Issue - 1

INDIAN ACADEMY OF PEDIATRICS

BENGALURU

PEDISCAN

MONTHLY NEWSLETTER OF

IAP BENGALURU

January 2024

CONTENTS

Message from The President

Dear IAP Members and Friends,

We extend our warm greetings for the new year 2024.

To all of my Guru's, Mentors, Colleagues, and friends, I extend my humble Pranams and greetings for the New Year&MakaraSankranthi. With deep gratitude to everyone, our team 2024 is prepared to take on the responsibilities of this fantastic year.

Our beloved Dr. Basavaraj person of Pan India attractiveness is taking over as CIAP president this year and it is a proud moment for all of us. He is recognized for his dynamic nature and has shown real leadership by embracing everyone and fostering their growth. IAP has commenced operations on a nationwide scale in India from January 1st 2024. I am certain that throughout his tenure, he would elevate it to a global level in the field of Pediatric academics.

This year has been of immense significance for us. Dr. Shivananda, renowned as 'The teacher of teachers' has been officially honored with a prestigious lifetime achievement award by the central IAP.

The fact that our senior members who are the pillars of the organization of IAP Bengaluru have achieved major positions is a source of pride and encouragement. Dr. Jagadish Chinappa Advisor for AI programme under presidential action plan 2024, Dr. Gnanamurthy Chief National co ordinator under presidential action plan 2024, Dr. Ravishankar Chief election commissioner CIAP, Dr. Nandish Joint national co ordinator under IAP presidential action plan 2024, Dr. Sumitha Nayak National scientific co ordinator & vaccination programme under presidential action plan 2024, Dr. Shiva Prakash Sosale Co ordinator for fever module under presidential action 2024, Dr. Geeta Patil elected as the new Chairman of the AHA, Dr. Bhaskar Shenoy elected as the Chairman of the National ID chapter, Dr. Kalappanavar as President of the IAP Respiratory Chapter.

Dr. Srinivas, former president of the Indian Academy of Pediatrics (IAP), elected as the President of the State Indian Medical Association (IMA). Dr. Karunakara B P former president of IAP, elected as the secretary of IMA. Additionally, IAP Constitutional expert and IAP KSB Vice President Dr. Nandeesh has been honored with the FIAP 2024 award.

I am delighted that we have a multitude of programs to accomplish. First priority of the team is to execute all the CIAP president Dr. Basavraj's action plan and carry out all the initiatives.

This year 2024, our teams action plan is to introduce research methodology for undergraduates and to initiate small student research projects and training Postgraduates towards New CBME curriculum, orientation towards Research, Paper publication, Statistics and exam preparedness along with routine postgraduate programs.

In light of the increasing prevalence of medico-legal concerns, it is imperative that we get a deeper understanding of legal protection. Additionally, it is essential to establish an internal team that can provide help and support during times of crisis and regarding the same our plan is to conduct small workshops and CMEs on documentation and medico-legal issues.

Adolescent issues, particularly increasing suicidal tendencies are on the rise. We must develop a well-devised strategy to deal with this problem and carry out various initiatives. Our plan of action is to establish a crisis management and counseling team for teenagers and to create a helpline.

Digital attractions and addictions are arising with related negative repercussions ranging from academic backwardness to behavioral problems; It's time for us to begin focusing on this issue in our office practice with a thorough scientific approach.

Given our extensive experience in COVID-19 epidemic, it is imperative that we form an emergency preparedness team to lead the crisis specially during epidemics.

Team 2023 under the leadership of Dr Prasad have accomplished an exceptional academic benchmark.

We are fortunate to have the guidance of highly respected advisors like Dr. Vasudev Dhananjay, Dr. Shantharaj, Historian Dr. Kishore Baindur, Dr. Geeta Patil, and Dr. Ravishankar, all of whom have served as presidents of IAP Bengaluru in the past.

Our secretary, Dr. Chidananda N K, and Treasurer, Dr. Harilal Naik, are the indispensable leaders of this team, and their efforts are of immense value.

We are confident that our team will continue to achieve success under the support of Academic Co-ordinator Dr. Raghunath C N, Legal Head Dr. Shivprakash Sosale, Assistant Treasurer Dr. Padmavathi, Digital Head Dr. Ravishankar and Dr. Gowri Somayaji.

Vice Presidents Dr. Nithyananda S K & Dr. Madhu GN, and our joint secretary Dr. Nagalatha S adds great value to the team who are well known for great service.

Dr. Bhaskar Shenoy, Dr. Sharath and Dr Vivek Kustagiare the pillars for both academics and financial strength.

Our President-elect, Dr. Sumitra Nayak, has already assumed all the responsibilities that come along with this team, and she has extended her cooperation.

Dr. Adarsh E, who has extensive expertise as a second-time Executive Board member and Dr. Priya Shivalli who has excelled already in 2022 as Secretary will be coordinating all CIAP initiatives.

My sincere thanks to IAP KSB President Dr. Mothi S N, Secretary Dr. Shashikiran and all the Obs & Ebs of IAP KSB for all the support.

I would like to acknowledge and give special recognition to all our dynamic enthusiastic EB Members: Dr. Abhijith, Dr. Jagadesh, AS, Dr. Keshav Murthy, Dr. Mridula A.M., Dr. Padmavati N, Dr. Pavithra Nagaraj, Dr. Poornima R.N., Dr. Raghu, Dr. Shalini, and Dr. Vivekananda M Kustagi.

My heartfelt thanks go to, Dr. M Venkatachalapathy, Dr. Sanjeev Chetty, Dr. Amaresh K Patilfrom the central EB.

The enthusiastic members of the PEDISCAN team, under the guidance of our own Dr. Sunil Kumar B M, are working to improve the program by integrating case studies, newsletters, reviews, research papers, and current information on all monthly events.

My sincere acknowledgement to our office incharge Mr. Harish for all coordination.

On behalf of Team 2024, we wish you all once again a happy new year and most and more the success and happiness in life.

Dr. Somashekar A R
President, IAP Bengaluru 2024
Professor and Head
Department of Pediatrics
Ramaiah Medical College.

Message from The Secretary

Dear Bengaluru IAPians and fellow Team Members,

I am thrilled to welcome each one of you to a new chapter in our professional journey. Today marks the commencement of a shared vision, and I am honored to stand alongside such a talented and dedicated team.

We are really very fortunate that we have Dr. Basavaraja Sir as the National president this year who will guide us through all the difficulties. Our President Dr. Somashekar Sir has always been very energetic and supportive and we have a seasoned, committed and experienced Treasurer Dr. Harilal who I am sure will sort out many pending financial issues with the help of the seniors and advisors

As we embark on this journey together, let us be mindful of the incredible opportunities that lie ahead. Our success will be driven by collaboration, innovation, and a commitment to excellence. Each one of you plays a crucial role in shaping the future of our mother IAP and I am confident that, as a collective force, we will achieve remarkable feats.

Remember, success is a journey, not a destination. Let us approach our work with enthusiasm, dedication, and a shared commitment to achieving greatness. Our collective efforts will shape the legacy we leave behind.

I am excited about the incredible possibilities that await us. Together, we will write a story of success, growth, and fulfillment.

Thank you for being a part of this remarkable journey.

Best regards,

Dr. Chidananda N K

Secretary, IAP Bengaluru 2023 - 24

Message from The Treasurer

Warm greetings to all the IAP members for the New Year and Makara Sankranti.

It gives immense happiness and pride to communicate to all the IAP members of Bengaluru through the flagship PEDISCAN magazine.

I am hopeful that the new Editorial Team of PEDISCAN led by Dr. Sunil Kumar B.M. will surpass the benchmark set by the previous Editorial teams. I wish the new Editorial team all the success to bring out numerous academic as well as non-academic activities in the year 2024.

I was happy to work as a Treasurer of IAP BPS under our National President Dr. G.V. Basavaraj Sir and Dr. S.M. Prasad Sir. I am looking forward to carry forward the baton successfully under our dynamic President Dr. Somashekar A.R. Sir and the New Team of 2024. I wish that the New Year brings some fresh hopes and aspirations and solve the financial issues IAP Bengaluru is entangled in with the support and cooperation of all the Seniors, Past Presidents, members of Team 2024, and of course all the members of IAP Bengaluru.

Looking forward for all your valuable suggestions and support throughout the year.

Dr. Harilal Naik M L

Treasurer, IAP Bengaluru 2022, 2023, 2024

Message from National IAP President

Greetings from Presidents Desk,

"United for Pediatric Excellence : AMessage from the President CIAP"

Dear Esteemed Members of the IAP Bengaluru Community.

I sincerely congratulate the entire team 2024 lead by Dr. Somashekhar A R, ably supported by Secretary Dr. Chidananda N K and Treasurer Dr. Harilal Naik M L. I also congratulate the President elect Dr Sumitha Nayak, Vice Presidents Dr Nithyanada S K, Dr Madhu G N, Joint Secretary Dr Nagalatha S and Other executive board members and team members of IAP Bengaluru 2024.

Best wishes to PEDISCAN team lead by Dr Sunil Kumar B M, Chief Editor for taking the responsibility of carrying forward the long legacy of excellence.

I am honored to address you as the President of our esteemed CIAP. Together, we form a dynamic community dedicated to the well-being and development of our youngest citizens.

In the face of evolving healthcare scenario, our commitment to pediatric excellence remains unwavering. It is with great pride and a profound sense of responsibility that I took the role of President, and I am eager to collaborate with each and every one of you in fostering positive change and progress.

Our collective efforts have the power to shape the future of pediatric healthcare, education, and research. In the spirit of unity, let us leverage our diverse expertise and experiences to address the unique needs of children and adolescents.

Key areas of focus for the future include :

1. **Education and Training :** The IAP is committed to providing educational opportunities that empower our members with the latest knowledge and skills. Together, we will strive to raise the standard of pediatric care.
2. **Advocacy for Child Health :** Our voice is a powerful advocate for the health and well-being of children. Let us work collaboratively to influence policies and promote initiatives that prioritize the needs of our youngest patients.
3. **Pediatric Research :** We will continue to support and promote groundbreaking research that enhances our understanding of pediatric diseases, treatments, and preventive measures

I invite each of you to actively participate in the various committees, working groups, and initiatives that align with your interests and expertise. Your contributions are vital to the success of our shared mission.

As we embark on this journey together, I am confident that the IAP Bengaluru will continue to be a beacon of excellence, innovation, and compassion. Together, let us make a lasting impact on the health and well-being of the children we serve.

Thank you all for the support I received during my stay in IAP Bengaluru and looking forward to work closely with each of you in the pursuit of pediatric excellence and take CIAP and IAP Bengaluru to new heights. I am Available and eager to serve the mother body which gave me everything.

Jai IAP

Warm regards,

Dr. G V Basavaraja

CIAP President 2024

Message from Secretary General IAP

Dear Esteemed IAPians,

Greetings from the Indian Academy of Pediatrics!!!

It is with great honor and enthusiasm that I extend my warmest greetings to the revered Pediatric Journal committee 'Pediscan' and the esteemed members of the Indian Academy of Pediatrics-Bengaluru. In our collective pursuit of advancing pediatric healthcare under the leadership of our visionary IAP President Dr. G.V. Basavaraja, 'Pediscan' stands as a beacon of knowledge, fostering invaluable discussions and insights into the multifaceted realm of child healthcare and management.

As dedicated pediatricians, researchers, and healthcare professionals, our commitment to nurturing the well-being of children resonates profoundly within these pages.

This esteemed journal not only serves as a platform for scholarly discourse but also embodies our shared dedication to enhancing the quality of care, addressing crucial issues, and continually evolving our understanding of pediatric medicine.

May 'Pediscan' continue to illuminate our path, inspiring innovation, collaboration, and excellence in the realm of child health. I extend my heartfelt appreciation to all contributors for their invaluable contributions and unwavering dedication in advancing the frontiers of pediatric healthcare.

Here's to the continued success and impact of *'Pediscan"* and our collective efforts in shaping a healthier, brighter future for the children under our care.

Warm regards,

Dr. Yogesh Parikh

Secretary - General

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Message from State President

Dear Team IAP- BPS 2024

Greetings from IAP-KSB and all the members of IAP Mysore District Branch.

I wish the new Team under the able leadership of our own popular and dear Dr. Somashekar all the very best…and of course we look forward to lots of academic and service activities during this year. Bangalore PEDICON is the flagship program which all of us look forward to attend.

Since this is the all-important year of Dr. Basavraj being our President at the national level we all need to collectively work to bring out the best we can.

Regards

Dr. Mothi S N

IAP-KSB and IAP Mysore District Branch

Message from State Secretary

Greetings from Mysuru : Karnataka's cultural capital city.

Best wishes on the inaugural edition of Pediscan for the year 2024. IAP BPS (IAP, Bengaluru) has always set new benchmarks in both academics and organisation activities. With every new edition, Pediscan has come out with new innovative ideas and will be eagerly looking forward to this year's editions. I would like to express my sincere admiration for the Editor and contributors of Pediscan for your outstanding efforts. I take this opportunity to congratulate all the esteemed members of IAP Bengaluru for living up to the saying 'Amazing things happen when amazing people get together'.

