leptospirosis **336**
Rakesh Bhadade, Ani Patel, Rosemarie de Souaza

18. Brucellosis **343**
Girish C Rajadhyaksha

19. Actinomycosis: The Great Imitator **348**
M Pavan Kumar, B Thrilok Chander

20. Scrub Typhus **352**
Raman Sharma, Mukesh K Sarna, Manish Pahadia

21. Nontuberculous Mycobacterial Infections **357**
Alladi Mohan, SK Sharma, Vishwanath Upadhyay

22. Rickettsial Infections **363**
Ravikeerthy M

23. Malaria **369**
Jyotirmoy Pal, Rupak Chatterjee

24. Amebiasis and Giardiasis **384**
Jyotirmoy Pal, Nandini Chatterjee

25. Leishmaniasis **393**
Shyam Sundar

26. Toxoplasmosis **399**
Madhukar Rai

27. Cryptosporidiosis, Trichomoniasis, Balantidiasis, and *Cystoisospora* **403**
Atul Bhasin, RK Singal

28. Ancylostomiasis (Hookworm Infestation), Ascariasis, and Other Nematodal Infections **407**
Swati Srivastava

29. Tapeworm and Hydatid Diseases **420**
Sudhir Bhandari

30. Lymphatic Filariasis and Related Diseases **427**
Suma Krishnasastry

31. Systemic Fungal Infections **436**
Dilip Mathai

32. Herpes Virus Infections **442**
Aditya Prakash Misra

33. Viral Respiratory Infections **448**
Agam Vora, Prasanta Raghab Mohapatra, Baijayantimala Mishra

34. Rabies **461**
SM Sapatnekar

35. Arboviral Infections **467**
Naval Chandra, Yerraguntla Shashidhar

36. **Dengue** 478
Pratit Samdani

37. **Chikungunya Infection** 484
Jayanta Kumar Panda, Nandini Chatterjee

38. **Acute Encephalitis Syndrome** 490
R Chandni, Aravind R

39. **Japanese Encephalitis** 497
R Chandni, Aravind R

40. **Emerging and Re-emerging Infections: Mpox, Zika, Human Metapneumovirus, and Primary Amoebic Meningoencephalitis** 501
R Chandni, Aravind R

41. **Nipah Virus Disease** 508
Sajith Kumar R

42. **Clinical Approach to Human Immunodeficiency Virus/Acquired Immunodeficiency Syndrome** 512
Naval Chandra, Chandana Kaspa

43. **Antiretroviral Therapy: Current Guidelines and Future Pipeline** 522
Bharat Bhushan Rewari

44. **Antiretroviral Drug Resistance** 531
Alaka Deshpande

45. **Coronavirus Disease 2019: Pathophysiology, Clinical Manifestations, and Evolving Therapeutics** 537
Sudhir Bhandari

46. **Adult Immunization** 544
Girish Mathur, Ashutosh Chaturvedi

47. **General Considerations of Infections** 551
MVS Subbalaxmi, P Umabala

48. **Allergen Immunotherapy: From Immunological Foundations to Clinical Implementation** 556
Shambo Samrat Samajdar, Saibal Moitra

SECTION 4: CARDIOLOGY

Section Editor: Nihar P Mehta

1. **Basic Considerations in Cardiology** 569
Nihar P Mehta

2. **Cardiovascular Diseases: A Clinical Approach** 578
Suraj Kumar, Gurpreet S Wander

3. **Heart Failure** 591
Shantanu P Sengupta

4. **Acute Rheumatic Fever and Rheumatic Heart Disease** 597
Prabhat Pandey

5. **Valvular Heart Diseases** 606
Nihar P Mehta, Vijaykumar Narwade, Advait Munagekar

6. **Infective Endocarditis** 628
Suresh V Sagarad

7. **Atherosclerosis** 634
Sadanand R Shetty

8. **Acute Coronary Syndrome: Non-ST-Segment Elevation Myocardial Infarction** 643
Prashant P Joshi, Sagar R Makode

9. **Hypertension and Its Management** 650
Anuj Maheshwari

10. **Resistant Hypertension** 659
KK Pareek, Girish Mathur, GD Ramchandani

11. **Bradyarrhythmia** 666
Amit Vora, Malav Jhala

12. **Tachyarrhythmias** 676
SB Gupta

13. **Sudden Cardiac Arrest: Practical Overview** 690
Vidya Suratkal

14. **Congenital Heart Disease** 699
Sivasubramanian Ramakrishnan, Jay Relan

15. **Diseases of Myocardium** 711
Ajay Bahl

16. **Diseases of Pericardium** 729
Sanjay Tyagi, Ankit Bansal

17. **Diseases of the Aorta** 742
Manotosh Panja, Soumitra Kumar, Madhumanti Panja

18. **Pregnancy and Heart Disease** 756
Amal Kumar Banerjee

19. **Varicose Veins** 765
Shoaib Padaria

20. **Pulmonary Hypertension** 773
Sandeep Bansal

SECTION 5: NEUROLOGY

Section Editor: Sudhir V Shah

1. **Neurological Disorders: Basic Considerations and Clinical Approach** 783
   Sreenivas S
2. **Neuroimaging** 789
   Sreenivas S
3. **Epilepsy** 799
   PK Maheshwari, Sita Jayalakshmi
4. **Disorders of Language and Speech** 813
   Girish S Soni
5. **Disorders of Cranial Nerves** 820
   Parthvi Ravat, Manali Chaudhari, Sangeeta Ravat
6. **Ischemic Cerebrovascular Diseases** 838
   Sudhir V Shah
7. **Stroke in Young** 849
   Mrinal Kanti Roy, Sohini Chakraborty
8. **Neurotuberculosis** 859
   Umang Agrawal, Roop Gursahani
9. **Dementia** 870
   Sudhir V Shah, Shubham G Malani
10. **Approach to Hyperkinetic Movement Disorders** 878
    Heli Shah
11. **Approach to Hypokinetic Movement Disorders: Parkinsonism and Related Disorders** 886
    Ratnesh Sharma, Heli Shah
12. **Cerebellar Disorders** 894
    Netravathi M
13. **Amyotrophic Lateral Sclerosis and Other Motor Neuron Diseases** 923
    Ashok Sirsat
14. **Demyelinating Disorders of the Central Nervous System** 931
    Girish S Soni
15. **Nutritional and Toxic Disorder of the Nervous System** 940
    UK Misra
16. **Peripheral Neuropathy** 947
    Amit Aggarwal, MPS Chawla
17. **Disorders of Autonomic Nervous System** 961
    Narsingh Verma, Shivam Verma, Abhinav Verma

