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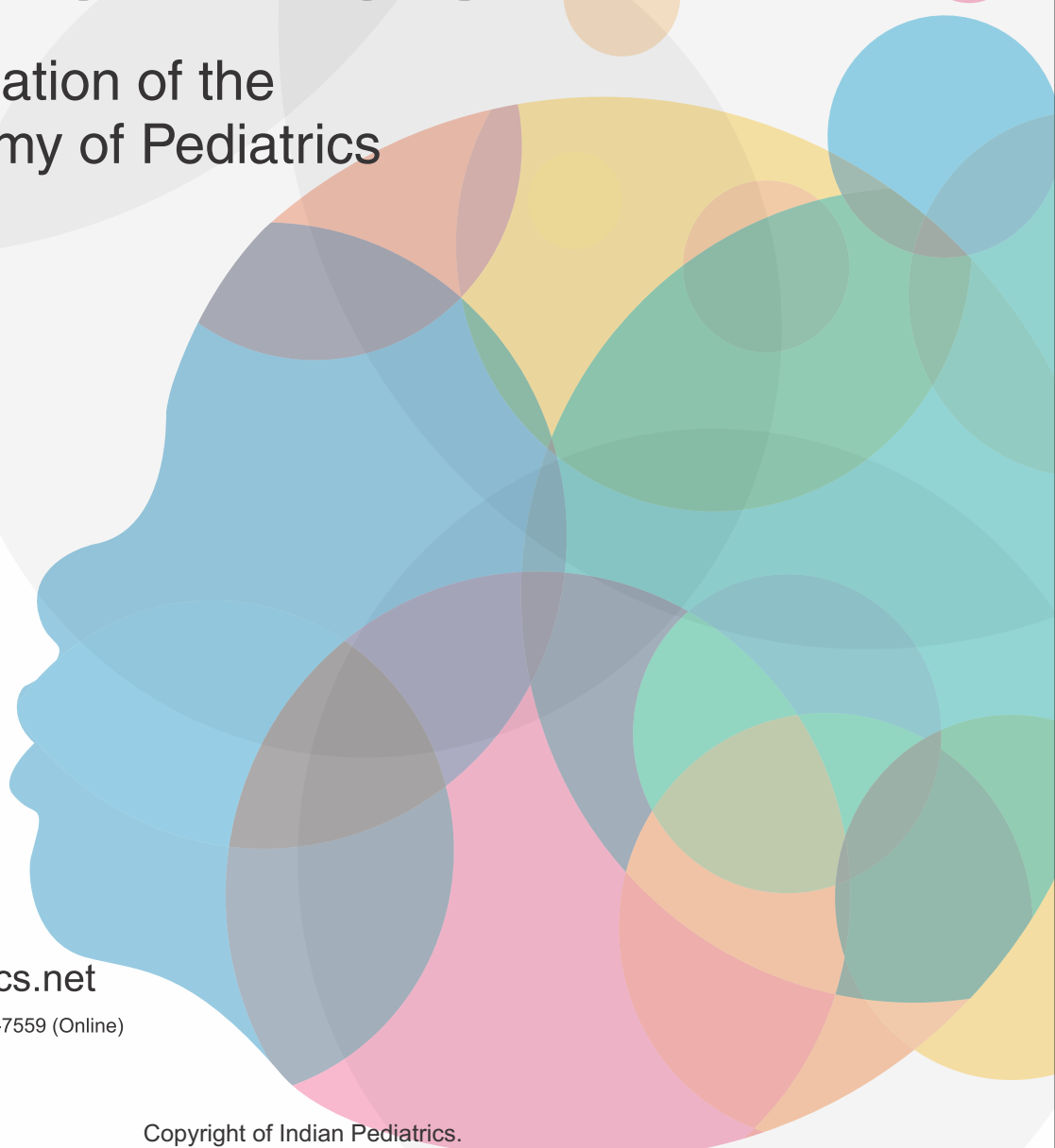

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PRESIDENTIAL ADDRESS

57th National Conference of Indian Academy of Pediatrics (PEDICON) 9-12 January, 2020, Indore

BAKUL JAYANT PAREKH
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Respected Chief Guest, Guest of honor, teachers, seniors, colleagues from SAPA countries, Egypt, AAP president, friends, Ladies and Gentlemen, a very Happy New Year to all of you, and a warm welcome on this pleasant evening at Pedicon 2020, Indore. I am honored and delighted to be here at Indore, and humbled by the faith you all have reposed in me.

In this year, I plan on doing a number of new things for our academy. Keeping the words of Gail Sheehy in mind that *"If we don't change, we don't grow,"* and that of Nelson Mandela stating *"education is the most important tool, which we can use to change the world"*; I have a vision for 2020, and I hope that you all will help me in achieving it for the benefit of our parent body, the Indian Academy of Pediatrics (IAP).

Routinely, we have most of the IAP Action Plans going ahead with Training of trainers (TOT) workshops and Continuing medical education (CME) activities. These will continue, with an added focus on quality and usefulness of the modules in day-to-day practice. A post-test will ensure that the trainers have understood the essence of the workshop and are ready to disseminate the knowledge to all our colleagues. I intend to start a new concept – Monsoon Pedicon (based on sub-specialty chapters) – wherein faculty will gather at a place and deliberate on scientific content for a couple of hours. The highlight of this will be that the delegates of this Pedicon will be at their own clinic or home, listening to the deliberations and these talks will also be archived so that they can be revisited as required. I am also working on science conclaves where 50 people will be meeting at a place in 5 groups of 10 each on a Saturday to discuss about one topic of a sub-specialty each, and on Sunday, all these 50 people will sit together, deliberate on all the topics, and come out with the guidelines. I call these as Protocons – five such Protocons will be held in the first half of the year and then we can have a national Protocon, which shall culminate in the form of national AWESOME in the month of September-October. This will show that we can also conduct a successful National-level conference without pressures on ourselves or pharmaceutical companies.

Clinical research is very much lacking in India as compared to the developed nations. I wish to initiate some incentive-driven programs with the help of Head of the departments (HOD) cell and ensure that the postgraduates are incentivized to take this forward. At the same time, we need to have capacity building workshops for practicing pediatricians. This will help to recognize their talents and propel our academy to reach greater heights. I am also in talks with UpToDate, wherein the annual subscription price for the service will be greatly reduced for IAP members. I am certain that this will help in strengthening point-of-care rational therapy and clinical research across all fields in IAP.

The Academy being a charitable institution, I intend to have a number of social and charitable activities wherein a district branch adopts a village and looks after the health parameters of its child community.We will also like to have palliative care centers (an initiative by one of my teachers and a very astute academician Dr. Armida Fernandez), school health programs, ALS and BLS courses, programs for AYA (adolescents and young adults), and YUVA CME (to help the newly graduated pediatricians to set up their practices). I am also trying to have affiliations with international universities for the recognition of IAP subspecialty courses.

Friends, in the last five years, I have travelled almost all over the country and have met many of our colleagues at the local chapters. I donot know how much they have benefitted by meeting me, but I have learned immensely from them. I found that their dedication to their work is far greater while their access to latest advancements in medicine, education, diagnostics, *etc* is comparatively much lower as compared to those in the big cities. The key challenges, I noticed, can be categorized into one or all of the following three buckets:

- Access to latest information;
- Ability to educate their patients on right practices related to health and hygiene; and
- Lack of quality support at point of care.

For many years, I have been thinking about digitizing education, and in the last few years the cost to access digital content has become practically zero.

Now, I would like to introduce again and share highlights about dIAP – a vision that will allow us to have our very own technology-enabled Academy to 'Reach the Unreached' and address the challenges we have just outlined. dIAP is not only a window to IAP's services, but it is also IAP's institutional digital backbone. In addition to IAPs existing digital assets, dIAP brings to us several new national services. The first is a professional education service for pediatricians. This service combines courses, scientific reference material and a reservoir of content - all created and published by IAP experts. The second is video-conferencing and webinar centers across IAP offices in India, which will allow for thousands of online lectures, clinics, webinars etc. that can be accessed by all IAP members using their mobile phones and also available as a searchable online archive. The third is patient education services, which can be used in a clinic. The fourth is diagnostic support, prescription guidelines, and diagnostic algorithms at the point of care.