I once again wish you all a very happy new year, filled with success, happiness and lots of quality academic activities.

Dr. Shashikiran K B

Hon. Secretary, IAP KSB 2024

Message from Chief Editor

From The Desk of Editor :

Dear Bengaluru IAPians,

Greetings from team IAP Bengaluru 2024

It gives me immense pleasure to be a part of this team as the Chief Editor of prestigious monthly Journal and news letter of IAP Bengaluru Pediscan. In the ever-evolving pediatric healthcare, we find ourselves at the forefront of shaping the well-being of the next generation. As pediatricians, we are not merely healthcare providers; we are guardians of the future, entrusted with the responsibility of nurturing resilient, healthy, and happy children.

We explore evidence-based strategies to communicate the significance of preventive care to parents, empowering them to be active partners in their child's health journey. As we look ahead, we see a landscape that continues to evolve, presenting us with new opportunities and challenges. As technological advancements, socio-economic shifts, and global events are shaping the world around us, the need for innovation, collaboration, and a shared sense of purpose has never been more critical.

In the future as we navigate the complexities of pediatric healthcare, collaboration and knowledge-sharing are paramount. We highlight recent advancements in pediatric research, shedding light on emerging trends and innovations that hold promise for the future of child health.

Thank you for your unwavering commitment to the well-being of children. Together, let us continue to champion holistic pediatric care and foster a healthier, happier future for the generations to come.

In this inaugural issue of Pediscan January 2024 Issue 1, I am delighted to share the wisdom of senior faculties from various esteemed institutions and renowned hematologist's insights, research findings, and practical tips that help us in the day to day management and workup of common hematological conditions. Our focus is not only Pediatricians but also post graduate students and fellowship students.

Furthermore, this edition features inspiring news of pediatricians being active in the community-based initiatives, advocating for child health beyond the confines of the clinic. From promoting vaccination drives to leading educational campaigns on childhood asthma, research, publications and scientific talks, these narratives exemplify the profound impact we can have on the well-being of entire communities

In the coming months, we will bring you thought-provoking articles, practical guidelines, and updates on the latest developments in sub specialties. We encourage you to actively participate – share your stories, insights, and feedback. I invite each paediatrician in our community to reflect on the profound privilege and responsibility we carry. Our dedication to nurturing the physical, emotional, and mental health of the next generation is not just a professionalduty—it's a calling that shapes the trajectory of countless lives.

Together, we can find strength in unity and forge a path toward a brighter future.

Regards

Dr. Sunil Kumar B M

Chief Editor, Pediscan

Message from Outgoing President 2023

Dear Senior IAP Members & My Colleagues

It was really my great journey of 12 months as a President, along with team members of IAP Bangalore BPS.

The whole team-2023 consisting of historian, advisors, office bearers, EC members, E B members, Editors, Chairman, conveners and members of monthly CME, PG Teaching, Financial, Legal took the activities of IAP BPS from the day 1 of our memorable year - 2023 to promote all the activities which became physical where we shifted from all virtual meetings and sessions of recent Covid-19 time.

This year was unique to us as follows :

- All the monthly CMEs rolled back to physical with good number of IAP members participating on 3rd Sunday monthly evenings designated specially as "System a month" covering most of the topics useful for Pediatricians where the expert faculty both from national & international delivered then scientific talks.
- Team -2023 Conducted as many CIAP workshops for IAPians as possible at various institutions.
- Able to conduct all the monthly Post Graduate teaching programs as possible on 3rd Sundays who were also as "system a month" so that the Post graduates can get well prepared with particular before they attend the same.
- IAP Bangalore BPS conducted most of the National Programs and WHO programs in various centers by our members in a grand success.
- In fact, this year, we were able to have good number of delegates of more than 840 for the well-known Bangalore Pedicon, a successful 10th year signature program of IAP Bangalore BPS from 9th to 11th June, 2023. It was inaugurated & attended by all the CIAP office bearers. We were also fortunate to have mid-Summer CME of IAP ID chapter (PIDA) to be associated for 10th Bangalore Pedicon. Hope all of our IAPians were comfortable with the popular workshops, scientific sessions, delicious hygienic food & a themed banquet by a doctor first of its kind. Among the workshops, Medico Legal workshop and Developmental workshop was as added feature.
- IAP Bangalore was able to conduct as many as possible "Health Camp a month" at R R Nagar site where all of our EC team took so much interest to participate and I expect more to happen for this year 2024.
- IAP Bangalore was co-host for National Developmental workshop, National Pediatric environment conference, State Endocrinology conference, Neurology update CME, Neonatal CMEs, etc in 2023.
- Also, this year to keep the unity & strength of members working for various activities, team had arranged "a day out" to nearby resort after 10th Bangalore Pedicon. Our members participated sport & fun activities with family members.

Friends, indeed a great year -2023 for me for follow the legacy & guidelines of my past Presidents of IAP Bangalore BPS and to carry out as much as possible. I humbly thank everyone in the team and IAP member who supported in all the activities of the team 2023 to get awarded for First prize by central IAP for overall activities of the IAP branch >1000 members in India. Also, IAP Bangalore is awarded with 6 prizes for different workshops in 2023 by CIAP at National Pedicon 2024.

IAP Bangalore gave me to learn more patience, perseverance, consistency, setting the goals in a

methodical manner. I had a wonderful experience interacting closely with many members during the year.

This year 2024, Team will have more academic programs & many activities, as our CIAP President Dr G V Basavaraja at the helm of affairs at national level. I wish a great journey for the new team IAP Bangalore 2024 headed by young and energetic President Dr A R Somashekar with active Secretary Dr N K Chidananda and very efficient Treasurer Dr M L Harilal Naik with Vice Presidents Dr S K Nithyananda, Dr G N Madhu, Joint Secretary Dr Nagalatha and all the elected EC members of team 2024.

I wish the Chief Editor, PEDISCAN Dr B M Sunil Kumar and his editorial board for informative and colorful monthly signature magazines of IAP BPS which will be rolling out in 2024.

Dr. S M Prasad
Past President - 2023
IAP Bangalore

Message from Guest of Honour

It gives me a great pleasure to pen few words to Pediscan on our IAP Bangalore branch (BPS).

Earlier it started as Bangalore Pediatric Society with few people from Govt. Medical Colleges monthly meetings. Soon private pediatric practitioners joins later followed with private institutions. Lakeside Education Trust is jointly conducting CME's since 41 years with the commitment to Prof. P. C. Bopiah.

BPS was hesitant to join IAP for various reasons in the AGM of 1992,the proposal received only one vote of the proposer Dr. H Paramesh. It took 2 years to convince the people at the helm and during the 1994 IAP conference at Indoor AGM under the discretion of Dr. Y K Ambdekar it was cleared and renamed as "IAP Bangalore Branch (BPS)".

Successive team have put their great efforts in upholding the academic activities with sincerity and commitment.

The old team under the leadership of Prof. S. M. Prasad done a great job and handing over to the new team under the leadership of Prof. A R Somashekar to take it go greater heights with same commitments, sincerity, transparency and humility which I don't have any doubts..

Let the team follow the values of :

- Positive thinking
- Protect Mother Earth
- Pursue research to sustain lives
- Promote our National Ethos Vasudaiva Kutumbakam

Our city branch is one of the most influencial in IAP in organisation, evolution, financial stability and leadership.

Jai Hind Jai IAP

Prof. Dr. H Paramesh

Pediatric Pulmonologist and Environmentalist

Divecha Centre for Climate Change, Indian Institute of Science Blr.

Message from Special Invitees

Congratulation IAP Bangalore Team 2023 lead by Dr. Prasad S M, Dr. Chidanand, Dr. Harilal for excelling on the national level and bringing many laurels for Bangalore!!

It's a great challenge for the incoming team of 2024 with Dr Somashekar at the helm, to work hard and reach that height.

It's a great honour for me to write a message for the Inaugural Edition of Pediscan.

IAP Bangalore has got a rich legacy of academics community work from its inception. I consider myself very honoured to belong to this organisation and have had the opportunity to serve as President of IAP Bangalore in 2017.

I started my journey in IAP Bangalore from 1994 as an EB member .

I was lucky to work under leadership of Dr. Somashekharaiah, Dr. Shivananda, Dr. PP Maiya and Dr. Govindrajalu . All of them and many seniors like Dr. D G Benkappa, Dr. H Paramesh, and Dr. Nisarga taught us, that we excel in our work if we work as a team, without a personal agenda.

IAP Bangalore is a family of like - minded people who toiled for its establishment and growth. We have seen Dr. Gnanmurthy, Dr. Nagabhushana, Dr. S G Kasi, Dr. Jagadish Chinnappa, Dr. Kishore Baindur, Dr. Shantaraj, Dr. Shubha Badami working selflessly for the organization and they should be our role models .

The IAP ian who works in IAP Bangalore sincerely as first grass root worker, will be able to master all the proceedings of conducting conferences , arranging CMEs, learning academics , holding posts in IAP and its subchapters subsequently .

This has been proved by our beloved National President of IAP 2024, Dr. Basavaraja by his work.

Let IAP Bangalore shine on national and international level.

Wish all the best to IAP Bangalore Team 2024 under the leadership of Dr. Somashekar A R

Jai IAP

Dr. Geeta Patil

Past President IAP Bangalore 2017

Chairperson AHA 2024

Message from Special Invitees

My Dear Seniors and Friends,

Greetings from Central ID chapter!

It is my honour and privilege to be a part of this August organisation. IAP Bangalore has a rich tradition and history with several stalwarts have been leading the branch from the front. The branch is known across the country for its academic excellence and social work. Our branch has given two IAP national Presidents (our state has given three).2024 has a special year for all of us when our beloved Dr Basavaraja G V is at the helm of affairs as national President of IAP. This is a matter of great pride to all of us. Under his dynamic leadership, I am sure IAP will reach greater heights.

IAP Bangalore has been organising an extraordinary academic feast every year in the form of monthly meetings, annual Bangalore Pedicon, preconference workshops, orations, endowment lectures, guest lectures and panel discussions by eminent faculty, poster and paper presentations and post graduate teaching programs regularly over the years. We have been conducting all national programmes of IAP every year. It will be a unique platform to update ourselves with advances in Paediatrics and an opportunity to keep abreast with latest updates and developments in Paediatrics.

I am proud to be a part of this great organisation. Under the leadership of Dr Prasad SM, the branch has done extremely well in the year 2023. I am sure the energetic team 2024 led by Dr SomashekarA R and Dr Chidananda N K will make the branch more robust and academically sound. .

Pediatric Infectious Diseases Academy (IAP ID Chapter) is one of the most vibrant subchaptersof IAP which aims at promoting the advancement of knowledge and expertise in the diagnosis, prevention and treatment of Pediatric Infectious Diseases in India. ID Chapter has been in the forefront for providing evidence-based care to the children of our country. I had the privilege of working in the chapter in various capacities like Joint secretary, Secretary, Chairperson elect and Managing Editor of Pediatric Infectious Diseases.

I am sure that IAP Bangalore will attain greater heights in the coming years and will be a proud branch of mother IAP. I wish the new team a grand success.

Jai Hind

Jai IAP

Dr. Bhaskar Shenoy

Chairperson Elect 2024

PIDA - Pediatric Infectious Diseases Academy (IAP - ID Chapter)

IAP BANGALORE - BPS TEAM 2023

Dr. Somashekar A R
President
IAP Bengaluru 2024
IAP Karnataka

Dr. Chidananda N K
Secretary

Dr. Harilal Naik M L
Treasurer

Dr. Nithyananda S K
Vice President

Dr. Madhu G N
Vice President

Dr. Sumitha Nayak
President-Elect 2024

Dr. S M Prasad
Immediate Past President

Dr Nagalatha S
Joint Secretary

EXECUTIVE BOARD MEMBERS

Major (Dr.) Abhijith Y V

Dr. Jagadish A S

Dr. Keshavamurthy M L

Dr. Mridula A M

Dr. Padmavathi N

Dr. Pavithra Nagaraj

Dr. Poornima R N

Dr. Raghu T Gokhale

Dr. Shalini Sharma

Dr. Vivekanand M Kustagi

IAP KARNATAKA 2024

Dr. Mothi S N
IAP KSB President

Dr. Shashikiran K B
IAP KSB Secretary

Dr. Nandeesh B
IAP KSB VP - BLR

Dr. Sunil Kumar B M
IAP KSB Joint Secretary

CENTRAL EB MEMBERS

Dr. Adarsh E

Dr. Amaresh K Patil

Dr. Sanjeev Chetty

Dr. Priya Shivalli

Dr. M Venkatachalapathy

KNOW YOUR TEAM

Dr. Geeta Patil
Advisors

Dr. Shantharaj A
Advisors

Dr. Vasudev Dhananjay
Advisors

Dr. Kishore Baindur
Historian

Dr. Ravishankar Marpalli
Digital Head

Dr. Gowri Somayaji
Digital Advisor

Dr. Bhaskar Shenoy
Accounts Head and Advisor

Dr. Sharath Chand S
Accounts Head and Advisor

Dr. Shivaprakash Sosale C
Legal Head

PEDISCAN TEAM

Dr. Sunil Kumar B M

Dr. Rajaneesh K V

Dr. Shiva Sharanappa

Dr. Namita Ravikumar

Dr. Shalini Sharma

Dr. Jeffrey Aaron

Dr. Dakshayani B

Dr. Nancy Jeniffer

Dr. Mridula A M

Dr. Sushma

“Congratulations to the Achievers ”

It is with great sense of pride and joy that we, IAP Bengaluru team 2024 extend our sincere congratulations to all the accomplished achievers, Heartfelt congratulations to professor DR SHIVANANDA sir on being endowed with lifetime achievement award an apt recognition for his selfless and relentless service towards the profession and the organization. It is indeed a moment of pride, joy and satisfaction for all of us, who are his students for life, in addition to his encyclopedic knowledge, sir is a astute clinician and administrator. His words of wisdom is sacrosanct and etched in our collective consciousness, for which we are eternally grateful.