18. **Myasthenia Gravis** 969
Ashok Sirsat

19. **Diseases of Muscles** 974
Satish V Khadilkar, Jharna P Mahajan

20. **Noncompressive Myelopathy** 990
Jimmy Lalkaka

SECTION 6: GASTROENTEROLOGY

Section Editor: Sanjeev S Khanna

1. **Clinical Approach to a Patient with Gastrointestinal Disease** 1001
Sanjeev S Khanna

2. **Gastrointestinal Imaging and Endoscopy** 1007
Prasanna S Shah

3. **Esophageal Disorders** 1015
Rohit Deshpande

4. **Diseases of the Stomach and Duodenum** 1025
Rohit Deshpande

5. **Dyspepsia** 1037
Ramandeep Singh, Gautam Bhandari, Piyush Dadhich, Mahesh Sharma, Sunil K Dadhich

6. **Inflammatory Bowel Disease** 1042
Ajit Sood, Vandana Midha, Arshdeep Singh

7. **Malabsorption Syndrome** 1054
BS Ramakrishna

8. **Ischemic Bowel Disease** 1062
Puneet Dhar

9. **Gastrointestinal Bleeding** 1068
Hardik Rughwani, D Nageshwar Reddy

10. **Acute Pancreatitis** 1077
Prasanna S Shah

11. **Chronic Pancreatitis and Pancreatic Tumors** 1084
Rupjyoti Talukdar, D Nageshwar Reddy

VOLUME 2

SECTION 7: HEPATOLOGY

Section Editor: Pradip Bhaumik

1. **Basic Considerations in Hepatobiliary Disorders** 1093
   Sanjeev S Khanna
2. **Hepatobiliary Disorders: Clinical Approach and Investigations** 1099
   Akash Shukla
3. **Acute Viral Hepatitis** 1111
   H Basavanagowdappa
4. **Chronic Viral Hepatitis** 1119
   H Basavanagowdappa
5. **Alcohol-related Liver Disease** 1131
   Pradip Bhaumik
6. **Cirrhosis of the Liver** 1141
   Sanjeev S Khanna
7. **Hepatic Venous Outflow Tract Obstruction, Extrahepatic Portal Venous Obstruction, and Noncirrhotic Portal Fibrosis** 1148
   Sanjeev S Khanna, H Basavanagowdappa
8. **Metabolic Dysfunction-associated Fatty Liver Disease** 1155
   Rajesh Upadhyay, VS Gaurav Narayan, Priyanka Ojha
9. **Acute Liver Failure** 1164
   Raju Kanakia, Rohit Deshpande
10. **Pregnancy and Liver Disease** 1172
    Pushkar A Shikarkhane
11. **Malnutrition in Chronic Liver Disease** 1179
    Puneet Rijhwani, Vidita Kalra, Deepak Gupta, Pradeep Agarwal
12. **Portal Hypertension** 1186
    Samir S Parikh

SECTION 8: PULMONOLOGY

Section Editor: Agam Vora

1. **Respiratory System: Basic Anatomy (Part 1)** 1201
   PS Shankar
2. **Respiratory System: Basic Physiology (Part 2)** 1206
   PS Shankar

3. **Pulmonary Disorders: A Clinical Approach** 1211
Nimish M Shah

4. **Diagnostic Procedures in Respiratory Disorders** 1217
Agam Vora

5. **Asthma: Pathophysiology, Diagnosis, Management, and Long-term Care** 1228
Raja Dhar, Arup Halder, Beauty Biswas

6. **Chronic Obstructive Pulmonary Disease: Evolution Over Past Two Decades** 1236
Agam Vora

7. **Pneumonia** 1245
Pratibha Singhal

8. **Suppurative Pleuroparenchymal Diseases** 1256
Pratibha Singhal

9. **Pulmonary Tuberculosis** 1270
Bineet Ahluwalia, Jalil D Parkar

10. **Diffuse Interstitial Lung Disease** 1277
Randeep Guleria

11. **Eosinophilic Lung Disease** 1285
Aamir Shokat, Deepak Talwar

12. **Sarcoidosis** 1298
Pralhad P Prabhudesai, Bhaumik J Kamdar

13. **Obstructive Sleep Apnea** 1313
Prashant N Chhajed

14. **Diseases of Pleura, Mediastinum, Diaphragm, and Chest Wall** 1321
Devendra Prasad Singh, Somesh Thakur

15. **Cor Pulmonale** 1331
Anupam Prakash, Rosmy Jose

16. **Lung Transplantation** 1336
PS Shankar

17. **Approach to Allergy** 1343
Shambo Samrat Samajdar, Saibal Moitra

18. **Pulmonary Rehabilitation** 1356
Sumedh S Hoskote

19. **Allergic Bronchopulmonary Aspergillosis** 1362
(Col) Puneet Saxena

SECTION 9: CRITICAL CARE MEDICINE

Section Editor: Rahul Pandit

1. **Basic Principles of Critical Care and Approach to Critically Ill Patient** 1373
   Dilip R Karnad
2. **Monitoring Critically Ill Patients** 1379
   Deepti Badwe, Hetal N Kalsariya
3. **Respiratory Failure and Mechanical Ventilation** 1387
   Rahul Pandit
4. **Electrolyte Imbalance and Management** 1396
   Puneet Saxena, Monika Saxena
5. **Acid–base Disorders: Diagnosis and Management** 1412
   Sanjay N Pandya
6. **Sepsis and Septic Shock** 1420
   Rahul Pandit
7. **Acute Respiratory Distress Syndrome** 1431
   Jigeeshu V Divatia
8. **Nutrition in Critically Ill Patients** 1440
   Jay Kothari
9. **Hemodynamic Disturbances and Shock** 1446
   Abdul Samad Ansari
10. **Oxygen Therapy** 1452
    Rahul Pandit

SECTION 10: ENDOCRINOLOGY AND BONE DISORDERS

Section Editor: Rakesh Sahay

1. **Basic Considerations of Endocrinology** 1459
   Rakesh Sahay
2. **Endocrine Disorders: A Clinical Approach** 1463
   Shashank R Joshi, Pooja Upasani
3. **Disorders of Hypothalamus and Pineal Gland** 1469
   Krishna G Seshadri
4. **Disorders of Anterior Pituitary** 1475
   Kaushik Pandit
5. **Disorders of Posterior Pituitary** 1490
   Gumpeny Ramachandra Sridhar

6. **Disorders of Parathyroid Glands** 1496
Ambrish Mithal

7. **Disorders of Adrenal Glands** 1502
Saba Samad Memon, Anurag Lila, Tushar R Bandgar