It gives me great pleasure to say that a part of the Plan has already been implemented and some of the dIAP services are available immediately to our members *via* the IAP courses. I am also very happy to say that the first webinar center has been successfully tested in Mumbai and we have started it off with the webcasting of popular Thursday PG clinics and lectures. In the coming months, several more centers will be setup.

The point of care system is also already being built and tested. As I already mentioned to our esteemed Executive Board members yesterday, we have created individual websites for all state chapters. As soon as their content is received and published, their website will be launched with complete control over content and management by the state chapter - totally free of charge.

I remember the words of Thomas Fuller – "*All things are difficult before they become easy,*" and those of John Wooden – "*Good things take time*." I look forward to your support so that the rest of the Action Plan is implemented and made available to our members in the coming months.

And lastly, a little surprise for all of you – the first version of the dIAP app is ready and available on Google Play Store for Android users. Please search for 'diapindia', download and register. In coming months, the technical team will be updating the app and will also make this available on other leading mobile platforms.

Last, but not the least, I feel truly honored and blessed to be working with such a dynamic team which is focused on taking IAP to even greater heights than what it currently is. I would like to end this with a maxim that I follow in my life:

"Do not walk in front of me; I may not follow you.
Do not walk behind me; I may not lead you.
Do not walk away from me; I need you."

Let us walk together for the glorious future of our mother IAP.

Jai Hind!
Jai IAP!

PERSPECTIVE

An Uphill Task for POSHAN Abhiyan: Examining the Missing Link of 'Convergence'

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The Participatory Approach for Nutrition in Children: Strengthening Health, Education, Engineering and Environment Linkages (PANChSHEEEL) project is a collaboration between University College London, Save the Children India, Jawaharlal Nehru University and Indian Institute of Technology Delhi to develop a socio-culturally appropriate, tailored, integrated and interdisciplinary intervention in rural India and test its acceptability for delivery through Anganwadi Centre (AWCs) and schools. Recognizing the socio-ecological determinants of under-nutrition, the POSHAN Abhiyan (POSHAN Mission) adopts a multi-sectoral approach to achieve five goals, of which two are directly related to children. The POSHAN Abhiyan resonates with the conceptual framework of the PANChSHEEEL study in its interdisciplinary scope and focus on local linka ges. This paper draws upon empirical evidence from the PANChSHEEEL Project in Banswara (one of the POSHAN mission districts), Rajasthan to help understand linkages between policy and practice, specifically the challenges of operationalizing 'convergence', the core strategy of the Abhiyan.

Keywords: *Co-designing, Complementary feeding, Intervention, Under-nutrition*.

The Sustainable Development Goals (SDG) shifted the focus from reducing mortality to ensuring healthy living and wellbeing [1]. The Global Strategy for Women's, Children's and Adolescent's Health 2016-30 called for a transformative change from the MDGs to the SDGs, advocating a continuum of survive (ending preventable deaths) – thrive (realizing health and rights in all settings) – transform (people centered movement for comprehensive change) [2]. Were, *et al*. [3] flagged three key essential child-nutrition related issues: (*i*) exclusive breastfeeding for six months and continued breastfeeding up to at least two years, with appropriate complementary feeding from six months; (*ii*) monitoring and care for child growth and development; and, (*iii*) ensuring food security for the family. Acknowledging the prevailing challenges of poverty, poor nutrition and insufficient access to clean water and sanitation as well as quality health services, the WHO called for a 'grand convergence' to make this transition [4]. An analysis of nutrition governance in India by the Institute of Development Studies pointed to three core roadblocks to achieve convergence: (*i*) lack of horizontal coordination; (*ii*) siloed, bureaucratic vertical articulation; and, (*iii*) inadequate financial outlays [5].

The NITI Aayog (National Institution for Transforming India) launched the National Nutrition Strategy in September 2017 [6] with five specific monitorable targets to be achieved by 2022 of which the first two focus on children below six years: (*i*) prevent and reduce stunting in children (0-6 years) by 6% at the rate of 2% per annum and (ii) prevent and reduce under-nutrition (underweight prevalence) in children (0- 6 years) by 6% at the rate of 2% per annum [7]. In December 2017, the National Nutrition Mission (NNM) subsequently approved a multi-ministerial convergence mission to monitor, supervise and fix targets, and guide nutrition related interventions [8]. It was renamed as the POSHAN (Prime Minister's Overarching Scheme for Holistic Nourishment) Abhiyan/ Mission (henceforth PM/PA) on 8 March 2018 [9]. The PM is guided by two policy documents, the National Nutrition Strategy and the Administrative Guidelines of the NNM across three core themes: (*i*) determinants of complementary feeding; (*ii*) convergence as the core strategy; and, (*iii*) IT enabled approach to monitoring.

This paper draws upon empirical evidence from our PANChSHEEEL study (that fosters collaboration between our interdisciplinary research team, local schools, frontline health workers and communities using schools and Anganwadi Centers as new innovation hubs to develop an integrated system that links health, education, engineering and environmental solutions for

optimization of ICYF) in Banswara District (one of the PA districts), Rajasthan to help understand linkages between policy and practice in the PA since its inception. This mixed methods study was conducted from April 2017 to July 2019 to obtain data on Infant and Young Child Feeding (IYCF) and care practices across domains of nutrition, health, water, sanitation and hygiene (WASH) as well as education, and create a multi-dimensional intervention package through a participatory health settings approach tailored to community needs.

The study was conducted across nine villages (selected on a set of consensus criteria) of Banswara District [five in Ghatol (canal irrigated) and four in Kushalgarh (semi-arid) blocks, respectively]. Community profiling and social mapping was conducted in each village with the help of Community Researchers. Qualitative data (Phase 1) was collected using two methods – key informant interviews (49 interviews) and focus group discussions (17 FGDs), with the help of pre-tested guides in local language. Quantitative data (Phase 2) comprised of household (445 households in the nine villages with children below the age of 24 months) and maternal time use surveys (in a sub-sample of 90 households). The household survey collected data on demographic, socio-economic (under the broad domains of health, education and WASH) and IYCF indicators.

RELEVANCE OF COMPLEMENTARY FEEDING

The conundrum of improvement in anthropometric indicators and decline in complementary feeding indicators in the National Family Health Survey 4 (NFHS4) makes a compelling argument for a dedicated focus on the issue of complementary feeding (CF), the first monitorable target of PA that is relatively neglected in policy, programmatic and academic discourse. IYCF practices encompass two age groups of children: 0-6 months and 6-24 months; with the latter being more critical as undernutrition sets in during this age due to lack of adequacy and diversity of foods as well as infection. Supplementary feeding interventions, infection prevention and curative measures are most effective in reducing malnutrition and promoting growth and development of a child [10].

NFHS4 data indicates a continued trend of improvement in breastfeeding practices in the first age group, but a 9.9 percentage point decline (NFHS 3: 52.6%; NFHS 4: 42.7%) in IYCF indicators [11]. Merely 9.6% children aged 6-23 months received an adequate diet including 14.3% of non-breastfeeding children and 8.7% of breastfeeding children. The declining trend is also noticeable in another indicator – children 6-8 months receiving solid or semi-solid food and breast milk.

The PA policy documents acknowledge the association of multiple factors with CF, identifying *nutrition sensitive* and *nutrition specific* factors such as access to maternal and child nutritional and health related services, drinking water, household food security, livelihood, girls' education and interventions for vulnerable communities [12-17]. **Box 1** summarizes factors that affect IYCF practices broadly classified into three levels: household, community and governance.

These factors are complexly intertwined both within and across categories; *eg*, one of the key emergent reasons for inadequate complementary feeding was lack of mother's time to feed young children.