Congratulations to DR GEETA PATIL, madam has been at the forefront and has played pivotal role in many IAP Bengaluru activities. It brings cheer and joy to note that madam has been elected chairperson of IAP Adolescent Health Academy (AHA).

Warm congratulations to DR BHASKAR SHENOY sir on being elected as IAP Infectious Diseases Chairman. Sir is always anchored in academics and teaching how to navigate complexities in ID cases. Have to admit sir has an infectious smile. Best wishes to you sir.

Many congratulations to DR SRINIVASA S on being elected IMA state president, a towering personality with vision to match, it is a proud feeling to see a pediatrician at the helm of IMA.

Congratulations to DR KARUNAKARA B.P, on being elected as IMA state secretary, a dedicated and disciplined member of the organization.

Kudos and wishing many congratulations to DR NANDEESH B, on being conferred with FIAP 2024. A remarkable achievement, we appreciate your fine efforts in the field of pediatrics and IAP Constitution Reforms committee.

It fills our heart with joy to acknowledge and congratulate all the achievers in this New Year.

Best wishes and regards from team IAP Bengaluru 2024.

“ One Swallow does not make a Summer ! ”
Interpretation of Laboratory Tests in Pediatric Hematology Oncology.

Dr. Anand Prakash
Professor and Head
Department of Pediatric Hematology Oncology and BMT
St. John's Medical College Hospital, Bangalore .

My teacher, the late Prof. Sylvan Rego, former Professor and Head, Department of Pediatrics at St John's Medical College would often teach on rounds that “One Swallow does not make a Summer”. His words of wisdom referred to the need for careful assessment of all pieces of information – history, clinical examination, and laboratory tests before trying to arrive at a diagnosis. He often cautioned us, his students, not to use just one piece of information in confirming a diagnosis. Rather, we should look at the patient as a whole, when doing our assessment. This holds true to medicine in general and Pediatric Hematology in particular, where at times, one piece of information (often a lab test) may point to a wrong conclusion regarding the possible diagnosis. This article lists some common laboratory tests that are very helpful, but which need to be interpreted in the context of the clinical history and examination, so as to not make erroneous diagnosis.

1. DCT : Direct Coombs test positivity suggests presence of antibodies against red cell antigens on the surface of RBCs. DCT positivity may suggest Autoimmune hemolytic anemia. However, DCT may also be positive in various other settings like presence of alloantibodies in a multi-transfused patient or autoimmune hemolytic anemia secondary to underlying malignancy (Leukemia/ lymphoma) or collagen vascular disease. Hence in a patient with anemia and DCT positivity, the clinical setting guides the etiology of the RBC antibodies. In a neonate Rh, ABO or minor blood group incompatibility can cause DCT to be positive. In a child with transfusion dependent anemia, alloantibodies are the likely cause of DCT positivity. In an older child with low reticulocyte counts or lymphadenopathy or hepatosplenomegaly underlying malignant lymphoproliferation needs to be ruled out. A hasty decision of starting steroids, merely based on the findings of anemia and DCT positivity may be counter productive.
2. Reticulocyte count : Retic counts are sometimes called the “poor man's bone marrow”. While reticulocyte counts definitely provide a clue to the functioning of the marrow, the reticulocyte count has to be interpreted in the clinical context. In a child with hemolytic anemia such as hereditary spherocytosis(HS), we often expect an elevated retic count. However, many of these children come to medical attention only during an intercurrent infection which causes a drop in hemoglobin. These infections can also cause a transient drop in reticulocyte count akin to an aplastic crisis. The presence of low reticulocyte count in a patient with HS may prompt workup along the lines of a hypo functioning bone marrow and hence delay the diagnosis. A past history of mild icterus, episodic pallor and family history will help us avoid performing bone marrow examinations for children presenting during an aplastic crisis.

   Conversely, a high reticulocyte count may not always mean a hemolytic anemia. Children presenting with anemia, mild unconjugated jaundice and high retics may suggest that there is an underlying hemolysis. A child with B12 deficiency who is started on hematinics will often respond with a brisk erythropoiesis. This will be seen in the blood picture as high retics and PS may show polychromasia and even nucleated RBCs. The mild icterus (often seen in B12 deficiency), increased retics and LDH and peripheral smear may be misinterpreted as hemolytic anemia. A careful history of medications used for anemia and the sequence of when hematinics were given and when the lab tests were performed will guide us to differentiate high retics of hemolysis from the elevated retics of response to hematinics in a child with nutritional

anemia.

3. B12 level: This test is freely available and as B12 deficiency is not uncommon in the community, it is often requested during the workup of a child with anemia. However, it is a test to be interpreted with caution, keeping the clinical context in mind. In a child with suspected nutritional anemia, oval macrocytes, hyper-segmented neutrophils and an improvement in Hb after a therapeutic trial of B12, is confirmatory of B12 deficiency. However, a low level of B12 can be a coexisting finding in various other diagnosis like aplastic anemia or leukemia, all of which would present with pancytopenia. Using only the low level of B12 to suggest megaloblastic anemia is not advisable. The other clinical features of duration of symptoms, need for blood products, presence of fever, lymphadenopathy or hepatosplenomegaly all have to be taken into account rather than only the low B12 level.

   The converse is also true that a normal B 12 level does NOT rule out megaloblastic anemia. Even a single dose of B12 can affect blood levels and hence in the clinical setting of megaloblastic anemia, a serial follow-up of blood counts to look for correction of all 3 blood cell lines is important. A normal B12 level alone does not mean that there is no B12 deficiency.

4. Ferritin: Elevated serum ferritin is well known to be a criterion for diagnosis of Hemophagocytic lymphohistiocytosis (HLH). However when using ferritin in the diagnosis of HLH, we must be cautious to interpret the ferritin in the context of the clinical presentation. Ferritin being an acute phase reactant, is elevated in a variety of conditions. Also HLH could have underlying infections, immune deficiencies or malignancies (leukemias/lymphomas) which trigger HLH. Using ferritin alone in isolation and treating a patient with suspected HLH without a careful assessment of triggers for the HLH are both counterproductive. A large number of infections cause macrophage activation as part of normal immune response and early use of immunomodulation may not be necessary unless there is evidence of cytokine release (persistent fever, worsening cytopenia, rapid progression to organ dysfunction). Only an elevated ferritin without evidence of cytokine release does not warrant any form of immunomodulation. In children who satisfy the criteria for therapy with immunomodulation, a careful assessment of underlying collagen vascular disease, immunodeficiency or hematolymphoid malignancy is essential before reacting to an elevated ferritin. Many malignancies like acute leukemias, lymphomas and neuroblastoma present with persistent fever, cytopenia, organomegaly and elevated ferritin. Early use of steroids in this setting will delay diagnosis and further blur an already challenging clinical scenario.

5. Large platelets: Large platelets on peripheral smear often suggest a peripheral destruction of platelets often immune mediated ie ITP. However it must be kept in mind that not every child with large platelets in the peripheral blood film has ITP. Any cause of peripheral destruction of platelets can cause large platelets. Large platelets are also seen in macro-thrombocytopenia syndromes. Some of these may have a symptomatic bleeding eg Bernard Soulier syndrome. An overall assessment of duration of symptoms, severity of bleeding and severity of thrombocytopenia are useful in making the diagnosis. In children with suspected ITP rather that evaluating for large platelets alone, a review of the peripheral smear for varying sizes of platelets is helpful to suggest an immune mediated peripheral destruction of platelets.

6. Spherocytes: Presence of spherocytes on the blood film may prompt a consideration of hereditary spherocytosis. The presence of a few spherocytes is not uncommon in various hemolytic anemias such as autoimmune hemolytic anemia, blood group incompatibility or Rh isoimmunization. The clinical presentation should be taken into account before labelling a patient as having spherocytosis.

7. Prolonged PT/PTT with no bleeding:

This is not an uncommon scenario, often causing a lot of anxiety to parents. In a child with no bleeding symptoms, an incidentally detected prolonged PT/PTT is most often due to a lab error. Delay in transport of samples from multiple collection centers to the central lab or improper collection of blood sample results in erroneously prolonged results. PTT is at times prolonged in the setting of transient inhibitors secondary to a recent infection. Hence before requesting for lab tests related to coagulation, a detailed bleeding history in the child and family members is essential for appropriate laboratory tests and accurate diagnosis.

In conclusion, the classical bedside approach of a detailed history and clinical examination to arrive at a list of possible differential diagnosis is essential. It prevents erroneous interpretation of lab results which may not fit into the clinical picture. While laboratory tests are indispensable in coming to a final diagnosis, a hasty interpretation of lab tests without consideration of the clinical details is to be avoided. After all, “one swallow does not make a summer!”

Overview of Paediatric Immune Thrombocytopenic Purpura (ITP)

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Introduction

ITP is the most common autoimmune disorder affecting a blood element, where in antiplatelet IgG antibodies are produced against GP Ib/ IIIa platelet glycoproteins, leading to a low platelet count.

Etiology

Majority of cases are primary with history of preceding viral infection/ vaccination in the past 2-3 weeks .

20% of cases are due to underlying systemic disorder. Host factors are also important in how patients respond to an immune trigger.

Clinical features

Peak age of onset is at 2-6 years.

Abrupt onset of bruising , bleeding in an otherwise healthy child is the usual presentation.

Patients can have petechiae and ecchymosis, less commonly epistaxis and oral mucosal bleeds and rarely hematuria, hematochezia or melena.

Oral palatal bleeding spots are considered a predicting factor for intracranial hemorrhage and hence guide the decision to treat.

10 % of cases can have mild splenomegaly / tip of spleen palpable.

Evaluation and diagnosis

First line investigations and features to be looked for

- **Complete blood counts** – platelet count less than 150000/mm3 are seen in ITP.

  Other cell line affection to be looked for - anemia, leukopenia, and low neutrophil count - When these abnormalities are seen , we might be dealing with conditions such as leukemia, aplastic anemia and myelodysplastic syndromes.

- **with detailed peripheral smear** – for atypical cells – blasts on smear in leukemia.

  PS can show giant platelets in ITP.

- **Platelet indices** – increased immature platelet fraction, and increased mean platelet volume is suggestive of ITP.

- **Urine routine** - for microscopic hematuria which also helps in predicting risk of CNS bleeding in ITP.

- **Bone marrow smear examination** - in newly diagnosed ITP is not routinely recommended.(American society of hematology)

  Bone marrow examination is indicated only if the child has systemic symptoms or atypical laboratory features suggestive of other bone marrow processes. For e.g., anemia, hepatosplenomegaly, elevated MCV and neutropenia.

- **The key difference between ITP and acute leukemia** which has the same age of presentation like ITP is that children with ITP present with acute onset of thrombocytopenia in an otherwise healthy child whereas children with leukemia present with a prodromal phase of feeling unwell or looking ill.

  Bone marrow examination, when done in ITP, shows increased megakaryocytes on the smear.

ITP is classically diagnosed in a well child with no hepatosplenomegaly, no lymphadenopathy, with no other cell line involvement, with raised IPF, and MPV

- Persistent and chronic ITP – Investigations such as Antinuclear antibody profile, HIV 1 and 2, HCV, H pylori can be considered on a case-to-case basis more so in adults, and in adolescents with persistent / chronic ITP. Children have high remission rates and low likelihood of disease recurrence compared to adults.

Terminology of ITP based on duration.

Newly diagnosed ITP = Less than 3 months duration

Persistent ITP = persistent for 3 – 12 months

Chronic ITP = More than 12 months

80 % of newly diagnosed ITP have spontaneous resolution within 3-6 months; 20% progress to have chronic ITP. However, there are no determinants of these at presentation.

Principles of treatments Newly diagnosed ITP - Treatment decisions are usually challenging as there is no strong correlation between severity of bleeding and platelet counts.