8. **Disorders of Thyroid** 1509
Prakash Keswani, Parth Jethwani

9. **Rickets and Osteomalacia** 1518
Varun Suryadevara, Sadishkumar Kamalanathan

10. **Osteoporosis** 1523
Lakshmi Nagendra, Shashank R Joshi

SECTION 11: DIABETOLOGY

Section Editor: Anil Bhoraskar, Banshi Saboo

1. **Basic Consideration in Diabetes Mellitus** 1529
Banshi Saboo, Subhajyoti Ghosh

2. **Pathophysiology of Diabetes and Its Subtypes** 1534
RM Anjana, V Mohan

3. **Lifestyle Management in Diabetes** 1541
L Sreenivasamurthy

4. **Type 2 Diabetes Remission** 1546
Shashank R Joshi, L Sreenivasamurthy

5. **Oral Antidiabetic Drugs** 1551
Vijay Panikar, Pooja Upasani

6. **Insulin** 1556
Anil Bhoraskar

7. **In-hospital Management of Diabetes Mellitus** 1563
Jimit Vadgama, Vijay Panikar

8. **Acute Complications of Diabetes Mellitus (Hypoglycemia, DKA, HHS, and Lactic Acidosis)** 1573
Jimit Vadgama, Piyush Desai

9. **Microvascular Complications of Diabetes Mellitus** 1591
Sunil Gupta, Jimit Vadgama, Dakshata Padhye

10. **Diabetic Foot with Indian Perspectives** 1597
Reshma Mirshad, Vijay Viswanathan

11. **Management of Preexisting Diabetes and Gestational Diabetes Mellitus during Pregnancy** 1604
Rajeev Chawla, Shalini Jaggi

12. **Macrovascular Complications of Diabetes Mellitus** 1607
Anushka Deogoankar, Narayan Deogoankar

13. **Primary Prevention of Type 2 Diabetes Mellitus** 1611
A Ramachandran, Priscilla Susairaj, Arun Nanditha

SECTION 12: METABOLISM

Section Editor: Soumitra Ghosh

1. **Lipoprotein Metabolism and Its Relevance to Indian Population** 1619
Vinod Vijan

2. **Clinical Approach to Obesity** 1631
Soumitra Ghosh

3. **Contemporary Obesity Management: An Update** 1640
Shashank R Joshi

4. **Disorders of Iron Metabolism and Iron Overload Syndromes** 1646
Sudhir Mehta

5. **Porphyrias** 1659
Dhanpat Kumar Kochar

6. **Wilson's Disease: An Update** 1667
Vivek Hande, Priyank Dhiman, Manasvi Kalra, Neel Kanth Issar

SECTION 13: RHEUMATOLOGY

Section Editor: Milind Y Nadkar

1. **Basic Considerations of Rheumatology** 1675
Puneet Mashru

2. **Soft-tissue Rheumatism and Regional Rheumatic Pain Syndromes** 1682
Ved Chaturvedi

3. **Approach to Polyarthritis** 1688
Udas Chandra Ghosh, Abhinaba Datta

4. **Gout and Other Crystal Arthritides** 1694
URK Rao

5. **Rheumatoid Arthritis** 1703
Rohini Handa, Air Marshal Shankar Subramanian

6. **Spondyloarthritis** 1717
Milind Y Nadkar

7. **Sjögren's Disease** 1727
Harshwardhan Patil, Mahabaleshwar Mamadapur

8. **Systemic Lupus Erythematosus** 1738
Vikram Londhey

9. **Systemic Sclerosis** 1744
Renu Saigal

10. **The Vasculitides** 1754
Aman Sharma

11. **Mixed Connective Tissue Disease and Overlap Syndromes** 1767
G Narsimulu, Rajendra Vara Prasad

SECTION 14: HEMATOLOGY

Section Editor: Balkrishna Padate

1. **Approach to Anemia and Polycythemia** 1775
Abhay A Bhave, Shreya Agrawal

2. **Approach to Bleeding and Thrombosis** 1788
Priyanka Shah

3. **Nutritional Anemia** 1795
SM Sapatnekar

4. **Hemolytic Anemias** 1802
Samiksha Singh, Abhishek Bhattacharya

5. **Aplastic Anemia** 1819
Balkrishna Padate, Digambar Panchal, Nazreen Desai

6. **Acute Myeloid Leukemia** 1823
Abhishek Bhattacharya

7. **Chronic Myeloid Leukemia** 1831
Mohan Menon

8. **Chronic Lymphocytic Leukemia** 1838
Mohan Menon

9. **Lymphoid Neoplasms** 1846
Mohan Menon

10. **Plasma Cell Disorders** 1860
Abhishek Bhattacharya

11. **Myelodysplastic Syndrome** 1869
Balkrishna Padate, Digambar Panchal, Nazreen Desai

12. **Myeloproliferative Neoplasms** 1875
Mohan Menon

13. **Bone Marrow Transplant** 1883
Balkrishna Padate, Digambar Panchal, Nazreen Desai

14. **Chimeric Antigen Receptor T-cell Therapy** 1888
Balkrishna Padate, Digambar Panchal, Nazreen Desai

SECTION 15: NEPHROLOGY

Section Editor: Vivek Kute

1. **Kidney: Structure and Function and Basic Renal Pathology** 1895
Rushi Deshpande

2. **Kidney Disease: A Clinical Approach** 1905
Vijay Kher

3. **Acute Kidney Injury** 1914
Smita Divyaveer, Vivekanand Jha

4. **Chronic Kidney Disease** 1927
Vivek Kute

5. **Glomerular Diseases** 1939
OP Kalra, Arunkumar Subbiah, Sandeep Mahajan

6. **Infections of Kidney and Urinary Tract** 1950
LH Suratkal, Juhi Bhargava

7. **Acute Tubulointerstitial Nephritis** 1959
Manisha Sahay

8. **Inherited Kidney Diseases (Including Polycystic Kidney Disease)** 1967
Richard Savio Fernandes Almeida, Alan Fernandes Almeida

9. **Hemodialysis and Other Extracorporeal Therapies** 1982
Arun Babulal Shah, Wasiyeeullah Shaikh

10. **Kidney Transplantation** 1989
Khushboo Saxena, Vivek Kute, Manish R Balwani

SECTION 16: SPECIAL TOPICS

Section Editor: Munish Prabhakar

PART 1: Toxicology

1. **Clinical Toxicology** 2001
Sandeep Garg, Bhvika Zutshi

2. **Snakebite** 2009
V Palaniappan, Subramanian Senthilkumaran

3. **Scorpion Sting** 2019
Himmatrao S Bawaskar

4. **Epidemic Dropsy** 2030
Partha Karmakar

PART 2: Psychiatric Medicine

5. **Assessment in Clinical Psychiatry** 2036
Shubhangi R Parkar

6. **Substance Use Disorders** 2043
Bharat R Shah

7. **Psychosis and Schizophrenia** 2048
Rashmi Joshi Shetty, Harish Shetty

8. **Anxiety Disorders** 2053
Manu Sharma, Jitendra Jeenger

PART 3: Clinical Pharmacology

9. **Drug-induced Disorders** 2064
Shambo Samrat Samajdar, Shatavisa Mukherjee, Santanu K Tripathi