The formative phase (triangulated qualitative and quantitative data) confirmed that IYCF indicators were dismally poor across both blocks in terms of introduction of semi-solid food during the previous day, minimum dietary diversity, minimum meal frequency, minimum acceptable diet and consumption of iron-reach food. Analysis of maternal time use confirmed a crisis of care (mean time allocated to caregiving was 76.9 and 65.7 minutes in villages of Ghatol and Kushalgarh blocks, respectively) with children aged 12-24 months receiving significantly less time allocated to caregiving than those aged 0-5 months. In short our formative phase confirmed

BOX 1 Levels of IYCF Determinants

Household

- Maternal time constraint, dwindling family size, mother's age and education
- Lack of adequate knowledge
- Poor uptake of existing nutritional services
- Child targeted market with wide availability and consumption of ready-to-eat market food items

Community

- Social and economic context
- Feminization of agriculture
- Fragile food security/seasonal food paucity due to less focus on food crops and vegetables
- Dwindling livestock – especially milk producing animals
- Low connectivity to remote locations
- Migration
- Exposure to media

Governance

- Inadequate and unresponsive ICDS (Integrated Child Development Services) and health care system
- Paucity of technical knowledge among service providers regarding IYCF

the determinants and processes summarized in ***Box 1***, and the evidence used to design and co-create an integrated intervention package. The syncretic model was constructed through synthesis of five interlinked processes: (*i*) data from formative phase; (*ii*) discussion with community groups; (*iii*) collation of NGO experiences; (*iv*) review of national and state policies and programs; and (*v*) expert group advice. The output of the intervention phase consists of a series of packages with its unique set of three aims (improving breastfeeding practices from first hour of childbirth to 6 months of age; increasing minimum acceptable diet for children aged 6-24 months; and, enhancing child care practices associated with growth and development of children below 24 months), relevant facilitators and barriers, and specific components – in terms of target recipient, function, content and channel.

To its credit, the PA approach recognizes the multiple determinants affecting undernutrition in general and some of these are relevant for IYCF practices as evident from our empirical data. The chosen programs for addressing these diverse determinants have been there for long with little demonstrable effect on the indicators in the 6 months to 2 years age-band. The Integrated Child Development Services (ICDS) is a case in point; it offers little for these children except the Take Home Ration (THR); growth monitoring is a weak component and infection prevention is hardly on the agenda. The supply of THR in our study areas was regular but consumption was erratic. While most mothers did not know the correct way to cook it, some mothers also did not have time to cook separately for the children and feed them. Inadequate capacity of the frontline health functionaries, high workload, and dissatisfaction about remuneration along with shortage of managerial staff for supportive supervision resulted in their inability to respond to utilization gaps.

To reiterate the relevance of the three cross-cutting PA core intervention themes: (*i*) the determinants of IYCF are complex and as exemplified above, the ICDS in its present siloed form shall continue to be ill-equipped to deliver a multi-dimensional package of interventions; (*ii*) the IT enabled approach is essentially designed to replace the registers and streamline monitoring and there is no scope (in its present vision) to engage with indicators from other sectors (that the convergent approach seeks to address); and (*iii*) convergence as the core strategy is thus intended to be the game-changer.

CONVERGENCE: THE CORE STRATEGY, AND THE WEAKEST LINK OF ALL

The PM correctly recognizes that a multi-dimensional problem like undernutrition requires multi-sectoral intervention; hence the centrality of convergence as the key strategy. Besides convergence at the political level, there will be a Committee of Secretaries from various ministries at central and state levels. Committees at district and block levels will draw up Convergent Action Plans (CAP). At the community level this is envisaged through the Village Health Sanitation and Nutrition Committees (VHSNC). Recent evaluations of VHSNCs revealed low awareness among members about their role and only few specified functions for decentralized planning and action were actually undertaken [18,19]. The PA documents call for a joining of forces by converging resources, skill and knowledge and outlines elements of engagement and specific contributions of a wide range of 'line departments' through the CAPs which is in sync with the WHO's call for 'grand convergence'. In order to do so needs assessment at village/Anganwadi Center (AWC) levels across related sectors have to be conducted jointly by frontline WCD (Women and Child Development) staff and supervisors and Panchayat (local self-government) members. Each 'line department' shall, on the basis of these needs, prepare 'action plans' that will be collated as Block Convergent Action Plans (BCAPs); and upwards to district (DCAPs) and state (SCAPs) levels.

Our extensive interactions (during the preparatory phase of the current CAPs) with block and district level officials of Banswara District point to several key challenges:

(*i*) The 'planning' process is limited to filling up templates circulated by the Technical Support Units; key specifications include: Year 1 (numeric) targets, activities/interventions, relevant departments and budget provisions.

(*ii*) There was little or no orientation to this process for staff at various levels.

(*iii*)Targets were arbitrarily specified by the officials at respective levels.

(*iv*) Actions/interventions were cursory and unimaginative at best; *eg* "organizing proper counseling of complementary feeding for a period of 15-20 minutes"; "maintenance of proper distribution of THR to the actual beneficiaries as per schedule"; "promotion of toilet use with less water and reuse of dysfunctional toilets"; or, "ensure tablets (iron and folic acid) are available at AWCs, Sub Centres, Primary Health Centres and Community Health Centres".

(*v*) CAPs are silent on 'how to' issues – the most challenging of all.

(*vi*) Budgetary provisions were not specified.

In contrast, our own community workshops adopted an integrated approach to formulate a package that was grounded on the core principles of: co-designing interventions that are flexible, feasible; acceptable, adaptable, accessible; sustainable, scalable; tailored and targeted; effective; resource efficient (Co-De FASTER) [personal communication-Lakhanpaul M 2019]. Co-De FASTER captured *emic* views from individual, household, community, organizational and governmental levels and were able to formulate a well-rounded package of interventions (in contrast to the CAPs prepared this year) that addressed aspects of target recipients, channels, content as well as barriers and facilitators than (***Box 2***). Policy makers need integrated evidence and support from academia that may act as 'policy entrepreneurs' and the PANChSHEEEL evidence provides a glimpse of that.

Convergent planning as envisioned by the PA is a multi-sectoral governance challenge and faces several key barriers, the first of which is political, not technical: how an issue is framed and the extent to which this resonates with high-level political agenda [20]. The extent to which an actor (departments, program managers or technical leads) engages with a problem reflects a match between the nature of the problem and their own nature. There is thus a difference in levels of participation by the different actors; bringing all actors out of their 'silos' requires collaborative and distributive leadership that entails trust, accountability, analysis of networks, and scope of mutual learning and fostering the ability to manage conflicts; the PM documents are silent on these vital aspects of governance. For the success of such a complex mission, it is therefore important to align all the departments to these core values.

BOX 2 The 8-step Approach to Co-designing an Integrated Intervention in the PANChSHEEEL Project

Step 1: Analysis of the formative research

Step 2: Creating a joint understanding about the Settings Approach

Step 3: Sharing the framework with the Community Champions for views about modifiability of these factors, validate findings, stakeholder mapping

Step 4: Intensive co-designing exercise with the community in one village in each block; consultations with teachers and School Management Committee members of all nine villages

Step 5: Mapping responses of the community and experiences of the partners and evidence from national and global programmes to formulate a consolidated Intervention Package 1 (IP1)

Step 6: Discussions related to IP1 with the Block and District officials of the relevant departments to formulate IP2

Step 7: Refinement (acceptability) workshops; IP2 shared with key members from all nine villages; based on the feedback/iteration; IP3 prepared

Step 8: Obtain inputs on IP3 from state and national policy makers to prepare a final IP4.

CONCLUSION

Windows of convergence open (and close) by the coupling (or de-coupling) of three streams: problems, policies and politics [21]. There is a need to focus on the relative roles of each department with respect to the commitment and motivation, funding, administration, organization and service delivery [22]. The PA is highly ambitious in aiming for a targeted reduction of key malnutrition indicators by 2022, and needs to meticulously address the emerging crisis of declines in IYCF indicators. Convergent Action Plans (CAP) is the capstone of this Abhiyan; and a lot rests on its systematic operationalization, and demonstrating a public health imagination. Effective convergence mechanisms, as visualized in the PA documents and emergent in our co-designing exercises, are crucial for breaking free of business as usual. PA recognizes the criticality of inter-departmental convergence for this multi-sectoral issue, but the implementation framework does not provide an adequate roadmap; without that CAPs are reduced to merely filling up templates with (numeric) targets. This reductionist framing of the CAPs, and the lack of well-rounded action plans, point to a lost opportunity as far as the first year of this Abhiyan is concerned. Building capacities across sectors and levels of government fast enough is an up-hill task that ought to be foregrounded in order to be able to rise to the challenge in the next planning cycle. Policy implementation is most likely when there is a 'synthesis of plausible evidence, political vision and practical strategies' [23]. At stake is the ambitious 2022 deadline, with little evidence in the first year that demonstrates convergence as the core strategy.

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EDITORIAL

Can Impulse Oscillometry be Used to Monitor Asthmatic Children?