1. **Therapeutic decisions** are individualized based on the patient's age, activity and the risk of bleeding, parental concern, access to medical care.
2. Children with skin bleeding only- Treatment is not indicated irrespective of platelet count in favor of observation as compared to adult patients who are treated when platelet count is less than 30,000/mm3 even in absence of bleeding.

   IVIG is used when a quick response is needed, however the effect can be transient. Response to the same is expected within 12 hours. Adverse events include headache, nausea, vomiting,infusion reactions etc.

   IVIG doesn't reduce the chance of having persistent ITP, however it does reduce the bleeding risk in children esp. in case of life-threatening bleeding and intracranial bleeds.

   In children shorter courses of steroids are preferred due to likelihood of spontaneous recovery within days to weeks of diagnosis. **2-4 mg/kg** divided in two doses of oral prednisolone can be used for 5-7 days. Response is expected in 4-5 days after the start of steroids.

   Other steroid options but less preferred is oral dexamethasone (0.6 mg/kg/day; maximum, 40 mg/kg/day, for 4 days).
3. **Anti D immunoglobulin** is not advised in children with hemoglobin that is decreased due to bleeding or with evidence of autoimmune hemolysis.
4. Newer modalities such as Thrombopoietin receptor agonist ROMIPLOSTIM (S/C) and ELTROMBOPAG (ORAL)are based on the recognition of impaired platelet production in ITP. Antiplatelet antibodies bind to megakaryocytes and cause their destruction, impair their function or delay their maturation and consequently interfere with platelet production in some cases.
5. The benefits of TPO- RA therapy are that they don't lead to immunosuppression as other second line therapies in ITP. Response to romiplostim is expected in 5-7 days.

   TPOPO RA agonists have been classically used in persistent / chronic ITP.

   Its use in newly diagnosed patients not responding to IVIg / steroids can be considered and is being researched.
6. **Intracranial hemorrhage** is consistently found in higher frequency in adults than in children with ITP, possibly explained by medication use due to comorbidities such as antiplatelet agents and VIT K antagonists. The majority of intracranial hemorrhage occurs in the newly diagnosed phase and with a platelet count less than 20,000 per cubic millimeter. Life threatening/severe bleeding is a rare entity. Platelet transfusions to control acute bleeding can be given along.
7. Other second line therapies in newly diagnosed ITP.

   Immunomodulatory therapy to induce remission is more likely to be needed in adolescent and adult age groups wherein we also find more relapses and recurrences, and in chronic ITP.

   Rituximab- It is CD20 monoclonal antibody that targets B lymphocytes and has 60% response rates in refractory ITP. Favorable responses are most commonly seen in patients

of systemic lupus erythematosus/ evolving disease . Caution to be exercised to rule out ITP due to Autoimmune lymphoproliferative disorder, Common variable immunodeficiency, Evan's and underlying immunodeficiency syndromes.

Splenectomy as an extreme measure to raise the platelet count is used with caution and is less preferable.

8. Fatigue, an important complaint noticed in ITP especially in persistent and chronic conditions can be considered as a factor in treatment planning.
9. Salvage options include - Oral dapsone and mycophenolate mofetil.

Conclusion

Treatment of ITP should be individualized. One size doesn't fit all. Considerations of age, underlying co - morbidities, lifestyle, access to health care, quality of life

(Health related quality of life-HRQoL) play a vital role in making treatment decisions.

Further reading

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Approach to Auto Immune Hemolytic Anemia (AIHA)

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Introduction

Auto immune hemolytic anemia is an acquired form of extra corpuscular hemolytic anemia. Immune mediated destruction of the red blood cells occurs due to antibodies directed against the surface antigens of an erythrocyte.

Classified as warm or cold auto immune hemolytic anemia based on the temperature at which the antibodies show maximal reactivity.

Direct anti globulin test positivity is single most important entity in warm AIHA but reportedly 11% of warm AIHA can have DAT negative results and need further evaluation. AIHA can be primary/Idiopathic or secondary due to underlying infections, immunodeficiency, medications, malignancy.

Pathogenesis

WARM AIHA

The term warm AIHA comes from the temperature at which the antibodies show highest affinity to the antigen. In warm AIHA at 37C there will be highest affinity to the antigen.

In warm AIHA the autoantibodies are IgG and polyclonal. The erythrocytes coated by the IgG antibodies are destroyed by the mononuclear phagocytic system and mainly in the spleen. Complement mediated hemolysis can occur to a variable extent by phagocytosis of the C3b labelled cells. Hemolysis mediated by the mononuclear phagocytic system and complement mediated is extravascular. Some amount of intravascular hemolysis occurs due to activation of terminal complement cascade and formation of MAC (Membrane attack complex). More than half of the patients with warm AIHA have an underlying disorder, more commonly SLE, CVID. With increasing spectrum of inborn errors of immunity(IEI), It is important to evaluate for underlying auto immune disorder/IEI.

Cold Agglutinin disease (CAD)

Auto antibodies in cold agglutinin disease bind to the antigen at 0-4 C but also can react at higher temperatures. Cold agglutinins are monoclonal and IgM antibodies. Exposure to the cold temperatures induce circulatory symptoms& hemolysis is mainly complement mediated. Erythrocytes are coated by C3b and these phagocytosedbythe mononuclearphagocytic system, mainly liver. Hemolysis os mainly extravascular and some amount of intravascular hemolysis occurs due to formation of MAC. Recent studies have shown that underlying lymphoproliferative bone marrow disorders are associated with cold agglutinin.

Cold agglutinin syndrome secondary to infection(Mycoplasma pneumoniae, EBV, CMV, SARS-CoV-2) and malignancy (B cell lymphoma) is being increasingly known.

In **Paroxysmal cold hemoglobinuria (PCH),** the hemolysis is predominantly intravascular. Donath-Landsteinar antibody is biphasic IgG autoantibody which binds to the RBC antigen at lower temperatures activation of the complement system at 37 C. This is seen as a post viral complication in children.

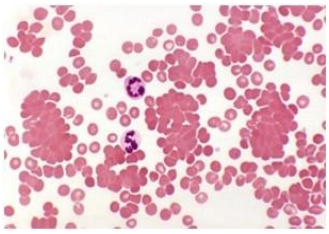
Mixed AIHA is characterised by presence of warm IgG auto antibodies and high titre cold agglutinins.

Clinical features

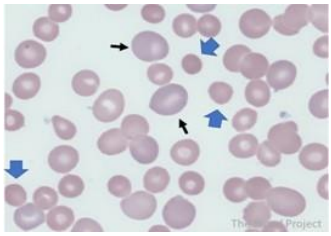
Children with AIHA will present with sudden onset pallor, jaundice and dark coloured urine. Examination features include pallor, signs of failure due to severe anemia, splenomegaly. Examination should also include looking for signs of underlying auto immune disease, malignancy, inborn errors of immunity.

Laboratory findings

Laboratory features of AIHA include marked anemia, reticulocytosis. Peripheral smear examination in IgG mediated warm hemolytic anemia include spherocytes due to spleen induced damage of the antibody coated erythrocytes. Polychromasia, fragmented &nucleated RBCs are seen. Peripheral smear in cold AIHA show RBC clumps due to IgM mediated RBC agglutination.



Spherocytes (Blue arrows) with loss of central pallor, polychromatophilic (black arrow) cells in a patient with warm AIHA



Peripheral smear showing RBC clumps in a patient with coldAIHA

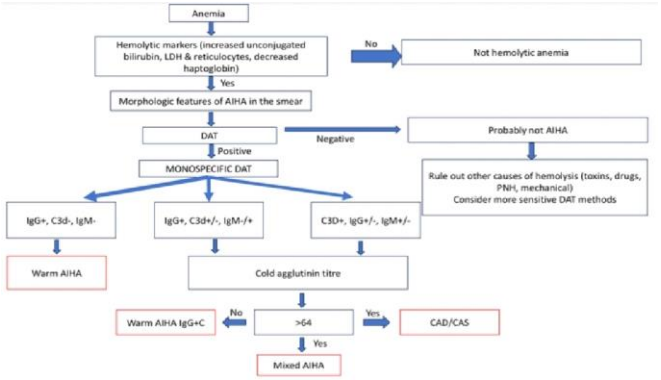
Other serologic evidence of hemolysis includes elevated LDH, elevated unconjugated bilirubin, elevated SGOT and normal SGPT, GGT levels. Reduced haptoglobin levels and hemoglobinuria seen are due to intravascular hemolysis.

With history of sudden onset pallor, jaundice, splenomegaly on examination, features of hemolysis in blood picture and serologic evidence (high LDH and elevated uncojugated bilirubin)next step of evaluation is direct anti-globulin test (DAT). DAT detects the Ig and/or complement on the surface of RBCs and helps in classifying as immune mediated hemolysis. In DAT positive patients AIHA is considered, and next step of evaluation includes a monospecific DAT and cold agglutinin titres to characterise the type of AIHA.

Classification of AIHA

Type	Antibody class	Temperature of Maximal reactivity	DAT Positivity
Warm AIHA	IgG	37 C	IgG +C3.
CAD	IgM	4 C	C3 only
Mixed AIHA	Cold IgM & warm IgG	4 C & 37 C	IgG and C3
PCH	IgG	4 C	+C3

Approach to AIHA



Management of AIHA

Primary warm AIHA

First line treatment includes steroids, Prednisolone 2-6mg/kg/day orally or IV methylprednisolone 30mg/kg/day pulse for 3 days followed by oral steroids. Response in the form of raising haemoglobin levels will be seen by 24-72 hours. After the normalisation of hemoglobin steroids should be slowly tapered over 6 months. Complete response is defined as achieving hemoglobin more than lower normal limit for age, with no signs of hemolysis and no response is defined as <2gm/dl raise in hemoglobin/transfusion dependence. 80% of the patients have an initial response to steroids but only 30-40% will have sustained response by the end on one year.

In patients who do-not respond to steroids he/she reevaluated and look for any secondary causes. Current recommendation for second line agent in primary AIHA is Rituximab 375mg/m2 weekly for 4 weeks. 70-80% of the patients respond to Rituximab.

Cold agglutinin disease

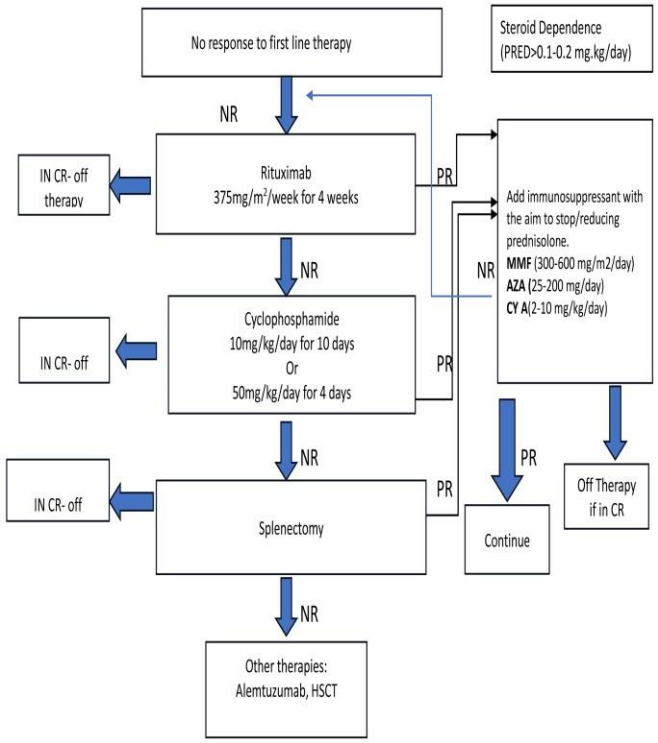
Steroids are ineffective in management of cold AIHA. Mild anemia monitoring and supportive management is advisable. Thermal protection to limit the hemolysis. Prospective trials showed response in 40-70% of patients with Rituximab.

Role of transfusion

Transfusion is limited to life threatening anemia. Difficulty in cross matching with identical blood will be faced and the blood with least incompatibility is to be chosen.

Conclusion

Identification of type of AIHA is an important step in the management of AIHA. DAT negative AIHA can be seen in 3-10% of patients. Steroids are the first line of management in warm AIHA. And reevaluation is important in patients who do-not respond to first line of management. Screening for underlying auto immune and inborn errors of immunity is important in patients with warm AIHA.



AEIOP guidelines for second line therapy in warm AIHA

Suggest reading :

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ACUTE MYELOID LEUKAEMIA (AML) MORPHOLOGY TO MOLECULAR !

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Heterogeneity of AML hasled to emerging **diverse classification systems.** These classifications have not paved way to specific initial treatments except in acute promyelocytic leukemia. The novel therapies targeting the molecularly defined variants of AML are expected to bridge the gap between evolving classifications and the treatment options.