10. **Clinical Applications of Pharmacokinetics and Pharmacodynamics** 2079
Shambo Samrat Samajdar, Noor Husain, Sougata Sarkar

PART 4: Hot Topics

11. **High-altitude Medicine** 2092
Munish Prabhakar, Aashna Gandhi

12. **Nuclear Medicine for Clinicians** 2105
E Prabhu, Sai Supriya Prabhu, T Anusha Chowdary, Pawan

13. **Perioperative Management of Surgical Patients** 2116
Mangesh Tiwaskar, Shilpa Tiwaskar

14. **Organ Transplantation in India: Progress, Challenges, and Ethical Frontiers** 2133
Ashok K Taneja, Vivekanshu Verma, Promod Kohli, Akshat Taneja, Awadhesh Kumar Dubey

15. **Disorders of Elderly** 2150
Yadati Sathyanarayana Raju

16. **Yoga and Medicine** 2156
Shambo Samrat Samajdar

17. **Artificial Intelligence in Medicine** 2163
Aniruddha Sapatnekar, SM Sapatnekar

18. **Chronomedicine: Harnessing Time for Precision Health** 2167
Narsingh Verma, Shivam Verma, Abhinav Verma

Index 2171

CHAPTER

10

Resistant Hypertension

KK Pareek, Girish Mathur, GD Ramchandani

JAYPEE BROTHERS

INTRODUCTION

Hypertension is a well-known risk factor for the development of cardiovascular (CV) diseases, MI, stroke, and end-stage kidney diseases. In spite of the best efforts to increase awareness and treatment for hypertension in the population, there is evidence for poorly controlled rates of hypertension worldwide.

Last few years have seen an impressive paucity of innovative studies and research on new antihypertensive drugs and therapeutic targets which are growing dramatically and may also be useful in future for the management of resistant hypertension (RHTN).

True resistant hypertension (TRH) can be defined as systolic blood pressure (SBP) or diastolic blood pressure (DBP) that remains ≥140 mm Hg or ≥90 mm Hg, respectively, despite appropriate use of lifestyle measures and use of optimal or maximally tolerated doses of a three-drug combination comprising either an angiotensin-converting enzyme inhibitor or an angiotensin receptor blocker, a calcium channel blocker and a thiazide/thiazide-like diuretic (ESH guidelines).

Patients taking four or more drugs to maintain blood pressure (BP) < 140/90 mm Hg are termed as *controlled resistant hypertension*. Refractory hypertension (RfH) can be defined as uncontrolled BP despite five or more drugs of different classes, including a diuretic shown in **Figure 1**.

PREVALENCE

Establishing the exact prevalence of RH is challenging. After strictly applying the European Society of Cardiology (ESC)-2024 definition of RH, a reasonable estimate of disease prevalence could be around 5% of the overall population with hypertension.

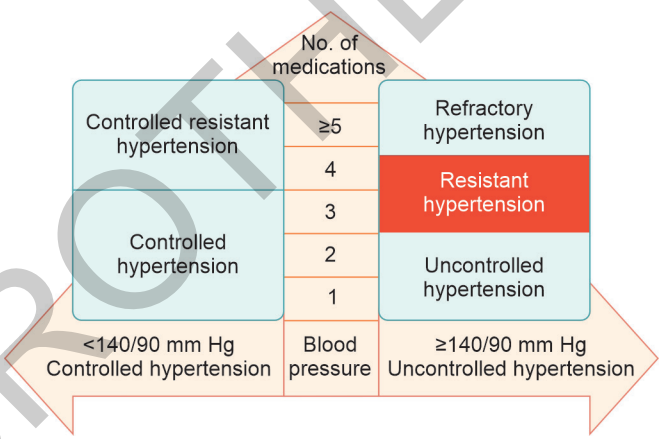


FIG. 1: Hypertension classification based on blood pressure control and number of antihypertensive medications (number of medications).

Source: Sheppard JP, Martin U, McManus RJ. Diagnosis and management of resistant hypertension. Heart. 2017;103:1295-302.

HOW TO APPROACH (DIAGNOSIS BY EXCLUSION) (FIG. 2)

Most of the time uncontrolled hypertensive patients are not truly resistant to antihypertensive drugs and results from the factors which maintain high BP independent of prescribed pharmacological treatment are termed as *apparent resistant hypertension* (pseudoresistance).

The AHA/ACC and ESC suggest that ABPM should be mandatory before diagnosing a patient of RH to rule out white coat hypertension. Many studies support the use of home BP monitoring (HBPM) six times a day including night time BP and early morning BP, which has been shown to have good correlation with ambulatory BP monitoring (ABPM).