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Children under six years of age find it difficult to control their breath, hence, spirometry is challenging and at times inaccurate. In asthma, estimation of lung functions is of assistance in establishing the diagnosis and monitoring the course of disease as well as response to treatment. Spirometry is based on the physiological changes which occur during maximal expiratory flow (MEF) and is currently used in the management of asthma. MEF, during mid or late expiration (MEF 25-75), is indicative of peripheral airway disease. However, forced expiratory volume in the first second (FEV_1) is mostly used to diagnose and monitor asthmatic children [1].

In 1956, Duboies, *et al*. [2] described a non-invasive method of superimposing externally created sound waves on subject's breath and document changes in respiratory mechanics. The resultant measurements were based on the principles of forced oscillatory technique. Later, this was refined and developed into impulse oscillometry (IOS), where low frequency waves of 5 Hz, which penetrate into the lung tissue, and high frequency waves of 20 Hz are delivered to the airways through a pressure transducer kept at the mouth of the subject. A pneumochromatograph is also kept at the mouthpiece to measure resultant changes in the wave patterns during breathing. The IOS works best at respiratory rates of 16-20/min. Some of the outputs are impedance to the generated impulse of 5 Hz (Z5); resistance to 5 Hz, primarily due to small or peripheral airways (R5); reactance, which is a combination of inertia of the air column to move and capacitance of the lung (X5) as well as area of reactance (AX); and resonant frequency where inertia of airways and capacitance of lung periphery are equal [3].

Theoretically, IOS can be done in small children in sitting posture, with nose clipped and cheeks kept flat manually. It does not require their cooperation during breathing. It is claimed that IOS can measure small airway resistance more accurately. However, reference ranges for IOS parameters are yet to be established.

Dawman, *et al.* [4] have compared IOS and spirometry in monitoring asthma in 256 children aged 5-15 y. Three monthly follow-ups were done and IOS and spirometry done at each visit. Children with physician-diagnosed asthma were included. At each visit the patients were classified as controlled, partly controlled, uncontrolled or in acute exacerbation, according to GINA guidelines [5]. The authors observed that FEV_1 and IOS parameters such as Z5, R5, X5 and AX and resistance 5-20 were correlated. Both machine parameters differentiated controlled and uncontrolled asthmatics, but in the Receiver operator curve analyses, areas under the curve for all the parameters ranged from 0.52 to 0.58. IOS parameters were assessed against the spirometry with FEV_1 as gold standard. However, FEV_1 itself does not measure functional status of small airways. Comparison of IOS with MEF25-75 has not been reported. Further analyses, controlling for respiratory rate, gender and anthropometry, from the data generated by the authors may show interesting results. The added value of IOS above standard spirometry in monitoring asthmatic children remains unclear from this work as younger children were not included.

Before IOS comes in routine practice, there is a need to establish normal values for various parameters across all pediatric ages in Indian children. Thereafter, the performance of IOS against commonly used spirometry parameters in specific pulmonary diseases in children has to be done. As of now, IOS seems to be a viable option for measuring lung functions in young children.

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EDITORIAL

Which Growth Charts for Today's Indian Children?

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Assessment of children's growth using anthropometric parameters is crucial to study the nutritional status of a population, and is also useful in analyzing growth disorders. Reference data are crucial to growth monitoring and help health care professionals and policymakers to diagnose under-nutrition (stunting and wasting), overweight and obesity. Children's growth patterns change with time and references need to be updated regularly; this is especially true in a country like India which is in a phase of nutritional transition [1,2]. Indian Academy of Pediatrics (IAP) therefore revised National growth references in 2015 [3]. These charts are based on large nationwide data collected on middle and upper middle class children (33148, 18170 boys) over last decade. A need to field test the IAP 2015 charts was pointed out previously, so that their applicability across India can be validated [4].

An important strength of IAP 2015 charts is that they do not 'normalize' obesity. IAP 2015 BMI charts have been adjusted to 23 and 27 adult equivalent cut-offs as per the WHO recommendation for Asian Indians and these cut-offs are very close to the Asian cut-offs by International Obesity Task Force (IOTF) [5]. This has been shown by a recent study from Srinagar [6].

Since the inception of IAP 2015 charts, several studies across India have used them to assess prevalence of short stature, and overweight/obesity [6-8]. IAP 2015 charts detect more children with overweight/obesity than the WHO, CDC or Agarwal charts. Marginally higher percentage of children are detected as short by IAP 2015 charts as compared to Agarwal charts because IAP 2015 charts incorporate the secular trend in height.

In this issue of *Indian Pediatrics*, Singh, *et al*. [9] have compared IAP 2015, Agarwal 1992 and WHO 2007 references in children in a narrow age group of 8-15 years from one urban private and one government school from north Delhi. Other studies mentioned earlier are on slightly larger numbers; 2175 children by Lohiya, *et al.* [7], and 1500 children by Chudasma, *et al.* [10], covering ages from 5-18 years. The study by Singh, *et al.* [9] shows a good agreement between IAP 2015 and Agarwal charts in classifying subjects into categories of BMI (K=0.82) and short stature (K=0.99). While this observation is valid, it is important to note the mean Z scores for height, weight and BMI are close to the IAP 2015 means as compared to the other charts, suggesting that urban Indian children's growth patterns are closest to the IAP 2015 reference standard [6-10].

Singh, *et al*. [9] also make a note of the secular trend in height in IAP 2015 charts as compared to the Agarwal charts (lower mean height for age Z scores in the IAP 2015). Similar data for weight and BMI are also presented by studies quoted in the earlier paragraphs.The observation by Singh, *et al*. [9] that IAP 2015 charts pick up more overweight and obese children than WHO and Agarwal charts has also been echoed by previous studies [6,7,10].

As IAP 2015 charts will be put to use more often in future in epidemiological studies as well as disease situations, their strength and limitations will be revealed further. Thus, articles such as the one by Singh, *et al.* [9] will help to improve and update future growth references for Indian children.

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EDITORIAL

Early Outcomes after Cardiac Surgery in Neonates and Infants in India

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The clinical landscape and outlook of critical congenital heart disease (CHD) and its management has been steadily advancing over the past three decades all over the world. India is not far behind in this race for betterment of care for the neonates and infants with CHD. As we step into the third decade of this millennium, the overall survival rate of many forms of CHD have improved. Critical CHD is generally defined as structural heart defects that are present at birth, and which require surgical or trans-catheter intervention either as a neonate or during the first year of life. Globally, CHDs are present in about 8-10 per 1000 live births. Among this group, critical CHDs account for nearly 25% [1,2]. The combination of good clinical examination after birth along with institution of the inexpensive universal pulse oximetry screening of neonates in the hospitals before discharge have resulted in increased identification of these major CHDs. Some of the critical CHDs diagnosed after birth with such screening include transposition of the great arteries, tetralogy of Fallot, pulmonary atresia, tricuspid atresia, total anomalous pulmonary venous return, truncus arteriosus, double outlet right ventricle, and left heart obstructive lesions such as critical coarctation and hypoplastic left heart syndrome.

In a recent large retrospective population-based cohort study in infants born with CHDs, covering nearly three decades, the 1-year survival for infants with critical CHDs was noted to improve from 67.4% in 1980s to 82.5% in early 2000s [1]. Advances in fetal cardiac imaging, widespread adoption of CHD screening as mentioned above along with improved perioperative critical care have all contributed to early diagnosis of critical CHD and prompt management. This has in turn led to better survival and outcomes in this vulnerable population. However, early and late outcomes of newborns with CHDs still largely depend on the individual characteristics of the lesion and its pathophysiology. In addition, other co-morbidities such as intrauterine growth restriction, genetic syndromes, malnutrition *etc*, have strong influence on the surgical results and overall survival in critical CHD. Current evidence supports improved surgical outcomes among newborns with critical CHDs operated in large volume surgical centers. This could be a result of multidisciplinary coordinated care with 24 hour access to advanced resources and expertise (extra corporeal membrane oxygenation (ECMO) support, availability of non-cardiac neonatal surgical specialties, advanced imaging, *etc*) [3]. Continued refinement of trans-catheter interventional procedures such as ductal stenting and right ventricular outflow tract stenting performed in neonates and infants have offered non-surgical palliative alternatives and has resulted in reduced morbidity and mortality in specific lesions (*eg*, duct-dependent pulmonary blood flow lesions like tetralogy of Fallot, pulmonary atresia) [4,5].