The French– American– British (FAB) classification of AML, introduced in 1976 revised in 1985, was mainly based on **morphologic and cytochemical features** of the leukemic blasts in the bone marrow (BM). The FAB required 30% blastsand subtypedbased on maturation in the myeloid series, presence of monocytic,megakaryoblastic and erythroid component. **Immuno-phenotyping improved** identification of the above said.

Genetic changes associated with leukaemia was recognised in 1980 s, provided better prognostication with modest FAB correlation. With further understanding of cytogenetic abnormalities haematologists called , **"favourable," "intermediate," and "adverse"** and used along with FAB or stand alone.

The AML **WHO classification published in 2001** redefined AML as requiring only 20% blasts in the BM or blood, and appreciated the importance of the associated cytogenetic abnormalities. Furthermore, the **inclusion of karyotypic abnormalities** helped in prognostication.

Newer technologies like next-generation sequencing, helped recognising the driver mutations in normal cytogenetics AML subgroup. Important and familiar mutations are FLT3, NPM1, KIT, CEBPα, TET2, DNMT3A, and IDH1. Relevance of these mutations and their coexistence is beyond the scope of this article and we need to understand that these developments led to **revisions of AML classification in 2016 (WHO).** The 2016 revisions include recognition of new cytogenetic subgroups, such as a provisional entity of AML with BCR-ABL and accompanied cryptic deletions of antigen receptors, particularly immunoglobulin heavy chain (IGH) gene, new and revised subgroups like AML with RUNX1 mutations, AML with CEBPα etc. **2016 WHO classification recognizes the importance of mutation studies.**

Cytogenetic studies, screening for gene rearrangements, and assessment of gene panels, including NPM1, CEBPA, RUNX1, are required to classify as AML with recurrent genetic abnormalities, an important category.

The **new ELN classification introduced in 2022** have given priority to **cytogenetic and mutational profiles** due to their significant **impact on prognosis and available targeted therapies.** The major changes include 1)hierarchical classification, 2)All recurrent genetic abnormalities that define specific subtypes of AML, with the exception of AML with t(9;22)(q34.1;q11.2)/BCR::ABL1, are diagnosedas AML if there are $\geq$ 10% blasts ,3) all other AML subtypes require $\geq$20% blasts for diagnosis, 4) new category of MDS/AML has been introduced in association with defined genomic abnormalities with 10% to 19% blasts,5) removal of AML with myelodysplasia-related changes (AML-MRC) and therapy-related myeloid neoplasms.

I conclude that in the era of personalized medicine, to recognize the molecular change at the gene level influencing disease classification, diagnosis, prognosis, risk stratification, and treatment **soon will not be an option, but will be a need!**

French–American–British (FAB, 1985)

M0: AML with minimal differentiation

M1: AML without maturation

M2: AML with maturation

M3: APL

M3v: micro granular variant

M4: AMML

M4eo: AMML with abnormal eosinophils

M5A: acute monoblastic leukaemia

M5B: acute monocytic Leukaemia

M6: erythroleukemia

M7: acute megakaryoblastic leukaemia

ELN CLASSIFICATION (2022)

AML with recurrent genetic abnormalities (requiring ≥10% blasts in BM or PB)

APL with t(15;17)(q24.1;q21.2)/PML::RARA

AML with t(8;21) (q22;q22.1) / RUNX1 : : RUNX1T1

AML with inv(16)(p13.1q22) or t (16;16) (p13.1;q22) / CBFB::MYH11

AML with t (9;11) (p21.3;q23.3) / MLLT3 : : KMT2A

AML with t(6;9)(p22.3;q34.1)/DEK::NUP214

AML with inv(3)(q21.3q26.2) or t (3;3) (q21.3;q26.2) / GATA2, MECOM(EVI1)

AML with other rare recurring translocations

AML with mutated NPM1

AML with in-frame bZIP mutated CEBPA

AML with t(9;22)(q34.1;q11.2)/BCR::ABL1

Categories designated AML (if ≥ 20% blasts in BM or PB) or MDS/AML (if 10-19% blasts in BM or PB)

AML with mutated Tp53

AML with myelodysplasia-related gene mutations Defined by mutations in ASXL1, BCOR, EZH2, RUNX1, SF3B1, SRSF2, STAG2, U2AF1, and/or ZRSR2

AML with myelodysplasia-related cytogenetic abnormalities

AML not otherwise specified

Diagnostic qualifiers

Therapy-related

Prior chemotherapy, radiotherapy, immune interventions Progressed from MDS

MDS should be confirmed by standard diagnostics and >3 months prior to AML diagnosis

Progressed from MDS/MPN (specify type)

MDS/MPN should be confirmed by standard diagnostics and >3 months prior to AML diagnosis

Germline predisposition

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Hemophagocytic - Lympho - Histiocytosis - lymphocytes and macrophages gone rogue

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Hemophagocytic- Lympho- Histiocytosis- HLH- is defined as a hyperinflammatory condition caused by excessive and uncontrolled activation and proliferation of lymphocytes and macrophages that produce high levels of cytokines with organ infiltration of these cells.

Pathophysiology :

It is essential to understand normal immune response first, so that the pathophysiology of HLH can be understood.

"Normal" Inflammation :

It all begins with undesirable structures in the body. These are broadly classified as Pathogen associated molecular proteins (PAMPS) and Damage associated molecular proteins (DAMPS)

PAMPS are microbial structures (parts of virus, bacteria or parasite) whereas DAMPS are parts of damaged endogenous cells. PAMPS and DAMPS trigger inflammatory response by binding to receptors called pattern recognition receptors(PRR) on immune and nonimmune cells- dendritic cells, macrophages, monocytes, neutrophils, as well as by epithelial cells. These cells are called antigen presenting cells (APC) as they present antigens attached to PRR to effector cells. The activated macrophages secrete IL-12 which stimulates the effector cells – the TH1 cells which in turn release cytotoxic granules and kill the target cell.

The other cell that is active in immune response is Natural Killer (NK) cell which directly attack damaged or infected cells in the body, killing them with release of cytolytic granules.

Cytolytic granules :

These granules are stored in lysosomes inside T lymphocytes and NK cells. They are basically proteins and are mainly of two types- granzyme and perforin. The granules undergo maturation, polarization, docking, priming, fusion, and finally release into the target cells resulting in killing of target cells. Perforin facilitates transfer of granules after exocytosis into the target cells by forming a connecting tubular channel. Inside the target cells granzymes cleaves a variety of targets, such as caspases, resulting in death of the target cell. The released debris contains proteins which are further presented by the APCs setting up a cycle until the trigger for the inflammation is reduced or absent.1

When these granules are released CD107 – a protein found on the membrane of the perforin gets attached to the outer part of the cytotoxic cell, expression of this is therefore indicative of effective degranulation.

The activation of macrophages, cytotoxic T lymphocytes and NK cells leads to release of cytokines. Mainly IL12, IFNy, IL 4, IL10. While IL 12, IFNy and IL 4 are proinflammatory leading to stimulation of all the above cells, IL 10 inhibits IL12 and stops the inflammatory cycle2. Macrophages engulf the debris. This process continues till the offending agent is cleared. The inflammation is terminated when the offending agent is cleared and all signs of inflammation abate.

What happens in HLH?

A triggering event such as a viral infection starts the cycle of inflammation with antigen presentation, interferon gamma secretion by APC, activation and recruitment of macrophages by IFN gamma, cytokine secretion by macrophages which in turn further activates the cytotoxic cells and stimulates the cytotoxic cells to proliferate.5

In HLH there are defective cytotoxic T cells and NK cells that lead to inadequate target cell kill and antigen removal.

Cytotoxic T lymphocytes fail to clear antigens and NK cells fail to kill target cells due to defective degranulation(one or more of the steps are affected- poor formation, maturation, polarization and fusion sand transfer of cytotoxic granules into the target cells). Hence,target cells (infected cells) are not killed and antigen are not cleared. The prolonged synapse between cytotoxic cell and the target cell leads to release of large number of cytokines. IFN gamma is the main proinflammatory cytokine which is secreted by macrophages due to persistent antigen presentation. Activated APCs, Cytotoxic cells and high levels of proinflammatory cytokines form a vicious loop of

hyperinflammation causing HLH. The hyperactivated cells multiply and accumulate in various organs.

Pathogenesis of Clinical and biochemical manifestations:

The following symptoms, signs and laboratory changes arise due to the mechanisms as described above.

- Fever- due to Cytokines and chemokines, TNF, IFN- γ, IL-6, TNF-α, IL-10, IL-12 and IL-18
- High Ferritin: released from the activated macrophages
- Low Fibrinogen – fibrinolysis by plasminogen activator released by macrophages
- High triglycerides - Cytokines suppress lipoprotein lipase
- Cytopenia – due to Cytokines suppressing hematopoiesis and haemophagocytic activity
- Organomegaly- inflammation and hemophagocytic infiltration
- Absent CD 107a- due to poor or absent degranulation
- Increased CD25 (IL2) – due to release of inflammatory cytokines

Terminology

Depending on the context various terminologies have been used3

HemophagocyticLymphohistiocytosis – general HLH

Macrophage activation syndrome- MAS- HLH due to rheumatic disease

Cytokine release syndrome – CRS- HLH due to CAR T cell or BiTe therapy

Types of HLH

HLH may be genetic or acquired (also called primary and secondary respectively)

Genetic (Primary) HLH:

In primary HLH the dysfunctional cytotoxic cells are the result of genetic mutation affecting the degranulation process and immune surveillance, latter in case of cytotoxic T cells.

Genetic Causes :

These can be classified as familial HLHand inherited genetic immune diseases where HLH is a syndromic association. Familial HLH- genetic mutations specific to cytotoxic T cell and NK cell degranulation is present are known.

These were called fHLH 1 to 5. Currently they are named after the associated genes:

Table 1: Genetic HLH [4]

Gene based name	Phenotype based name	
PRF1-fHLH	FHL 2	Earlier age onset
STX11-fHLH	FHL4	Later onset, milder course
STXBP2-fHLH	FHL5	Onset later than PRF1 fHLH, may be variable in the same family 1/3rd have additional findings like colitis, bleeding disorders, hypogammaglobulinemia
UNCL13D-fHLH	FHL3	CNS involvement common
PRF1 hypomorphic variants in PRF1, MUNC13-4, STXBP2		Late onset - adulthood

Inherited immune disorders with HLH- these are immune disorders with HLH as one of its many manifestations.

Disorder	Gene	MOI	Immune defect in HLH	Distinguishing clinical features
HermanskyPudlak syndrome 2	AP3B1	AR	Defective granule mediated cytotoxicity	Abnormal pigment, neutropenia, susceptibility to infections, bleeding
Lymphoproliferative syndrome 1 and 2	CD27	AR	Variable mechanism	Chronic EBV infection; hypogammaglobulinemia; lymphoma
Chediak- Higashi syndrome	LYST	AR	Defective granule mediated cytotoxicity	Abnormal pigment, nystagmus, neurologic manifestations, giant granules and other granule abnormalities in leukocytes and
X linked lymphoproliferative disease	XIAP	XL	TNF receptor signalling and NLRP3 inflammasomedysgranulatiom, increased cell susceptibility to cell death	Inflammatory bowel disease, arthritis, uveitis, recurrent fever, hypogammaglobulinemia, infections
Griscelli syndrome type 2	RAB27A	AR	Defective granule mediated cytotoxicity	In most but not all affected persons abnormal pigment

Acquired (secondary) HLH:[6]

Causes :

- Infectious agents

Viruses – EBV, CMV, VZV, HHV6, Adeno, HIV, Influenza, COVID

Bacteria – Mycobacterium tuberculosis, Listeria, Brucella, Rickettsia Fungi- candida, Histoplasma

Parasite- Plasmodium, Toxoplasma

- Autoinflammatory and autoimmune diseases (MAS) – Rheumatological disorders (in this context HLH is called MAS), systemic JIA, SLE
- Malignant diseases- T and B cell neoplasms including lymphoma, neuroblastoma
- Immunosuppression, HSCT, organ transplantation, AIDS , CAR T cell therapy
- Metabolic diseases

Unlike primary HLH, the pathophysiology of secondary HLH is more complicated and involves multiple mechanisms working at the same time. Patients with secondary HLH may have variants or monoallelic mutations that predispose them to progress to HLH with infection unlike those without the mutations. NK cell function may be normal in secondary HLH.