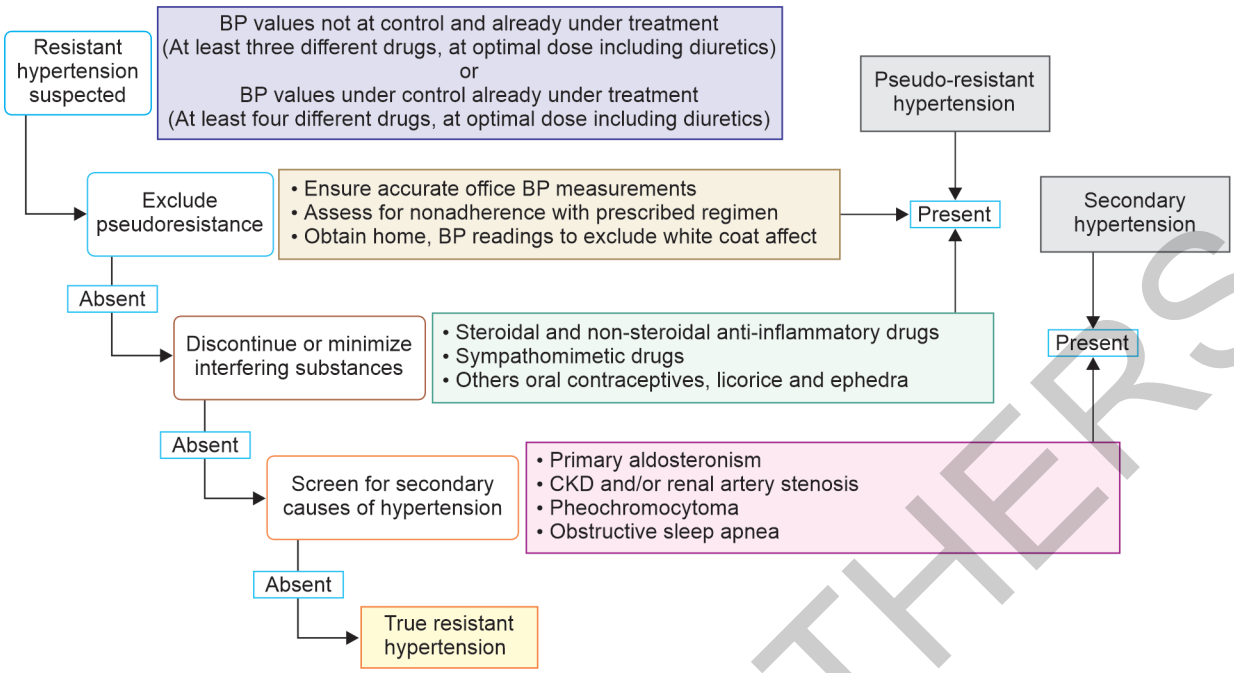


FIG. 2: How to approach resistant hypertension (diagnosis by exclusion).

Causes of pseudo-RHTN are:

- Inaccurate BP measurement
- The *white coat HT*, where in-office BP is persistently elevated but out-of-office BP is at target level (less target organ damage than TRH, detected by home or ambulatory BP monitoring)
- Clinical inertia—not adequately treat a condition despite knowing that it is present
- Nonadherence and noncompliance to medications (polypharmacy, complexity of the regimen, issues of cost, and side effects of drugs)
- Not adopting lifestyle modifications (LSMs)

Discontinue or minimize interfering substances such as NSAID, COX-2 inhibitors, oral contraceptives, corticosteroids, tricyclic antidepressant, monoamine oxidase inhibitor, and illicit drugs (cocaine, alcohol, and caffeine).

Rule out secondary causes of resistant hypertension: Secondary causes account for 5–10% of hypertension cases, particularly primary aldosteronism and atherosclerotic renal artery stenosis **(Table 1)**.

TABLE 1: Causes of secondary hypertension.

Renal	Endocrine	Others
• Chronic kidney disease • Renal artery stenosis	• Primary Hyperaldosteronism • Cushing's syndrome • Pheochromocytoma • Hypothyroidism • Hyperparathyroidism • Acromegaly	• Obstructive sleep apnea • Drugs (alcohol, hormone replacement therapy, anabolic steroids, and NSAIDs) • Coarctation of aorta • Pregnancy related

PATHOPHYSIOLOGY OF RESISTANT HYPERTENSION

The pathophysiology of resistance hypertension involves an interplay between increased sympathetic activity and levels of aldosterone causing fluid retention and sodium overload contributing to increased peripheral vascular resistance, arterial stiffness, and HMOD occurrence. Environmental factors, physical inactivity, and recurrent hypoxia occurring in patients with OSA may also contribute to the increased risk of RH. Patients having older age, female sex, excessive salt ingestion, LVH, high base line blood pleasure, obesity, diabetes, chronic kidney disease (CKD), and black race are at higher risk of developing RH **(Fig. 3)**.

CURRENT THERAPIES FOR RESISTANT HYPERTENSION

Lifestyle Modification

Lifestyle modification is base line therapy for treatment of any hypertensive patients. These measures include weight reduction, a low sodium diet, consuming a diet rich in fruits and vegetables, and low-fat dairy products with less saturated fat and total fat, smoking cessation, alcohol and caffeine limitations, increased regular physical activity, and good night sleep. Drugs that can

JAYPEE BROTHERS

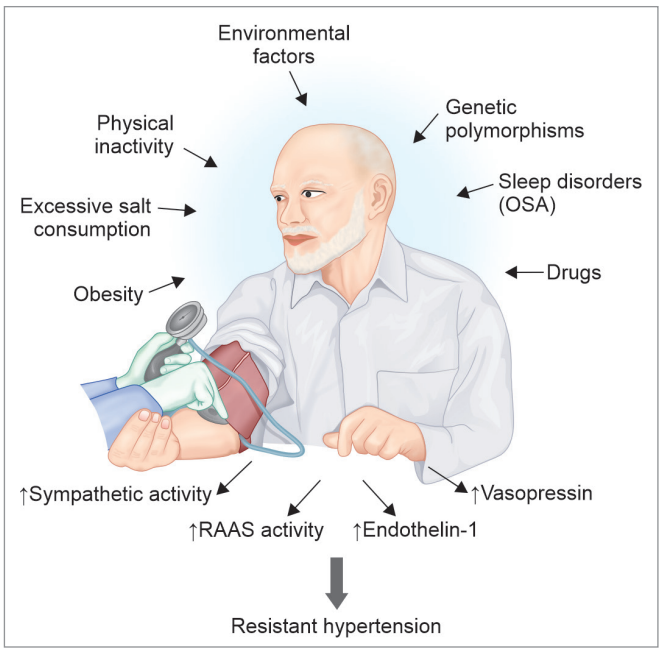
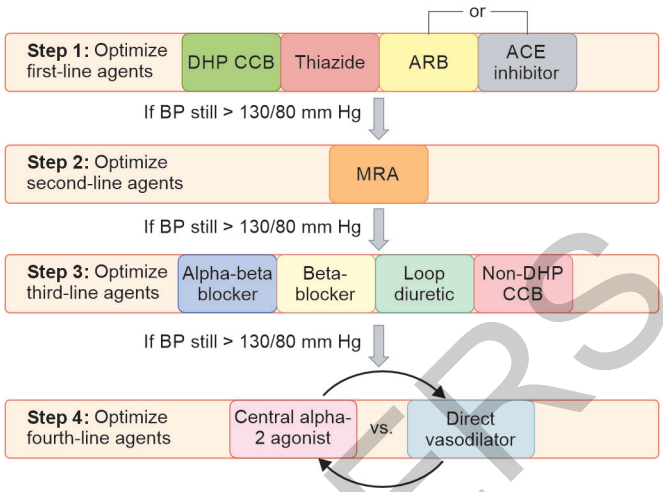


FIG. 3: Pathophysiology of resistant hypertension.



FLOWCHART 1: Pharmacologic management of resistant hypertension.

increase BP are nonsteroidal anti-inflammatory drugs, glucocorticoids, and sympathomimetics. Reducing stress by yoga and meditation besides reducing exposure to air pollution and cold temperature are also important in lifestyle management and all put together can reduce 20–55 mm Hg SBP.