Even though all major metropolitan cities and a vast number of tier-2 cities in India have centers offering advanced care for critical CHD, a national level pediatric cardiac surgery registry is not present. As a result, currently in India, total pediatric cardiac surgical volumes and clinical outcomes remain speculative. In a study of 330 consecutive neonates in a tertiary care center in India, the overall mortality for all neonatal corrective and palliative cardiac surgical procedures was 8.8% [6]. However, many high risk lesions such as hypoplastic left heart syndrome and severe Ebstein anomaly were excluded in that study. In another study, early extubation in infants after cardiac surgery lowered pediatric intensive care unit (ICU) stay and sepsis, without increasing mortality or reintubation rate [7]. In a large multicenter multinational study of more than 2100 children who underwent tetralogy of Fallot (most common cyanotic congenital heart disease) repair, involving 32 centers across 20 low- and middle-income countries, older age at surgery was not a risk factor for death (overall mortality of 3.6%). However, nutritional status and severity of hypoxemia were significantly associated with higher postoperative infection and mortality rates [8].

In this issue of *Indian Pediatrics*, Shukla, *et al.* [9] have evaluated the outcomes of cardiac surgeries in neonates and infants in India. In this retrospective study

done at a tertiary care center over a 7-year period, 200 neonates with high complexity CHDs (Risk Adjustment in Congenital Heart Surgery (RACHS-1) median score of 4) underwent cardiac surgeries. The authors report an overall mortality rate of 13.5% (27/200 patients). Despite the limitations of a retrospective study design, this analysis of a robust number of study subjects shows that the mortality in this population after cardiac surgery was independently predicted by the presence of preoperative shock, duration of mechanical ventilation, residual lesions after surgery, and cardiopulmonary bypass time. The conclusions in this study highlight the important factors that may affect the overall outcome of pediatric cardiac surgery in India. These include prompt recognition and appropriate referral of critical CHDs in neonates and infants, universal access to quality tertiary care, and appropriate utilization of finite resources and expertise.With these efforts, the overall morbidity and mortality in infants with critical CHD will continue to improve in the coming decades in India.

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RESEARCH PAPER

Role of Impulse Oscillometry in Assessing Asthma Control in Children

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Background: Impulse oscillometry is an effort-independent technique of assessment of airway resistance and reactance, and can be performed in children unable to complete spirometry.

Objective: To evaluate the utility of impulse oscillometry and spirometry for assessing asthma control in children.

Study design: Prospective cohort study.

Participants: Children aged 5-15 years, with mild to severe persistent asthma.

Intervention: On each 3-monthly follow-up visit, clinical assessment, classification of control of asthma, impulse oscillometry and spirometry were performed.

Outcome: Utility of impulse oscillometry parameters [impedance (Z5), resistance (R5), reactance (X5) at 5 Hz, and R5-20 (resistance at 20Hz -5Hz) (% predicted), and area of reactance (AX, actual values)] and FEV_1 (% predicted) to discriminate between controlled and uncontrolled asthma was assessed by receiver operating characteristic (ROC) curve. Association of FEV_1 and impulse oscillometry parameters over time with controlled asthma was evaluated by generalized estimating equation model.

Results: Number of visits in 256 children [mean (SD) age, 100 (41.6) mo; boys: 198 (77.3%)], where both impulse oscillometry and spirometry were performed was 2616; symptoms were controlled in 48.9% visits. Area under the curve for discrimination between controlled and uncontrolled asthma by FEV_1, AX, R5-20, Z5, R5, and X5 were 0.58, 0.55, 0.55, 0.52, 0.52 and 0.52, respectively. FEV_1 [OR (95% CI): 1.02 (1.01-1.03)] and AX [OR (95% CI): 0.88 (0.81-0.97)] measured over the duration of follow-up were significantly associated with controlled asthma.

Conclusion: Spirometry and impulse oscillometry parameters are comparable in ascertaining controlled asthma. Impulse oscillometry being less effort-dependent may be performed for monitoring control of childhood asthma, especially in younger children.

Key words: *Spirometry, impedance, resistance, reactance.*

Early diagnosis and good control of asthma is expected to improve the course of the disease, the most common chronic respiratory illness in children [1]. According to the current guidelines, treatment of asthma should aim at achieving and maintaining asthma control [2]. However, assessing control of childhood asthma is challenging and subjective as there is discordance in the perception of severity of symptoms between children and their parents. Various non-invasive techniques to objectively measure the lung functions in children have been developed which include spirometry, impulse oscillometry, body plethysmography, multiple breath washout test, forced oscillation techniques [3-6].

Conventional spirometry is considered as the gold standard test for assessment of airflow obstruction; however, it has certain shortcomings. Firstly, it is an effort-dependent test, younger children and those with acute exacerbation are generally unable to perform the test; hence, there is a poor correlation between symptoms and test results. Secondly, spirometry cannot properly differentiate between distal and peripheral airways. The forced expiratory volume in one second (FEV_1) and the mid-forced expiratory flow (FEF_{25-75}) mainly represents the large and small airways, respectively [7]. Thirdly, the effort dependent nature of the test interferes with the reproducibility of the test [8].

Accompanying Editorial: Page 114.

Impulse oscillometry (IOS) is a much simpler, non-invasive technique of assessment of airway resistance and reactance in children. It is effort-independent, requires minimal patient cooperation, can be performed in tidal breathing, and can distinguish between the degree of obstruction in central and peripheral airways [4-6]. In young children where reliable spirometry is difficult to obtain, IOS allows for evaluation of lung function through measurement of both airway resistance and

reactance [3]. There is limited number of studies on utility of IOS to assess asthma control, and there is no consensus on the cut-off values of IOS parameters to determine asthma control in children [5,9].

The aim of our study was to compare the utility of IOS and spirometry parameters for assessing asthma control in children 5-15 years of age.

METHODS

Children aged 5-15 years, attending Pediatric Chest Clinic and Pediatrics OPD of the All India Institute of Medical Sciences, New Delhi, between 2010 to 2016, were eligible for screening. Inclusion criteria were physician-diagnosed asthma and the ability to perform spirometry. Patients were excluded from the study if they had interstitial lung disease, congenital heart disease, tuberculosis, cystic fibrosis, bronchomalacia/laryngomalacia, tracheaesophageal fistula, vocal cord dysfunction, hypersensitivity pneumonitis, chronic liver/renal disease, took medications that could induce chronic cough such as ACE inhibitors/α blockers, or residing outside Delhi or were unlikely to follow-up. Written informed consent was taken from the parent/guardian of the study participants. The study was approved by the Ethics Committee of the institution. Children were followed up regularly at an interval of three months.

Baseline spirometry and IOS were performed in all the children. At each three monthly visit, clinical assessment, IOS and spirometry were performed. After each visit, the symptom control was classified as controlled, partly controlled, uncontrolled or acute exacerbation according to the GINA guidelines and appropriate treatment were prescribed according to the control status of the patient [2]. To assess the symptoms in the interval between the visits, a symptom diary was provided, and medications (adherence and technique) were checked at each visit.

All study procedures were performed using MasterScreen IOS (CareFusion, Germany 234 GmbH) and Spirolab III. Spirometry and IOS were performed and anthropometric measurements taken by trained research officer and technician at each visit. Patients were explained about the procedure and were then allowed to perform the test. The best among three readings was taken in spirometry to ensure reproducibility of the test. FEV_1 value was taken as a measure of airflow obstruction.

IOS was performed in the sitting position, with the child breathing at tidal volume through a mouthpiece with the nose-clip in place and head held in neutral position and the cheeks supported by hands to decrease the dead space. Readings for normal tidal breathing through the mouthpiece for 30 seconds were taken. The MasterScreen IOS was used to calculate the pulmonary impedance (Z) which compromises of pulmonary resistance (R) and reactance (X) and pressure-flow relationship of the respiratory system as a function of oscillation frequency. The IOS indices taken into consideration were R5 (resistance at 5 Hz), X5 (reactance at 5 Hz), Z5 (pulmonary impedance at 5 Hz) and AX (area of reactance). R5-20 were calculated by subtracting values of R20 (resistance at 20 Hz) from R5. IOS was performed before spirometry in each child.