The mechanism of HLH secondary to infection maybe one or more of the following: (most are studied in viral infections)[8]

- Direct but reversible cytotoxic dysfunction by the microbe
- Increased levels of IL6 in infection reduces perforin and granzyme expression- seen in bacterial and rheumatological disorders
- Overactivation of innate immune system in MAS, bacterial infection. 7
- Continuous pathogen receptor triggering and bone marrow exhaustion –

  Eg: EBV, CMV, (that establish lifelong latency with sporadic reactivation) HHV-6, VZV, Hep A and C, dengue and parvo viruses cause BM exhaustion
- Infection of key cell types (cells involved in pathogenesis of HLH) and hematopoietic stem cells:

  Eg: HIV infected NK cells showed reduced viability, influenza infected DCs are linked to lymphopenia and thymic cell destruction, EBV, HHV6 and 8 infected CTLs show lymphoproliferation and immortalization causing cytokine producing cells to persist and predominate. Parvo virus B19 infects erythroid stem cells inhibiting their cell division.
- Immune Evasion and Resisting apoptosis:

  Eg: EBV encodes decoy TNF receptor and avoids TNF mediated apoptosis, Adenovirus induces internalization of FAS receptors and avoids death Interfering with CTL and NK cell cytotoxic function:

  Eg: EBV causes immunological deficit resulting in XLP1 mutation associated like HLH

Incidence of HLH:

Data in western countries show the incidence of familial HLH to be 1 in 50000 live births. The mortality is 90% if left untreated. Incidence in India is not known. Overall incidence of HLH in children <18 years across ethnicities and races is approximately 1 in 1,00,000.9

Incidence of secondary HLH is not known

Diagnosis:

Based on above mechanism the following diagnostic criteria – HLH 2004, can be better understood and remembered.

HLH 2004 diagnostic criteria (Henter et al (2007):The diagnosis of HLH can be established if either A or B is fulfilled:10

A. A molecular diagnosis consistent with HLH

B. Any 5 of the 8 following clinical and laboratory criteria for HLH:

1. Fever >38.5oC
2. Splenomegaly
3. Cytopenia (affecting>/= 2 of 3 lineages in peripheral blood)

   -Haemoglobin <9 g/dl (in infants < 4 weeks: Hb <10 g/dl)

   -Platelets <100 x 109/L

   -Neutrophils <1.0 x109/L
4. Hypertriglyceridemia and /or hypofibrinogenemia: fasting triglycerides >3.0 mmol/L (>265 mg/dl) or fibrinogen </= 1.5 g/L
5. Hemophagocytosis in the bone marrow, spleen, liver, lymph node or other tissues
6. Low or absent natural killer (NK) cell activity
7. Serum ferritin concentration>/= 500 mcg/L
8. Soluble CD25 (soluble IL-2 receptor) >/= 2400 U/mL

Symptoms may mimic the following:

- Fever of unknown origin (FUO)

- Acute liver failure
- Neonates - hydrops fetalis and liver failure
- Veno-occlusive disease
- Disseminated intravascular coagulation
- Bone marrow failure
- Skin manifestations
- Pulmonary dysfunction, neurologic manifestations

Sepsis or HLH?

In a diagnosed sepsis or viral infection, whenever there is persistent fever despite appropriate antimicrobial treatment, with progression to cytopenia and/or organomegaly, HLH should be suspected.

High index of suspicion is needed to make an early diagnosis of HLH as the mortality is high if left untreated with HLH directed therapy. Furthermore,HLH requires steroids while in sepsis immunosuppression is contraindicated.

Fardet et al proposed a scoring system called HScore.It helps to recognize progression from sepsis to secondary HLH. Hence the clinician can make an early diagnosis of secondary HLH. It was mainly used in adults. Subsequent studies have shown that Hscore is useful to diagnose or suspect HLH in pediatrics too. This scoring system is useful when the clinical and laboratory features are difficult to differentiate between sepsis and HLH.12Hscore is simple, cost effective and less restrictive tool for the diagnosis of reactive HLH

Table 2:HScore

Parameter	No of points
Known underlying immunosuppression#	0(no) or 18(yes)
Temperature (^{0}C)	0(<38.4),33 (38.4 -39.4), or 49 (>39.4) Performance of HScore in Reactive Hemophagocytic Lymphohistiocytosis Neerav Khare
Organomegaly	0(no),23(hepatomegaly or splenomegaly), or 38 (hepatomegaly and splenomegaly)
Number of cytopenia*	0 (1 lineage),24 (2 lineages), or 34 (3 lineages)
Ferritin (mcg/l)	0(<2000), 35 (2000-6000), 50 (>6000)
Triglyceride (mmol/l)	0(<1.5),44 (1.5-4), or 64 (>4)
Fibrinogen (g/l)	0 (>2.5), or 30 (=/<2.5)
Aspartate aminotransferase (U/l)	0(30), or 19 (=/>30)
Hemophagocytes in bone marrow	0(no), or 35 (yes)

#HIV positive or receiving long term immunosuppressive therapy

*Hb<9.2 g/dl and /or WBC <5000/mm3 and /or platelet<110,000/mm3

Hscore calculator is available online. The median overall H-score is 238 (range 129-337)

Interpretation of Hscore:

> 169 - confirmed (positive) secondary HLH

< 169 - unconfirmed (negative) cases for a diagnosis of HLH

Genetic or acquired?

The only curative treatment available today for genetic HLH is hematopoietic stem celltransplantation (HSCT).As HSCT is an expensive, high risk and intensive treatment, early diagnosis is essential for planning the treatment, such as establishingremission,donor selection and making financial arrangements for the same.

The following features favour genetic HLH:

- Age of diagnosis < 1 year of age
- Family h/o HLH+
- Recurrent HLH during or after treatment

Investigations to diagnose genetic HLH[7]-

- Chromium release natural killer (NK)–cell cytotoxicity test (also known as the **NK cell function test)-NK cytotoxicity – measured as Lytic unit value**

Absent - 0

Low - <2.6 but still detectable

Normal - ≥2.6

Patients who lacked biallelic mutations have exhibited abnormal NK cell killing

Disadvantages:

NK cytotoxicity is a poor diagnostic tool to differentiate genetic HLH from acquired HLH as in the latter NK cell may be low.

NK cell viability and cytotoxic activity can be falsely low:

- by exposure to steroids, which are commonly used to treat HLH

-by delay in testing after sample is collected

-when the absolute number of NK cells is low

(a common finding seen incytopenic HLH patients)

-temporarily abnormal in patients with secondary HLH

- Flow cytometric measurement of cytotoxic lymphocyte perforin expression- (the protein product of PRF1): absent or markedly decreased in HLH (beware of missense variants where this may be normal)

Interpretation of results:

A sample's NK-cell perforin expression low if perforin MCF was below 98 and normal if the NK-cell perforin MCF was ≥98

-Measurement of perforin expression is an excellent diagnostic test for detecting biallelic PRF1 mutations

-If perforin protein expression is normal or increased, molecular genetic testing id advised

u **Evaluation of NK-cell degranulation using flow cytometric measurement of CD107a upregulation.** Expression of CD107a on the surface membrane of the cytotoxic t cell and NK cell suggests successful degranulation while absent expression indicates no degranulation as seen in HLH.

Perforin and CD107a assays are not affected by HLH d i rected t reatment. Hence are excellenttests to diagnose HLH. These two tests in combination yields good diagnostic accuracy for detecting primary HLH

u Genetic studies–NGS to identify the genetic mutation- takes a month for the report

It is important to note that finding an acquired cause of HLH does not rule out genetic HLH and 30% of FHLH have no identifiable genetic mutation.

Table 3: Genetic causes of HLH and associated (source: originally published in Blood. Hines and Nichols)

Disease	Gene name	Encoded protein	Perforin expression	CD107a upregulation	NK cell cytotoxicity
FHL 2	PRF1	Perforin	Markedly reduced	Normal	Low or absent
FHL3	UNC13D	Munc13-4	Normal	Reduced	Low or absent
FHL4	STX11	Syntaxin 11	Normal	Reduced	Low to absent
FHL5	STXBP2	Munc 18-2	Normal	Reduced	Low to absent
Griscelli	RAB27A	Rab27a	Normal	Reduced	Low to absent
Chediak Higashi	LYST	LYST	normal	Reduced	Reduced or absent
XLP1	SH2D1A	SAP	Normal (SAP expression decreased)	Normal	Reduced or normal
XLP2	BIRC4	XIAP	Normal	Normal	Reduced or normal
HPS2	AP3B1	AP3	Normal	Reduced	Reduced

XLP- X – linked lymphoproliferative syndrome

SAP- signaling lymphocytic activation molecule (SLAM) – associated protein

XIAP- X- linked inhibitor of apoptosis

HPS- HermanskyPudlak Syndrome

AP- adaptor protein 3 complex

Recommended laboratory studies:[13]

For diagnosis of HLH:

Complete blood count

Ferritin

Fibrinogen level

Serum triglyceride – fasting

Soluble IL2 receptor or CD25 kevel

NK cell function

Bone marrow aspiration and biopsy

For genetic HLH:

CD107a mobilization (report available in 3-4 days)

Perforin/granzyme B expression (report available in 3-4 days)

HLH genetic panel (report takes a month)

In males:

XIAP and SAP expression (report takes 1 -2 weeks)

Tests for HLH monitoring:

Ferritin- Once to twice weekly

Soluble IL-2 receptor or CD25 level- once weekly

Tests for infection:

Depending on clinical features, viral related tests- CMV and EBV are advisable in genetic HLH

Blood culture and sensitivity

PCR for CMV, EBV, HHV6 etc

HIV, Hepatitis B and C testing

Other microbial testsas per clinical suspicion

Tests to assess disease impact and complications:

Liver function test

Renal function test

LDH

Coagulation studies

Albumin

CSF cell count and microscopy for Hemophagocytes

MRI brain

PET CT/CT chest for lymphoma if indicated

Treatment:

Principles of treatment:

- Suppression of hyperinflammation - (immunosuppression, Immunomodulation) - Corticosteroids, IV immunoglobulins, cyclosporin A, anticytokine agents
- Elimination of activated immune cells and (infected) APCs (CTLs, macrophages) - Corticosteroids, etoposide, T- cell antibodies, (antithymocyte globulin, alemtuzumab), rituximab
- Elimination of trigger - Anti-infectious therapy, treatment of primary cause in acquired HLH
- Supportive therapy - (neutropenia, coagulopathy, infection) - Antifungals, antibiotics, antivirals, blood products, diet, etc.
- Replacement of defective immune system – HSCT

The treatment protocol was formulated by the Histiocyte Society;

HLH-1994[14] - chemotherapy and immunotherapy (etoposide, corticosteroids, cyclosporine A, and intrathecal methotrexate for individuals with CNS diseases)

HLH-2004- differs from HLH 1994 in initiation of cyclosporine from onset of induction therapy, outcome was similar as 1994 protocol, hence it is not necessary to start CSA upfront.

HLH Protocol;

Dexamethasone – 10 mg/m2 per day to be started as soon as diagnosis is made, continued for 2 weeks then taper every 2 weeks at 5,2.5 and 1.25 mg/m2/day and stop at the end of 8 weeks

Etoposide -150 mg/m2/dose twice weekly for 2 weeks then once a week for 6 weeks

Cyclosporine – start at week 9 to continue until completion of treatment

Intrathecal methotrexate: All patients with CNS HLH proven by csf analysis/MRI brain

Curative treatment:

HSCT is the only curative therapy in persistent, recurring, and/or familial disease, however the disease has to be treated to remission before HSCT for a good outcome.

Trigger specific treatment:

- Severe EBV-HLH: glucocorticoids combined with rituximab should be the preferred treatment
- HIV-associated HLH (HIV-HLH)

o Exclude lymphomas and opportunistic infections

o Antiretroviral treatment

o Corticosteroids should be given only in hyperinflammatory cases

- Infectious agents affecting the mononuclear phagocyte system such as rickettsia, brucella and Coxiella

o Avoid corticosteroids since these pathogens respond well to disease-specific treatment

- In rheumatological diseases (macrophage activation syndrome, MAS- HLH), corticosteroids are the preferred treatment, followed by an anti-IL-1 or anti-IL-6 drug when the immediate response is insufficient.

Response to treatment:[15]

Improvement is typically seen within first 48 hours of starting Dexamethasone and first dose etoposide.

- Complete response:

  Characterized by disappearance of all symptoms, normalization of HLH biological signs such as ferritin, triglycerides, hemoglobin, neutrophil counts, glutamate pyruvate transaminase, and sCD25.It is important to follow up regularly to recognize recurrences, in which case acquired HLH should be treated as genetic HLH.

- Refractory HLH:4

  There is no clear definition of refractory HLH.