Principles of Pharmacotherapy

The initial three-drug regimen according to the National Institute for Health and Care Excellence (NICE) is a standardized therapeutic scheme which includes combinations of ACE inhibitor/ARB, CCB, and diuretics (A + C + B) including along acting thiazide for RH.

Combinations have to be individualized based on patients' comorbidities, prior medications intolerances, and financial considerations.

These agents are available in various dual or triple pill combinations [single-pill combination (SPC)] allowing simple regimens, reduction in pill burden, and lesser cost.

The inclusion of mineralocorticoid receptor antagonist (MRA) is recommended as fourth-line therapy. This recommendation is primarily supported by findings from the PATHWAY-2 study, which was a substantial, multicenter, randomized double-blind, placebo-controlled, and crossover trial.

The third substudy of PATHWAY-2 assessed the antihypertensive effect of *amiloride* as an alternative to spironolactone suggesting that amiloride can be as effective as spironolactone as a fourth medication in treating RHTN.

If BP remains uncontrolled even after the four-drug regimen, than fifth or sixth drugs options are beta-blockers (preferably those with a vasodilating effect, such as carvedilol, bisoprolol, or nebivolol), central alpha-1 agonists (clonidine or doxazosin), and direct vasodilators (hydralazine or minoxidil) **(Flowchart 1)**.

Eplerenone seems to possess a better safety profile than spironolactone and, thus, it might be an alternative to the latter. However, hyperkalemia is an adverse effect of mineral-corticoid receptor antagonists that should be considered in patients treated with these drugs. The recent Chlorthalidone in Chronic Kidney Disease (CLICK) trial demonstrated that thiazide-like diuretics are a viable option for persons with advanced CKD.

In stage 4 and 5 CKD, thiazide diuretics can also be administered in conjunction with loop diuretics. It has been believed that chlorthalidone is more effective than hydrochlorothiazide, especially when it comes to treating RH.

Finerenone

With just a slight impact on office BP, finerenone, a novel selective third-generation nonsteroidal MRA, has been demonstrated to both slow the course of CKD and lower the risk of CV events in patients with both CKD and T2D. The recently released phase 3 Finerenone in Reducing Cardiovascular Mortality and Morbidity in Diabetic Kidney Disease (FIGARO-DKD) experiment further supported these findings.

Recently a large trial, Fine-ARTS trial was published which explored the role of finerenone in patients with heart failure (HF) with preserved ejection fraction (HFpEF). The benefit was driven by reduction in HHF with a modest mortality reduction. Considering that HT is an important contributor to HFpEF, the use of finerenone in HT becomes promising. When compared to a placebo, finerenone decreased 24 hours, daytime, and nighttime SBP, according to the ARTS-DN ABPM substudy. Even though finerenone had a brief half-life, its effects on SBP persisted over 24 hours. SBP dropped between 8 and 11 mm Hg with 10–20 mg doses of finerenone in T2D and

JAYPEE BROTHERS

CKD. Finally it looks that finerenone is another game changer after sodium-glucose cotrasporter-2 (SGLT-2) inhibitor in DKD/CKD because of its ability to reduces CV mortality by 14%, HHF by 22%, decline in eGFR by 23%, and dialysis by 20%.

Sodium-glucose Cotrasporter-2 Inhibitors

Several meta-analyses have confirmed that the ability of SGLT-2 inhibitors to reduce BP in patients with T2DM is a class effect. Inhibition of SGLT-2 causes natriuresis in addition to the osmotic diuretic effect due to the resulting glycosuria.

The EMPA-REG BP trial in patients with T2DM and hypertension, empagliflozin reduced mean daytime SBP, 24-hour SBP and office SBP by –9.5, –7.7, and –8.6 mm Hg, respectively, compared to placebo. SGLT-2 inhibitors also reduce HbA1c, albuminuria, eGFR, and office BP and suppress sodium overload during daytime to reduce night time BP and albuminuria. There are likely to be multiple renal, metabolic and vascular mechanisms for these beneficial BP effects. In future SGLT-2 may prove to be an important molecule for the use in patients with resistant hypertension. The cardiorenal protection from SGLT-2 inhibitors is significant and these drugs are becoming part of standardized care.

NEW AGENTS UNDER INVESTIGATION

Baxdrostat

Baxdrostat is an aldosterone synthetase inhibitor. In multiple preclinical studies, baxdrostat lowered aldosterone levels without affecting cortisol levels. Two studies investigated the role of baxdrostat and its effect on BP reduction in the RH population. In the phase 2 multicenter, placebo-controlled study of BrigHTN, patients with BP of 130/80 mm Hg or higher and receiving at least three stable doses of antihypertensives including a diuretic were randomized to receive baxdrostat (0.5 mg, 1 mg, and 2 mg) or placebo for 12 weeks. Results from the study of 248 patients showed dose-dependent changes in SBP of –20.3 mm Hg, –17.5 mm Hg, –12.1 mm Hg, and –9.4 mm Hg that were observed in the 2 mg, 1 mg, 0.5 mg, and placebo groups, respectively.

Doses of 2 mg and 1 mg produced a significant reduction in BP. This was accompanied by reduction in aldosterone levels and compensatory rise in renin activity.

Importantly, serum cortisol levels did not change, indicating selective inhibition of aldosterone production. Currently, a new large trial, Bax-HT9 is under way, enrolling patients with uncontrolled HT on two drugs or RHT on three or more drugs, one of which must be a diuretic in both the arms. It is likely to report in 2025.

The combination of baxdrostat and a MRA should be avoided, because that combination would greatly increase the risk of severe hypoaldosteronism.

Aprocitentan (Dual Endothelin Antagonist)

In the PRECISION study, a multicenter, blinded, randomized, parallel group phase 3 investigation, participants from 193 sites in 22 countries assessed the impact of dual endothelin antagonist aprocitentan on BP in patients with resistant hypertension. In the context of RH, the study showed that aprocitentan significantly reduced SBP and DBP when added to a standardized antihypertensive regimen. Additionally, the improvement persisted for 48 weeks. In addition to lowering BP, aprocitentan significantly decreased proteinuria in part 1 of the research, with reductions of 28% and 31% at doses of 12.5 mg and 25 mg, respectively.