Statistical analysis: All statistical analyses were performed using STATA version 13 (StataCorp, College Station, TX, US). IOS parameters (percentage predicted of Z5, R5, X5, R5-20, and actual values of AX) and FEV_1 (percentage predicted) were compared by Pearson correlation coefficient. The above mentioned parameters were individually compared in controlled and uncontrolled state of asthma by *t* test or rank-sum test as appropriate. The receiver operating characteristic (ROC) curves were used to evaluate the discriminatory powers of FEV_1 and the IOS parameters in assessing control of asthma. Generalized estimating equation (GEE) was used to evaluate the association between controlled state and FEV_1 and IOS parameters over time.

For the purpose of analysis, children with partly controlled or uncontrolled asthma were grouped together as uncontrolled asthma. Acute exacerbations were excluded from the analysis.

RESULTS

A cohort of 256 children with mild to severe persistent asthma was enrolled and followed up for a mean (SD) duration of 37.6 (13.1) months. The total number of follow-up visits (excluding the exacerbations) in 256 children were 3152 (range: 1-15 visits/child). Based on the treating physician's assessment, asthma was assessed to be controlled on 1542 (48.9%) and uncontrolled (partly controlled or uncontrolled) on 1610 (51.1%) visits. Demographic profile of all patients and airway indices are presented in ***Table* I**. Both IOS and spirometry were performed in 2616 visits and data from these visits were used for analysis. In 140 visits only IOS, but not spirometry could be performed, and only spirometry was performed in 396 visits because IOS was not available at that point of time.

FEV_1 and the IOS parameters Z5, R5, X5, R5-20 and AX were all significantly correlated with each other in both controlled and uncontrolled state (data not shown). FEV_1 and all the IOS parameters were significantly

TABLE I Baseline Demographics and Pulmonary Function Test of Children with Asthma (*N*=256)

Characteristics	*Values*
Age, mo	100 (41.6)
Boys, *n* (%)	198 (77.3)
FEV_1 (% predicted)	87.7 (17.9)
R5 (% predicted)	95.7 (28.3)
*R5-20, cm H_2O/L/s	5.02 (-5.9, 21.04)
Z5 (% predicted)	98.6 (28.6)
X5 (% predicted)	116.5 (55.3)
AX (kPa/L)	2.2 (1.8)

*Values are expressed as mean (standard deviation) or *median (IQR); FEV_1: Forced Expiratory Volume in the 1st second, R5 (resistance at 5 Hz), X5 (reactance at 5 Hz), Z5 (impedance at 5 Hz) and AX (area of reactance). R5-20 were calculated by subtracting values of R20 (resistance at 20 Hz) from R5.*

different in the controlled and uncontrolled state (***Table* II**). The areas under the ROC curve (95% CI) for discriminating the controlled and uncontrolled state were comparable (***Table* III**).

GEE showed a significant association of FEV_1 and AX measured over the duration of follow-up with the controlled state of asthma. For each unit change (increase) in FEV_1 over time, the odds of control of asthma was 1.02 (95% CI: 1.01-1.03). For each unit of increase of AX over time, the odds of control of asthma was 0.88 (95% CI: 0.81-0.97).

TABLE II Comparison of Impulse Oscillometry and Spirometry Parameters in Controlled *vs* Uncontrolled Asthma

Parameters	*Controlled (n= 1315)*	*Uncontrolled (n=1301)*	*P value*
Spirometry parameter			
FEV_1 (% predicted)	91.3 (15.3)	86.0 (18.1)	<0.001
IOS parameters			
R5 (% predicted)	98.1 (31.8)	101.3 (32.9)	0.01
Z5 (% predicted)	103.9 (38.9)	107.7 (41.7)	0.01
X5 (% predicted)	147.9 (79.2)	157.4 (87.9)	0.003
AX (kPa/L)	1.9 (1.8)	2.2 (2.09)	<0.001
*R5-20, cm H_2O/L/s	1.9 (-9.5, 14)	3.3 (-7.3, 17.9)	<0.0012

*Values are expressed as mean (standard deviation) or *median (IQR); FEV_1: Forced Expiratory Volume in the 1st second, R5 (resistance at 5 Hz), X5 (reactance at 5 Hz), Z5 (impedance at 5 Hz) and AX (area of reactance). R5-20 were calculated by subtracting values of R20 (resistance at 20 Hz) from R5.*

TABLE III IOS and Spirometry Parameters in Assessing Control of Asthma

Parameters	*AUC of ROC (95% CI)*
FEV_1 (% predicted)	0.58 (0.56-0.60)
AX (kPa/L)	0.55 (0.52-0.56)
R5-20, cm H_2O/L/s	0.54 (0.52-0.56)
Z5 (% predicted)	0.52 (0.5-0.55)
R5 (% predicted)	0.52 (0.5-0.55)
X5 (% predicted)	0.52 (0.5-0.55)

Total numbers of episodes = 2616; FEV_1: Forced Expiratory Volume in the 1st second, R5 (resistance at 5 Hz), X5 (reactance at 5 Hz), Z5 (impedance at 5 Hz) and AX (area of reactance). R5-20 were calculated by subtracting values of R20 (resistance at 20 Hz) from R5.

DISCUSSION

Our study demonstrated that IOS and spirometry have comparable ability to detect the control state of asthma in children. Both IOS and spirometry yielded similar results in differentiating children with controlled and uncontrolled state of asthma. There was a significant association of increase in FEV_1 and AX measured over the duration of follow-up, with the controlled and uncontrolled state of asthma, respectively. The FEV1 values were statistically different in the controlled *versus* uncontrolled groups; however, the uncontrolled group too had a fairly good lung function.

IOS is a form of forced oscillation technique which is based on the physiologic concepts originally described in 1956 [10], and can measure the mechanical properties of lung [11-13]. Spirometry, being effort dependent is difficult to perform in younger children, particularly those who present with uncontrolled or acute exacerbation of asthma. There are limited numbers of studies in children which have observed the utility of IOS in assessing long term control of asthmatic children [5,9]. IOS is especially important in determining the status of smaller airways and studies have also inferred that AX, which is a parameter representing the smaller airways, is the best indicator of long-term control and treatment response in childhood asthma [4,9,14]. A recent trial found that assessment of pulmonary function over time with IOS might offer additional insights into the response of asthmatic patients to therapy, and might detect alterations in airway mechanics not reflected by spirometry [4]. Over a prolonged period in their study, the area of reactance (AX) showed continued improvement compared to spirometry parameters [4].

In our study, a significant difference in R5-20 and AX in controlled and uncontrolled state was observed.

What is Already Known?

- Assessment of control of asthma is presently done primarily by clinical scores and spirometry in case of older children.

What This Study Adds?

- Spirometry and Impulse oscillometry are comparable in assessing control in children with asthma.
- Impulse oscillometry may be used in place of spirometry in children who are unable to perform spirometry.

Similar findings were demonstrated prior to bronchodilator therapy in asthmatic children where both IOS and spirometry were performed, and small airway measurements by IOS in uncontrolled asthma were significantly different from those of controlled asthma [14]. IOS parameters that reflect smaller airways like the difference in resistance between 5 Hz and 20 Hz (R5-R20) and the area under the reactance curve (AX), are more closely related to asthma control [15]. The assessment of asthma control over a period of time in our cohort showed that both IOS and spirometry measurements were equally useful in the assessment of asthma control, as concluded in a study in adults with persistent asthma [16].

The strength of our study is that it is one of the few studies in children with prospectively collected data on long term follow-up of children with asthma. However, limitation of our study is that we were unable to comment on the utility of IOS in preschool children from this study; preschool children being a group who would benefit the most from an effort independent test like IOS. The assessment was done clinically, and children were labelled as controlled or uncontrolled depending on the symptom diary and feedback of the caregiver's version during the follow up visits. Uncontrolled group consisted of both partly controlled and uncontrolled cases. Both these features might have led to overestimation of the uncontrolled state.

As the GINA 2019 guidelines [17] recommend monitoring of lung function at baseline and during follow-up, it will be desirable to determine the cut-offs of various parameters of IOS which could be used instead of spirometry, particularly in young children. AX is a particularly important IOS parameter associated with the controlled state of asthma. IOS being less effort dependent can be performed for monitoring control in childhood asthma, especially in younger children and in sicker children who are unable to perform spirometry. Thus, IOS may be a good alternative for evaluation of asthma in children.