  Absence of response (partial and/or complete) at 2–3 weeks, after starting standard HLH therapy is often suggestive of refractory HLH

- Partial response is generally defined as an improvement of at least $\geq$ 2 symptoms and laboratory markers within 2 weeks after initiation of treatment

Problems during treatment:

Ø Steroid induced complications- hypertension, endocrine problems, infections, cushingoid features, difficult line access

Ø Infections: due to impaired cytotoxic function

and treatment induced immunosuppression

Ø Cyclosporine: hypertension, renal failure, Posterior Reversible Encephalopathy Syndrome, hirsutism

Treatment of relapsed/ refractory HLH:

- **Alemtuzumab:** anti-CD52 antibody (dose 1 mg/kg split over a median of 4 days)
- **Ruxolitinib** - orally at a dose of 15 mg twice daily during 28-day cycle or until progression of HLH or occurrence of severe toxicity
- **CHOP-like protocols plus etoposide** and ruxolitinib
- **Plasmapheresis** or the use of cytokine adsorption columns may aid in rescuing critically ill patients from a deleterious cytokine storm
- **Emapalumab** (anti–IFN-γ monoclonal antibody) as a second-line therapeutic agent for primary HLH in children and adults-given intravenously at a dose of 1 mg/kg combined with dexamethasone (5–10 mg/m2). Emapalumab is given twice per week, and the dose can be increased to 10 mg/kg according to patients' tolerance and clinical evolution
- **Anakinra**-Recombinant human IL-1 receptor antagonist effective in treating pediatric HLH/MAS associated with non-oncologic diseases, especially with rheumatologic disorders
- Nivolumab, a PD-1 inhibitor- Nivolumab has the advantage of restoring the expression of HLH- associated degranulation and costimulatory genes in CD8 T cells. Nivolumab can be considered only for EBV-HLH
- DEP(L)- doxorubicin, etoposide, methylprednisolone (L Apsaraginase)- EBV HLH-(used in adults with refractory HLH), With advent of ruxolutinib and other novel therapies DEP chemotherapy may be tried only in selected patients.
- HSCT: When there is complete or partial response HSCT should be started as quickly as possible, as further delays can cause relapse or complications in the heavily immunocompromised child. The transplantation may be done with a matched or mismatched donor stem cell with myeloablative or reduced intensity conditioning. Sibling should be tested for nascent homozygous mutation before being accepted asa stem cell donor.HSCT is not done in the milder forms with variant mutations, namely, heterozygous or homozygous A91V variant in the PRF1 gene, except if there are other severe mutations associated with it.

Life expectancy:[4]

- Median survival in typical fHLH without treatment is less than two months
- Five-year survival of children treated with chemotherapy alone in fHLH– 10 %
- With HSCT:Overall 50-60% of the patients are cured
- Reduced intensity regimens prior to HSCT - 70-80% of patients are cured
- Established CNS complications are irreversible
- Active HLH disease at the time of HSCT portend poor outcomes and is associated with higher mortality

Precautions:

- Live vaccinations are contraindicated during treatment until cure
- Avoid exposure to infections
- Dietary advice to be taken when child is on dexamethasone, with regular blood sugar monitoring
- Avoid NSAIDS during liver failure
- Transfuse only irradiated blood products

Prevention:

In familial HLH, future births with HLH can be prevented with prenatal genetic testing

Risk of family members:

Siblings should be tested when parents are consanguineously married and history of fHLH exists. If both parents are heterozygous for fHLH genes, each sib of proband has 25% chance of inheriting biallelic variant, 50% chance of pathogenic variant, 25% chance of neither variant.

Parents of an affected child are obligate heterozygotes. If only one parent is having genetic abnormality, then the other pathogenic variant in the proband is a de novo event or the genetically normal parent is a mosaic. Heterozygotes are asymptomatic.

Conclusion:

HLH is a hyperinflammatory disorder with hyperactive macrophages, dysfunctional cytotoxic T lymphocytes and NK cells and increased inflammatory cytokines mainly IFNy, IL12, IL6, IL10. Symptoms mimic severe sepsis.Hscore helps in early diagnosis of secondary HLH. HLH 2004 diagnostic criteria can be used for diagnosis. HLH may be genetic or acquired. High index of suspicion is required to initiate tests for diagnosing HLH. Early recognition and prompt treatment is necessary to prevent mortality. HLH 1994 protocol is used for treatment. Novel therapies are given for refractory HLH. The only curative treatment is HSCT without which survival is only 10% in familial HLH. Family and prenatal testing is advised to identify at risk persons.

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MANAGEMENT OF THALASSEMIA

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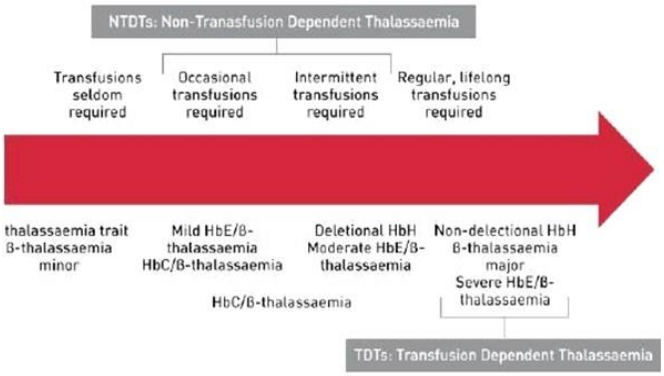
The term 'thalassaemia' refers to a group of blood diseases characterised by

decreased or absent synthesis of one or more of the normal globin chains.

✔ Most thalassaemia are inherited as recessive traits.

TYPES

- Transfusion-Dependant Thalassemia (TDTs) (1)
- Non-Transfusion-Dependent Thalassemia (NTDTs)



CLINICAL FEATURES:

✔ **Carriers**-Clinically asymptomatic but sometimes have mild anaemia.

✔ **β thalassaemia major**

- Presents between 6 - 24 months of age
- Severe Microcytic anaemia, mild jaundice and hepatosplenomegaly.
- Failure to thrive
- Feeding problems, irritability, recurrent bouts of fever, intercurrent infection, and progressive enlargement of spleen and liver.

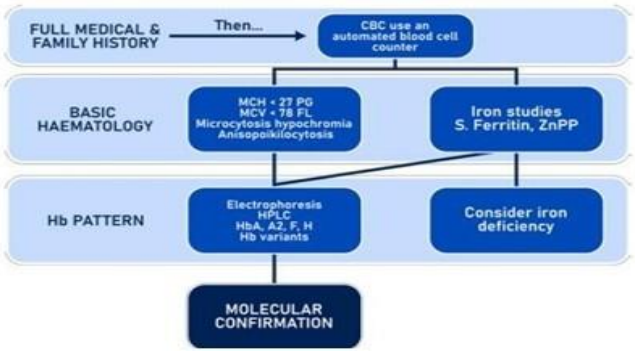
CLINICAL PICTURE IN PATIENTS WHO ARE UNTREATED OR POORLY TRANSFUSED

- Growth retardation, pallor, jaundice, poor musculature
- Genu valgum, leg ulcers,
- Hepatosplenomegaly,
- Extramedullary haematopoiesis and skeletal changes resulting from expansion of the bone marrow.

β THALASSEMIA INTERMEDIA :

- Present later than those with thalassaemia major
- Milder anaemia which do not require or only occasionally require transfusions.
- At the severe end of the clinical spectrum, patients are brought to medical attention between the ages of 2 and 6 years with retarded growth and development.
- Legulcers ,Hepatosplenomegaly with extramedullary Haematopoiesis
- Cardiac involvement in thalassaemia intermedia is mainly characterised by a high-output state and pulmonary hypertension with Preserved systolic left ventricle function
- Myocardial siderosis is rare.

DIAGNOSTIC STRATEGY:



TREATMENT:

A) MEDICAL MANAGEMENT

B) HEMATOPOIETIC STEM CELL TRANSPLANT

BLOOD TRANSFUSIONS:

An effective transfusion regimen will result in:

Good growth and development

Good energy levels

Sufficient suppression of intra and extramedullary haematopoiesis

- Leukodepletedblood products

Reduction to 1 X 106/l or less leucocytes per unit is considered the critical threshold for eliminating adverse reactions attributed to contaminating white cells(4)

- Before embarking on transfusion therapy, patients should have extended red cell antigen typing that includes at least A, B, O, C, c, D, E, e, and Kell
- If the patient is already transfused, antigen typing can be performed using molecular rather than serological testing.
- All patients with thalassaemia should be transfused with ABO and Rh (C, c, D, E, e) and Kell compatible blood to avoid immunization against these antigens.

CRITERIA FOR INITIATING TRANSFUSION THERAPY :

- Confirmed diagnosis of thalassaemia.
- Laboratory criteria:

✔ Haemoglobin level (Hb) <70 g/l on 2 occasions, > 2 weeks apart (excluding all other contributory causes such as infections) AND/OR

- Clinical criteria irrespective of haemoglobin level:

✔ Significant symptoms of anaemia

✔ Poor growth / failure to thrive

✔ Complications from excessive intramedullary haematopoiesis such as pathological fractures and facial changes

Clinically significant extramedullary haematopoiesis.

TRANSFUSION THRESHOLDS AND FREQUENCY :

✔ Lifelong regular blood transfusions, usually administered every two to five weeks

✔ To maintain the pre-transfusion haemoglobin level 9.5-10.5 g/l.(2).

VOLUME TO BE TRANSFUSED:

(Desired – actual Hb (g/l)) x weight (kg) x 0.3 = ml to be transfused assuming the haematocrit of the unit is 0.58 (3)

MONITORING OF IRON OVERLOAD:

S.Ferritin<2500 ug/l-Lower risk of Cardiac disease and death

Falsely elevated in acute infections and inflammations

LIVER IRON CONCENTRATION:

✔ SQUID((superconducting quantum interference device)-Under research

✔ MRI R2 or R2* using liver iron content (LIC) (mg of iron/g dry weight) is considered the method of choice.

✔A yearly LIC assessment should be performed in all patients in order to monitor chelation therapy effectiveness

✔LIC values greater than 7 mg Fe/g dry weight and 15mg/g dry weight are associated with moderate and severe iron overload respectively.

✔ S.Ferritin values > 2000 ng/ml are associated with liver iron overload(1!)

MYOCARDIAL IRON OVERLOAD:

Magnetic resonance T2-star (T2* MRI) is a method for assessment of high molecular weight iron complexes like ferritin and hemosiderin. induced T2 relaxation

It has a shorter acquisition time and can be taken in a single breath hold.

FOLLOW UP:

T2* MRI<20ms-Cardiac iron overload-Requires Iron chelation

T2* MRI- 10-20ms-Repeat MRI every 12 months.

T2* MRI<10ms-Repeat MRI every 6 months.

T2* MRI>20ms-Repeat MRI every 24 months

MONITORING OF OTHER ORGAN FUNCTION AND IRON- MEDIATED DAMAGE:

Growth and sexual development

Diabetes mellitus (yearly oral glucose tolerance test (OGTT)

Hypothyroidism and

Hypoparathyroidism.

INDICATIONS OF IRON CHELATION:

Start after the first 10-20 transfusions

Ferritin level rises above 1,000 µg/l.

TYPES OF IRON CHELATORS :

A) Monotherapy

B) Combination Therapy

✔ Desferrioxamine(DFO)

30-60 mg/kg/day, s.c./i.m. or i.v Injection, 5-7

times/week

Can be used in combination to chelate the iron overload

Used for pretransplant Iron chelation

Dilute 500 mg in at least 5 ml water(10%)

Rotate infusion sites

Prefilled syringes,Balloon pumps.

Ensure Compliance

ADR:Ocular, auditory,bonegrowth retardation, localreactions,allergy.

✔ Deferasirox(DFX):-More commonly used oral iron chelator

20-40 mg/kg once daily of a dispersible tablet.

Dispersible tablets to be dissolved in water or juice

Not to be dissolved in milk or aerated drink

To be taken empty stomach

ADR:Gastrointestinal,increased creatinine and hepatic enzymes

Contraindicated in Renal failure and Advanced liver disease and hepatic decompensation.

✔ Deferiprone(DFP)-Good cardiac iron chelator

75-100mg/kg/day in three divided doses.

Oral, tablet or liquid

ADR:Gastrointestinal,Arthralgia,Agranulocytosis and Neutropenia.

COMBINATION THERAPY:

✔ DFX 20-40 mg/kg/d 7 days per week plus DFO 40mg/kg/d 5 days per week, a significant reduction in ferritin and LIC, of 44% and 52%, respectively, and an increase in cardiac T2* of 33% were achieved (8).

✔ DFP 75 mg/kg in two divided doses was combined with DFX 20 mg/kg once daily SF, LIC and mT2* improved significantly and in quality of life in the oral combination group with no serious adverse events.(9)

STEM CELL TRANSPLANT IN TRANSFUSIONDEPENDANT THALASSEMIA

✔Should be done as early as possible preferably at preschool age possibly<7yrs

PESARO CLASSIFICATION FOR RISK ASSESSMENT PRIOR TO HSCT FOR TM(10)

Risk factor	Class 1	Class 2 (min. 1, max. 2)	Class 3
Inadequate chelation	×	×/✓	✓
Hepatomegaly >2 cm	×	×/✓	✓
Portal fibrosis	×	×/✓	✓

Class I-No Risk factors

Class II-One or two Risk factors

Class III-All three risk factors

PRETRANSPLANTWORKUP:

✔ MRI and FIBRO SCAN analysis to evaluate liver iron load and liver fibrosis

✔ Cardiac MRI to evaluate cardiac iron load and function.

✔The key to reducing graft rejection is to reduce erythroid expansion prior to HSCT.

✔ Thalassemia trait can be a stem cell donor

✔ HSCT can be done from HLA-matchedRelated,unrelated donors and Haploidentical match

CONDITIONING REGIMEN : Bu/CY/ATG

FOLLOW UP:

✔ Careful monitoring of haematological and engraftment parameters, infectious complications and GvHD is essential.