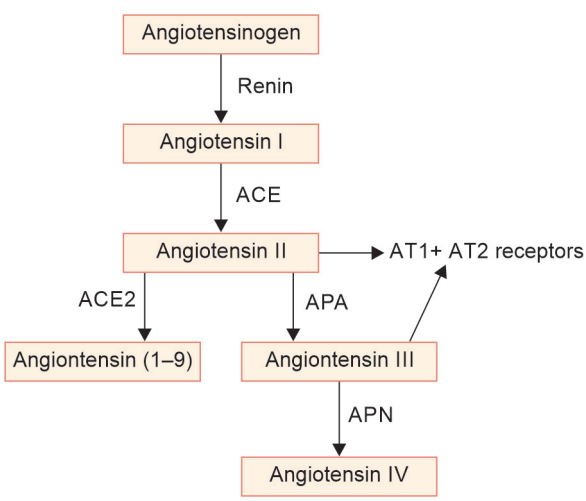
However, aprocitentan resulted in fluid retention in some patients, which could be a concern in patients with HF or renal diseases. Further investigations into the role of this class of drugs are continuing.

Firibastat

Firibastat is the first-in-class centrally acting APA inhibitor prodrug. Pharmacologically, it prevents the conversion of angiotensin-II to angiotensin-III, one of the main effector peptides of the brain RAS which exerts central stimulatory regulation over BP. Firibastat may be potential alternative therapy in the management of very high-risk patients with difficult-to-treat or resistant hypertension **(Flowchart 2)**.

Angiotensin Receptor-neprilysin Inhibitors and Hypertension

In hypertension, due to RAAS activity there is salt and water retention, vasoconstriction, sympathetic activation, and CV remodeling. These changes contribute to resistant hypertension and more over to the development of nocturnal hypertension and blunting of normal nocturnal BP dipping.



FLOWCHART 2: Conversion of angiotensin-II to angiotensin-III.

JAYPEE BROTHERS

Angiotensin receptor-neprilysin inhibitor (ARNI) is now a well-established drug for the treatment of HF, but was originally developed as a treatment for HT. In fact, the first trial assessing its efficacy in the management of HT was published well before the landmark PARADIGM trial for heart failure with reduced ejection fraction (HFrEF).

Neprilysin inhibition limits breakdown of these peptides resulting in natriuresis, vasodilatation and reduced sympathetic tone; these effects lower BP. Neprilysin inhibitors lower BP, arterial stiffness, cardiac hypertrophy, and fibrosis when used in conjunction with RAAS blocking **(Flowchart 3)**.

Sacubitril/valsartan (LCZ696) dual ARNI is the first-in-class ARNI, consisting of the ARB valsartan and the neprilysin inhibitor.

It is reasonable to foresee that sacubitril/valsartan will be increasingly used in the future not only in HF, but also for improving BP control, particularly in patients with RH. Till now not included in guidelines but looks that stage is all set for a growing role of this drug in the treatment of resistant hypertension.

Zilebesiran

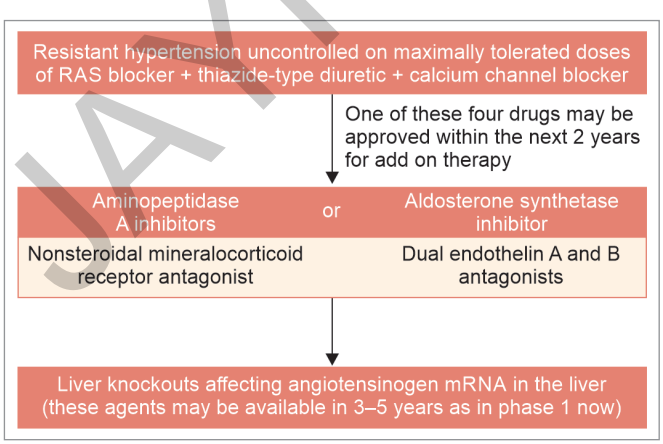
The KARDIA-3 will provide efficacy and safety data on zilebesiran in patients with or at high risk of developing CV disease, including those with the common comorbidity of advanced CKD.

This is the first phase 2 trial of a RNA interference therapeutic targeting angiotensinogen (AGT) in patients with inadequately controlled hypertension who are at high CV risk, which addresses a population with high unmet need.

This global trial is ongoing; the first patient was enrolled in KARDIA-3 in April 2024.

Lorundrostat

Aldosterone synthase inhibition for uncontrolled hypertension (the Target-HTN randomized clinical trial), among individuals with uncontrolled hypertension, use of lorundrostat was effective at lowering BP compared with placebo, which will require further confirmatory studies.



FLOWCHART 3: Recent pharmacotherapy for RH.

Continuous Positive Airway Pressure

Although the benefits in BP reduction with continuous positive airway pressure (CPAP) in resistant hypertension with moderate to severe sleep apnea are not well established, CPAP is indicated as an adjuvant treatment, >4 hours per night, improving the quality of life, and probably reestablishing the dipper pattern of night time BP.

DEVICE-BASED THERAPIES

Baroreceptor activation technique has been studied in RfH patients. The Rheos Pivotal Trial did not identify long-term benefits.

Creation of a Central Iliac Arteriovenous Anastomosis

The ROX Medical arteriovenous coupler is a stent-like device that exhibits shape memory to self-expand, forming an AV anastomosis in central iliac. The magnitude of office BP reduction seen after 6 month follow-up was greater than reported after the use of renal denervation in TRH and also the use of spironolactone as a fourth antihypertensive drug strategy for TRH.

Catheter-based Renal Sympathetic Denervation

Although the momentum for device-based therapy to treat hypertension dampened after the results of SYMPLICITY HTN-3 in 2015, a new impetus for renal denervation has emerged, given more recent data showing modest but significant BP lowering in selected populations using an updated and more perfected catheter and procedure as shown in the recent studies such as RADIANCE HTN SOLO and REQUIRED and SPYRAL HTN-ON MED and OFF MED showed the promising result of RDN, and the practice is rejuvenated with availability newer SPYRAL catheter by Medtronic **(Fig. 4 and Table 2)**.

ULTRASOUND RENAL DENERVATION: THE RANDOMIZED SHAM CONTROLLED RADIANCE-HTN TRIO TRIAL

RADIANCE-HTN TRIO trial concluded in the study that in patients with hypertension resistant to guideline-recommended triple combination therapy in a single pill, ultrasound based RDN was associated with a reduction of 8.0 mm Hg in daytime ambulatory SBP (4.5 mm Hg greater decrease than a sham procedure).

JAYPEE BROTHERS

The greater BP lowering effect of RDN versus sham was consistent for 24 hours, night time, and office SBP. These results in concordance with those of RADIANCE-HTN SOLO (patients with mild-to-moderate hypertension), confirming that ultrasound RDN can lower BP across a spectrum of hypertension. Longer-term assessments for efficacy and safety are ongoing.

In conclusion, renal artery denervation has the potential to be adopted in clinical practice over the next few years.

The RDN was approved by the United States FDA in late 2023 for the reduction of BP in patients with uncontrolled hypertension despite the use of antihypertensive medications or in patients who have documented intolerance to antihypertensive medications. Further work in the field is needed to determine optimal patient selection as well as the long-term benefits and safety risks.