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RESEARCH PAPER

Impact of Using Different Growth References on Interpretation of Anthropometric Parameters of Children Aged 8-15 Years

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Objective: To compare the effect of the application of three growth references (Agarwal, 1992; Indian Academy of Paediatrics (IAP), 2015; and World Health Organisation (WHO), 2007) on interpretation of anthropometric parameters in schoolchildren.

Setting: Cross-sectional school-based study.

Participants: Children 8-15 years studying in one government school and one private school of Delhi.

Procedure: The age- and gender-specific standard deviation scores of height-for-age and BMI-for-age were estimated for each student enrolled, using the three growth references independently.

Main outcome measure: The proportion of children with short stature, thinness and overweight/ obesity determined by each growth reference were compared.

Results: A total of 1237 students participated in the study. A significantly higher proportion of children (both sexes) were classified to have short stature using WHO 2007 reference (8.8%) as compared to the Agarwal (3.3%) charts and IAP, 2015 references (3.6%). The combined prevalence of overweight and obesity was highest (34.8%) by the IAP, 2015 reference as against 32% by Agarwal charts and 29.1% by WHO, 2007 reference. Good agreement existed between the IAP, 2015 reference and Agarwal charts in classifying subjects into different BMI categories (Kappa=0.82) and short stature (Kappa=0.99).

Conclusions: In view of differences noted, use of national population derived reference data is suggested to correctly define growth trajectories in children.

Keywords: *Comparison, Growth charts, Obesity, Short stature*.

Anthropometry is the universally accepted tool for the assessment of a child's growth and nutritional status. The anthropometric parameters of an individual are interpreted by comparing with the age- and sex-matched reference data. The interpretation of an individual child's anthropometric parameters would depend upon the reference data used. Clinicians often face a dilemma on the choice of growth reference for anthropometric assessment among the different national and international growth references/ standards available. International consensus exist on the use of the World Health Organization (WHO) Child Growth Standards derived from the multi-centric growth reference study for assessing growth of children up to 5 years of age [1]. However, there is no similar multi-nation data for children beyond five years of age, and most nations use local population-derived reference data for this age group. In India, the growth reference charts developed by Agarwal, *et al*. [2] are more than two decades old. The newer Indian Academy of Pediatrics (IAP) growth references [7] for Indian children 5-18 years are based on collated national data generated during last 10 years [7]. Besides, there exist the International WHO growth reference charts for children 5-19 years of age, which are primarily based on growth of American children [8,9]. The availability and use of multiple references for clinical and research purposes can create confusion amongst healthcare providers and difficulty in correct interpretation of epidemiological and research data. A difference in prevalence of stunting, wasting, and thinness in school children from low income countries was reported on application of WHO, 2007 and NCHS growth references [10]. Similar inferences were drawn when the prevalence of overweight and obesity in school children was compared using the WHO charts, Agarwal charts and International Obesity Task Force (IOTF) growth reference charts [11].

Accompanying Editorial: Pages 115-116.

We compared the effect of the application of three different growth references; that developed by Agarwal, *et al*. [2] (Agarwal reference), IAP growth reference, 2015 [7] (IAP 2015) and the WHO growth reference [9] (WHO 2007) on estimation of proportion of school children (aged 8-15 years) classified as having short stature, thinness, severe thinness, overweight, and obesity.

METHODS

This cross-sectional study was conducted in July 2016 on schoolchildren aged 8-15 completed years, studying in 3rd-10th grades at two schools in northern Delhi. We selected a government and a private school to enable enrollment of children belonging to different socio-economic strata and diverse nutritional status. Children suffering from systemic illnesses or who had undergone a major surgical procedure likely to interfere with the growth, and those with obvious skeletal or neurological problem hindering evaluation of physical growth were excluded. A prior permission from school authorities was obtained. Passive parent consent and verbal student assent was also taken prior to enrollment in the study. The parents were given a patient information sheet containing the relevant details of the study and their written consent taken. The study protocol was approved by the Institutional Ethics Committee.

Prior to the start of the study, one researcher was trained to measure the bodyweight and height using standard procedures. The investigator collected the date of birth of the enrolled subjects from the school records. Using standardized equipment and techniques, the weight and height of all children fulfilling the inclusion criteria were recorded. The weight was recorded to the nearest 0.1 kg using electronic digital weighing machine without footwear and minimal clothing. Height was measured to the nearest 0.1 cm using a portable stadiometer (Seca 222; Seca GmbH & Co. Germany). Body Mass Index (BMI) was calculated by standard formula.

Using each of the three growth references - Agarwal reference [2], IAP 2015 [7] and WHO 2007 [9], age- and gender-specific standard deviation scores (SDS) of height-for-age (HFA-SDS) and BMI-for-age (BMI-SDS) were calculated for all students. Children with HFA-SDS < –2 were considered to have short stature across each of the three reference charts. Definition of thinness/obesity varies among the different references. For WHO 2007 reference, subjects with BMI-SDS <-2 were considered thin, with BMI-SDS between 1 and 2 as overweight and >2 as obese [12,13]. For IAP 2015 and Agarwal reference charts, the cutoff of BMI/age <3rd percentile and <5th percentile, respectively were used to define thinness [27]. The cutoff of BMI/age at 23rd adult equivalent (71st centile in boys and 75th centile in girls) and 27th adult equivalent (90th centile in boys and 95th centile in girls) was applied to classify overweight and obesity, respectively according to the IAP 2015 reference charts. As per the Agarwal charts, overweight and obesity were defined by the BMI /age cut off between 85th and 95th centile and >95th centile, respectively. The proportion of children with short stature, thinness, overweight or obesity obtained on applying each of the three growth references was compared.

Statistical analyses: The data was analyzed by statistical software SPSS version 20 (IBM Crop, Armonk, NY). For the purpose of statistical inference, a 2-year interval was used to show the height and BMI distribution of the subjects enrolled. The three-way ANOVA test was applied to evaluate the differences in the growth parameters between the students of the government school and private school across different age intervals on using the three different growth references. The McNemar test was applied for height variable and McNemar-Bomker test was applied for the BMI to assess the agreement between the two reference charts. A linear mixed model with suitable covariance structure on the basis of minimum Akaike's Information Criteria (AIC) was applied to compare the mean (SD) score obtained by the use of different reference charts and to assess whether mean Z score difference is influenced by gender. The Kappa statistic value was adjusted when prevalence and bias influenced the Kappa statistic. A *P*-value less than 0.05 was considered as statistically significant.

RESULTS

Of the 1256 students screened from the two schools, 1237 students (767 boys) participated in the study; 16 students were excluded because either the date of birth was unknown or the age was more than 16 years. Data pertaining to three students was removed as outliers because they were severely obese (BMI >35 kg/m^2). The proportion of students enrolled from the government school was 46.6%. The age and sex distribution, and height and BMI of the children is summarized in ***Web Table* I**. The mean SDS for height and BMI among children in government and private school across all age groups and both sexes were significantly different on application of the three growth reference charts (***Web Table* II, III**).

The mean SDS for HFA and BMI for age determined using the three growth references is given in ***Table* I**. Linear mixed model revealed no significant difference between genders among the three growth references. However, the mean SDS of HFA estimated by WHO 2007 reference was significantly lower than the Agarwal and

TABLE I Comparison of Standard Deviation Scores of Height for Age and BMI for Age of Children Aged 8-15 Years Using Three Different Growth Reference Charts (*N*=1237)

Variable	*WHO, 2007 [9]*	*Agarwal, 1992 [2]*	*IAP, 2015 [7]*
Height for age			
Girls	-0.46 (1.19)	0.45 (1.55)	0.16 (1.16)
Boys	-0.35 (1.24)	0.44 (1.23)	0.08 (1.18)
Total	-0.41 (1.22)	0.44 (1.36)	0.11 (1.17)
BMI for age			
Girls	0.07 (1.43)	0.41 (1.31)	0.25 (1.17)
Boys	-0.06 (1.68)	0.66 (1.60)	0.12 (1.15)
Total	-0.02 (1.60)	0.56 (1.50)	0.17 (1.16)

**All values in mean (SD); P<0.001 for all comparisons between WHO, 2007 [9] vs IAP, 2015 [7] and Agarwal [2] vs IAP 2015; WHO: World Health Organization; IAP: Indian Academy of Pediatrics.*

IAP 2015 references (*P*<0.001). Thus, a significantly higher proportion of children (both sexes) were classified to have short stature using WHO 2007 reference (8.8%) as compared to the Agarwal (3.3%) and IAP 2015 references (3.6%) (***Fig.* 1**). The visual comparison of distribution of height for age and BMI for age SDS among the three growth references along with the normal SDS is presented (***Web Fig*. 1** and **2**).