✔Appropriate immunisation is necessary if there is no GvHD.

✔ Long-term follow-up should be done with respect to iron overload, pubertal development, growth and endocrine deficiencies.

NEWER THERAPIES:

1. LUSPATERCEPT-Recombinant fusion protein – trap for activin receptors
2. Mini hepcidins (MH): short, engineered peptides with an increased half-life and potency, able to mimic the iron-restrictive effect of endogenous hepcidin
3. VIT-2763 is a small, oral compound that competes with hepcidin for ferroportin binding.
4. Targeting iron metabolism through
   TMPRSS 6 (Transmembrane Protein Serine esterase 6) inhibition
   Ferroportin inhibition
5. Synthetic human hepcidin
6. Ruxolitinib – JAK Pathway inhibition
7. Gene Therapy

Further reading

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Vitamin B 12 Deficiency, a common occurrence than we think!

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Vitamin B12, also known as cobalamin, is a water-soluble vitamin that is required by the body for the synthesis of desoxyribonucleic acid (DNA) and ribonucleic acid (RNA). It plays a role in both erythropoiesis and central nervous system myelination. It is not synthesized by the body and must therefore be obtained through diet.

Dietary sources of vitamin B12 include dairy products, eggs, meat, and fish. In children and adolescents, vitamin B12 requirements range from 0.4 mcg to 2.4 mcg per day1.

Vitamin B12 deficiency is one of the most common vitamin deficiencies. It is more common in developing countries. The Indian Comprehensive National Nutrition Survey (CNNS) was conducted on 1,05,243 children and adolescents during 2016–18 across all the Indian geographic states. The prevalence of B12 deficiency was found to be high among adolescents (31%), with a 50% lower prevalence in preschool (13.8%) and school-age (17.3%) children.2

Deficiency occurs most frequently in children and adolescents because of decreased oral intake, primarily because of a strict vegetarian or vegan diet.

It could also be due to a lack of vitamin B12 transport protein or poor intestinal absorption including Imerslund-Gräsbeck syndrome. Long-term use of proton pump inhibitors, Helicobacter pylori infection, previous gastric bypass surgery, pancreatic insufficiency, Celiac disease, and Crohn's disease are all risk factors.3

The mother's vitamin B12 level has the greatest influence on an infant's vitamin B12 level.An infant born to a deficient mother not only has low blood leve-ls of B12, but also has insufficient liver storage of the vitamin. Furthermore, low-Vitamin B12 breast milk is more likely to be a mother deficient in cobalamin4. Infants born to mothers with low vitamin B12 stores can develop clinical symptoms as early as 6–18 months of life.5

Children usually present with hematological and neurological symptoms. Infants frequently exhibit nonspecific characteristics such as weakness, lethargy, feeding difficulties, and failure to thrive. In children, symptoms include weakness, vomiting, and diarrhea, as well as pallor, icterus, glossitis, and skin pigmentation. Neurologic manifestations include paresthesia, sensory deficits, hypotonia, seizures, developmental delay, developmental regression, and neuropsychiatric changes. Even in the absence of hematologic abnormalities, neurological problems can arise.

RBC indices that are elevated, indicating macrocytic anemia, and a peripheral smear with macrophages and hypersegmented neutrophils with pancytopenia in some cases are laboratory findings that indicate vitamin B12 deficiency. Serum LDH is raised, suggesting ineffective erythropoiesis. The reticulocyte count is low. A definitive diagnosis of vitamin B12 deficiency is determined by measuring vitamin B12 levels. Levels less than 200 are considered deficient. Serum homocysteine and methylmalonic acid levels are elevated, confirming the diagnosis. Excessive excretion of MMA in urine is a reliable and sensitive indicator of vitamin B12 deficiency1. Here we describe two interesting cases presenting to us with varied clinic manifestations.

Case 1 : 13 month old infant was brought with H/O Decreased activity, developmental delay in all fields and failure to thrive, He was exclusively breast fed for 9 months, and was on semisolid, dilute diet. On examination was found to have Gr 2 PEM, Had pallor and Hyper pigmentation of knuckles (Fig B and C), generalized hypotonia was present. His investigations showed Hb 10.7 gm/dl, Tc-5700 /cumm, Platelet count- 3.7 lakhs, PS showed macrocytic normachromic anemia (Fig D), his iron studies were normal, Vitamin B 12 levels were low at 70.75 pg/ml (normal 200-835), Serum Folate levels were normal (9 ng/ml), Serum homocysteine levels (62) and serum methylmalonic acid levels (978) were raised there by confirming the Vitamin B 12 deficiency. He was treated with Dietic advice and Parenteral Vitamin B 12 IV infusions. His condition improved drastically, his activities improved, started looking at the mother once again which he had stopped and on subsequent follow up his development was normal for the age. Reiterating the fact that Vitamin B 12 deficiency is one of the common causes of preventable cause of developmental delay.

CASE 2 : A 11-year-old male adolescent presented to us with generalized weakness,

weight loss from 1 month, and vomiting in the last 1 week. On examination, he was noted to be pale, had knuckle pigmentation (Fig A), mild icterus was present. He had mild Hepato-splenomegaly on abdominal examination. A complete blood count revealed pancytopenia with a hemoglobin level of 4.5 gm/dl, a total leukocyte count of 2870/cumm, and a platelet count of 50,000 cells/cumm. RBC indices were raised (MCV= 104.1 fL, MCH = 36.9 pg, and MCHC = 35.4%). A peripheral smear showed macrocytes and hypersegmented neutrophils, suggesting macrocytic anemia, thrombocytopenia without blasts. LDH was raised (7756) with a low reticulocyte count (0.6%). Serum folic acid levels were within normal limits (5 ng/mL). Serum homocysteine levels (53) and serum methylmalonic acid levels (1470) were raised, which confirms Vitamin B 12 deficiency Anemia.

The child was started on parenteral vitamin B12, after which the child showed clinical and hematological improvement. The reticulocyte count done at the end of 72 hours of starting Vitamin B12 therapy showed an increasing trend (2.3%). Dietary history showed faulty diet with low intake of Vitamin B12 rich food like meat and dairy products. His condition improved drastically and icterus disappeared on follow up.

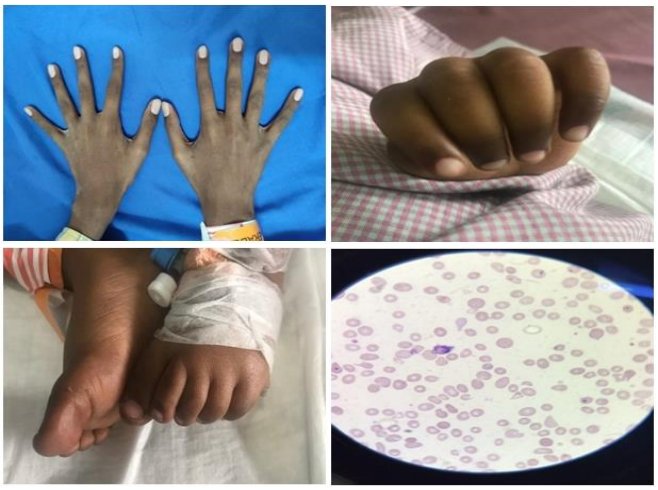

Figure A, B, C showing Pallor and Knuckle Pigmentation and Fig C Peripheral smear showing Macrocytic RBCs

CONCLUSION

India is largely a vegetarian population, and micronutrient deficiencies abound in the community. Deficiency of Vitamin B 12 is not only an important cause of anemia but its deficiency may cause impaired myelination, axonal degeneration, and cerebral atrophy resulting in substantial neurological deficits such as hypotonia, cognitive deficits, and developmental delay in children. This may remain undiagnosed and lead to a poor neurological and cognitive outcome for the child. It is critical to identify infants, children, and adolescents with Vitamin B12 deficiency as early detection and treatment has a favorable prognosis. Early vitamin B12 replacement results in a rapid and significant improvement in symptoms, both hematological and neurological. The longer the deficient period, the greater is the risk of permanent disabilities. Familiarity with risk factors, manifestations, and diagnostic studies of vitamin B12 deficiency by pediatric health care providers is crucial to enable early recognition and treatment.

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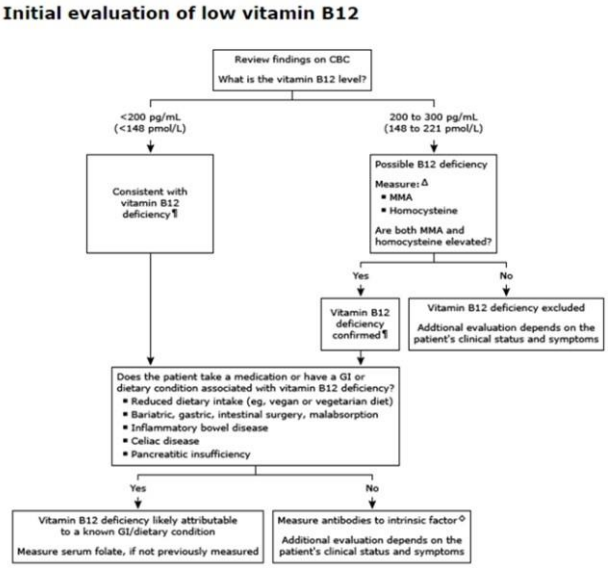

Platelet Distribution Width : A Novel Biomarker ?

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Introduction :

Platelets play an important role during the process of coagulation ,inflammation and immune response. Platelet distribution width (PDW) is one of the platelet indices which reflects platelet anisocytosis, it is also a marker for platelet function and activation. It reflects heterogeneity of platelet morphology. An increase in PDW indicates a deterioration in the size consistency of platelet volume. Hyperplasia of megakaryocytes is associated with PDW increase. In contrast, a decrease in PDW correlates with increased consistency. Under normal bone marrow function, MPV is positively associated with PDW. In inflammatory disease conditions PDW has an inverse relationship with the severity of the disease. PDW is measured using automated analyzers or by flow cytometry. It is given as a part of the complete blood count and it requires EDTA sample. Normal range of PDW is 10 % - 17.9 %.

Implications :

Sepsis is a commonly occurring severe disease of childhood . It contributes to a majority of the mortality in children (1-26%) and leads to significant morbidity (5%).

Sepsis is considered a worldwide public health problem. But it is not tracked in the Global Burden of Disease report published by the WHO and World Bank.

Many studies done to identify the prognostic markers for sepsis showed PDW a good correlate for ongoing infection. 1,2 Thrombocytopenia, platelet indices and their ratios, especially plateletcrit and MPV/PCT, are readily available, sensitive, prognostic markers, that can identify the severe sepsis patients with poorest outcome.

Further studies have compared PDW with other septic markers like CRP and Procalcitonin which suggested that PDW and MPV had statistically significant correlation with procalcitonin as a marker of bacterial infection. 3 PDW has also been evaluated as a potential adjuvant for the diagnosis of Kawasaki disease. But it was found to be not statiscally significant. In a study by Sepas HN et al titled “Evaluation of the Potential Association of Platelet Levels, Mean Platelet Volume and Platelet Distribution Width with Acute Appendicitis”, results showed that the MPV and PDW were significantly higher in acute appendicitis in comparison to perforated appendicitis and acute gangrenous appendicitis. Their study indicated that PDW < 10.05 had a sensitivity of 35%. 4 Awad A, et al concluded that MPV, PDW, and plateletcrit were elevated in children with PAH-CHD. They were good predictors of poor prognosis with 75% sensitivity and 61.5% specificity. 5

Ventriculoperitoneal shunt infection (VPSI) causes significant mortality and morbidity in hydrocephalus. Celik U et al conclude that PDW can be used for the diagnosis of VPSI in children. It has an accuracy of at least 75%. PDW >12.25 had sensitivity and specificity of 68% and 80% for diagnosis of VPSI. PPV and NPV of 77% and 71%, respectively.6

Conclusion :

PDW parameter has been shown to have good prognostic implications in wide range clinicopathological states. However, they are still largely under utilized by clinicians and there is a need to increase awareness of the clinical benefits of this parameter. It's role as a biomarker needs further research.

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Photo Gallery

ATM Workshop

Dr. Somashekar's Kannada Book Review

Guest Lecture at MSR

Photo Gallery

Respiratory Emergencies Workshop
at Chikkaballapur - by
Dr. Somashekhar and Dr. Venkatachalapathy

Respiratory Emergencies Workshop

Valedictory CME

Valedictory Program

On 13/1/24 SSS program was done at government school Saregovanahalli for 8th and 9th students by SSS trained IAP BPS members Dr. Vimochana, Dr. Padmavathi, Dr. Kanchana and Dr. Hema Sharma.

Total no. of students present were 176. In Association with BAHA and IMA Women 's wing Bangalore.

Kasi sir honoured after his deliberation at the installation of Kar IAP, Mysore IAP and MAHA