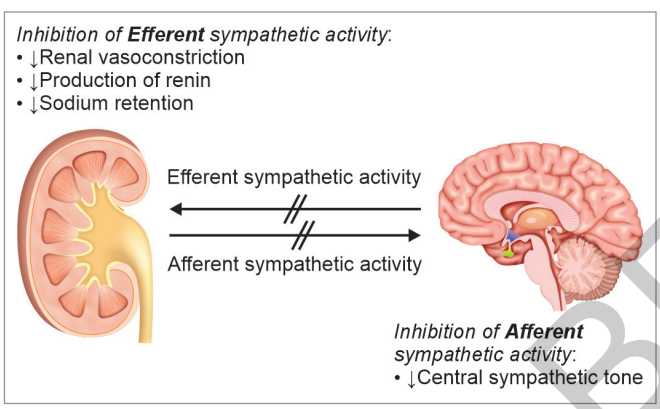


FIG. 4: The main effects of inhibition of afferent and efferent sympathetic activity induced by renal denervation.

There are new recommendations (ESC CONGRESS 2024) for managing specific patient groups. Catheter-based renal denervation may be considered for patients with RH and who express a preference to undergo renal denervation after a shared risk-benefit discussion and multidisciplinary assessment, and if performed at a medium-to-high volume center.

PRECISION MEDICINE AND HYPERTENSION—HAS THE TIME COME?

It is known that hypertension is primarily a polygenic disease strongly influenced by behavioral and environmental factors. Advances in the genomics and information technology will be of great help for more precise treatment of hypertension. Precision medicine includes individual patient variables, including environment, genetics, clinical, and behavioral factors, to guide treatment decisions.

Patients can be classified into following subgroups which differ in susceptibility to disease biology/prognosis of disease, and response to treatment.

- Optimization of medical treatment based on the individual characteristics of each patients
- Genetics (susceptibility and response to therapy pharmacogenomics)
- Environmental factors
- Behavioral factors
- Clinical variables

The future role of Al in arterial hypertension is given in **Table 3**.

TABLE 2: Recent renal denervation studies.

Human trials	Experimental design	Catheter type, ablations per renal artery	BP primary end point, duration	Change in office SBP/DBP
INSPIRED 2017	RCT	EnligHTN; multielectrode	Systolic AMBP	RDN (n = 9) −22/−13 mm Hg[†]
	Control-drug alone	11 ablations	6 months	Drug alone (n = 6) +1/0 mm Hg
	No change in medication			
SPYRAL HTN-OFF MED 2018	RCT	Spyral; multielectrode	AMBP	RDN (n = 37) −10/−5 mm Hg[†]
	Single-blind, sham-control	20 ablations including proximal branches	3 months	Sham (n = 41) −2/0 mm Hg
	Off medication			
SPYRAL HTN-ON MED 2018	RCT	Spyral; multielectrode	AMBP	RDN (n = 40) −10/−5 mm Hg[†]
	Single-blind, sham-control	20 ablations including proximal branches	6 months	Sham (n = 42) −3/−2 mm Hg
	On medication			
Radiance-HTN SOLO 2018	RCT	Paradise; multielectrode	Day-time AMBP	RDN (n = 74) −11/−6 mm Hg[†]
	Single-blind, sham-control	5.4 emissions	2 months	Sham (n = 72) −4/−1 mm Hg
	On medication			

[†] Controlled resistant hypertension: Blood pressure <140/90 mm Hg achieved with ≥4 drugs, including a diuretic.

JAYPEE BROTHERS

TABLE 3: AI in hypertension.

Applications		Benefits
Measuring BP	Estimate BP by analyzing PPG signal with ML and DL algorithms	Self-monitoring BP for hypertension
Predicting AH development	Predict the risk of developing AH by using genetics, medical data, and behavioral, environmental, and socioeconomic factors	Timely intervention
Diagnosing AH	Accurately diagnosing AH by using CV risk factors, anthropometric data, vital signs, and laboratory data	Precision diagnosis
Predicting AH treatment success	Identify factors contributing to treatment success	Personalized treatment plan
Predicting AH prognosis	Stratify patients and predict CV outcomes	Treatment plan adjustment

CONCLUSION

We all know that BP is a very potent risk factor for CV disease, renal outcomes, and cost burden to the society. True RH is less prevalent, and most RH can be attributed to apparent RH with medication adherence being the major barrier. Rule out secondary causes of hypertension before labeling a patient with RH. Clinicians should follow a standardized approach to therapy as discussed earlier to meet individualized BP goals.

The exact guidelines for a proper BP measurement in clinical practice are frequently not followed, and BP recording is nonetheless generally obtrusive. Due to the large amplitude of the white coat effect, ABPM is required for both the diagnosis and follow-up of RH. The inclusion of new medicines, such SGLT-2 inhibitors and ARNIs, in hypertension guidelines is currently hindered by the lack of clinical trials examining their major BP endpoints. Future clinical management of hypertension may be completely transformed by the use of genetic and molecular technology, which could bring about a new era of focused and personalized therapy.

RECOMMENDED READINGS

1. Carey RM, Calhoun DA, Bakris GL, et al. Resistant hypertension: detection, evaluation, and management: a scientific statement from the American Heart Association. Hypertension. 2018;72(5):e53-90.
2. Fay KS, Cohen DL. Resistant hypertension in people with CKD: a review. Am J Kidney Dis. 2021;77(1):110-21.
3. Brambilla G, Bombelli M, Seravalle G, et al. Prevalence and clinical characteristics of patients with true resistant hypertension in central and Eastern Europe: data from the BP-CARE study. J Hypertens. 2013;31(10):2018-24.
4. Weitzman D, Chodick G, Shalev V, et al. Prevalence and factors associated with resistant hypertension in a large health maintenance organization in Israel. Hypertension. 2014;64(3):501-7.
5. Muntner P, Anderson A, Charleston J, et al. Hypertension awareness, treatment, and control in adults with CKD: results from the Chronic Renal Insufficiency Cohort (CRIC) Study. Am J Kidney Dis. 2010;55(3):441-51.
6. Salles GF, Cardoso CR, Muxfeldt ES. Prognostic influence of office and ambulatory blood pressures in resistant hypertension. Arch Intern Med. 2008;168(21):2340-6.

JAYPEE BROTHERS

for detailed information on medicine books, visit our website www.ejaypee.com, for detailed information on medicine books, visit our website www.ejaypee.com, for detailed information

API Textbook of MEDICINE



Shelving Recommendation
MEDICINE

ISBN 978-93-6616-583-7
9 789366 165837

Buy from ejaypee

JAYPEE BROTHERS