***Figure* 2** shows the comparison of the BMI categories in boys and girls using the three growth reference charts. Among boys, the IAP reference classified the maximum proportion with obesity (17.7%), while the Agarwal charts identified the highest proportion of overweight (20.6%) children. In girls, the IAP reference reported highest proportion with overweight (21.7%) and obesity (13.4%). The combined prevalence of overweight and obesity was highest (34.8%) by the IAP 2015 reference as against 32.0% by Agarwal charts and 29.1% by WHO2007 reference. The proportion of children (boys and girls combined) classified as obese was maximum (16.1%) by IAP 2015 as compared to 12.1% and 10.9% by Agarwal and WHO 2007 references, respectively. The IAP 2015 reference classified least proportion of children with thinness (2.4%) as compared to Agarwal reference (4.4%) and WHO 2007 reference (11.2%). The degree of agreement in classifying subjects into different BMI categories was best between the IAP 2015 and Agarwal references (Kappa=0.82), followed by WHO and Agarwal (Kappa=0.75) and least with WHO and IAP references (Kappa=0.60).

DISCUSSION

The comparative assessment of anthropometric parameters in school children using three different growth references yielded the following key observations. The low mean SDS of HFA by WHO 2007 reference resulted in classifying higher proportion of children with short stature as compared to IAP 2015 and Agarwal reference. Application of WHO 2007 reference also led to diagnosing higher proportion of children with thinness as compared to the IAP 2015 reference. Use of IAP 2015 reference accounted for a greater proportion of children classified with overweight and obesity as compared to Agarwal and WHO 2007 references. Amongst the three growth reference charts, a good concurrence existed between Agarwal and IAP 2015 references in identification of short stature, thinness, and overweight/ obesity.

The primary limitation of this study was the lack of assessment of the divergent growth pattern observed in adolescents with the attainment of puberty. Also, since the objective was primarily to compare the three growth

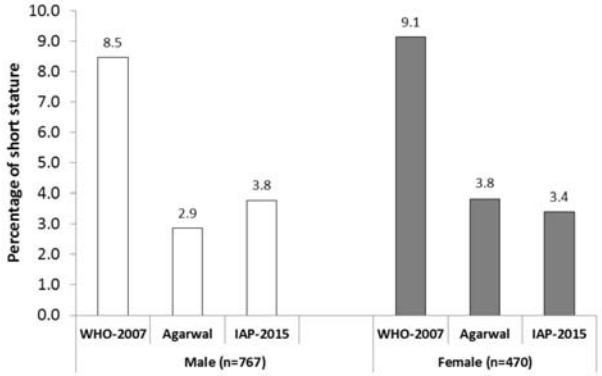

FIG. 1 *Proportion of children aged 8-15 years with short stature using three different growth reference charts.*

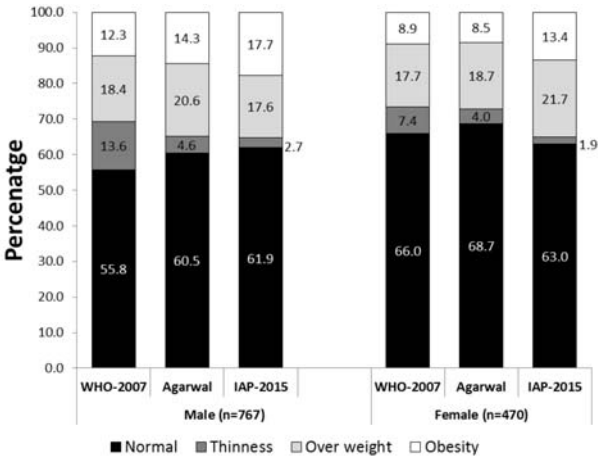

FIG. 2 *Body mass index (BMI) categories in children aged 8-15 years using three different growth reference charts.*

references, results on interpretation of anthropometric data cannot be generalized to represent nutritional status of children in this area.

The higher HFA-SDS of the subjects on application of IAP 2015 reference charts as compared to WHO 2007 reference shows that the Indian children are shorter than their Caucasian counterparts. Similar inference was drawn after the publication of the IAP 2015 growth reference charts [7,9]. Use of WHO charts will thus lead to an increase in diagnosis of short stature, creating undue anxiety among parents and unnecessary referrals to the health facility. The higher mean HFA-SDS obtained on application of Agarwal reference as compared to IAP 2015 reflects the secular trends in height in India over the past two decades, and is consistent with previous observations [15,16].

The WHO 2007 reference classified participants in lower weight strata compared to the IAP 2015 and Agarwal references. This led to diagnosing higher proportion of children with thinness by WHO references as compared to the other two references. Likewise, application of WHO 2007 references underestimated the proportion of overweight and obese children among the study group as compared to that obtained by applying IAP 2015 charts. This can lead to missing the opportunity of identifying these children and offering them appropriate screening and management. The IAP 2015 BMI centiles/Z scores are lower as compared to Agarwal *Z* scores in Agrawal charts, indicating a steep rise in obesity/overweight in recent times [6,16]. Thus, application of a similar criteria of 85th and 95th centile to define overweight and obesity as used by Agarwal, *et al.* [2] would have led to a much lower proportion of children being identified with these conditions on application of IAP 2015 reference. This has been taken care of in the IAP reference by linking the definition of overweight and obesity to adult BMI equivalent of 23 and 27, respectively. This led to lowering of cut-off for defining, and a corresponding higher detection rate of overweight and obesity by IAP 2015 reference. A rise in the weight and BMI centiles of both boys and girls on application of recent reference data from India as compared to Agarwal reference charts has been reported by Khadilkar, *et al.* [15] and Marwaha, *et al.* [6].

The present study brings out the impact of using updated national growth reference charts on interpretation of anthropometric data of older children and adolescents. We conclude that IAP 2015 growth reference remains in excellent agreement with Agarwal reference for recognition of short stature while identifying less children with short stature and more children with overweight and obesity as compared to WHO 2007 reference. This will have an impact on screening and management of children with both short stature and overweight/obesity.

Contributors: PS: execution of the study, data analysis and writing the manuscript; SG: execution of the study and writing the manuscript; RKM: contributed in execution of the study, data analysis and writing the manuscript and AS: conceptualized the paper, was overall responsible for quality of data collection and maintenance, modified and finalized the draft.
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NOTES AND NEWS

WEB TABLE I Age and Sex Distribution and Descriptive Statistics (Height and BMI) of Subjects Studying in the Private and Government Schools

Age (years)		Private School, mean (SD)			Government School, mean (SD)	
	No. (%)	Height (cm)	BMI (kg/m^2)	No. (%)	Height (cm)	BMI (kg/m^2)
Boys						
8-10	76 (20)	136.1 (6.5)	18.05 (3.4)	74 (19)	127.7 (7.8)	15.5 (2.1)
10-12	105 (28)	144.3 (7.9)	20.4 (4.4)	99 (26)	138.8 (7.6)	15.5 (1.9)
12-14	88 (23)	158.6 (9.0)	22.1 (4.4)	138 (36)	150.1 (10.6)	17.1 (3.0)
14-16	112 (29)	167.5 (8.7)	23.0 (5.3)	75 (19)	157.7 (8.4)	17.5 (2.6)
Total	381 (100)	152.8 (14.6)	21.1 (4.9)	386 (100)	144.4 (13.7)	16.5 (2.6)
Girls						
8-10	76 (27)	135.0 (7.5)	18.6 (3.9)	49 (26)	127.2 (8.8)	15.3 (2.6)
10-12	81 (29)	145.5 (7.7)	19.7 (4.1)	45 (24)	137.0 (8.2)	15.7 (2.3)
12-14	57 (20)	155.7 (7.0)	21.4 (4.2)	75 (39)	150.0 (8.2)	17.8 (2.9)
14-16	66 (24)	158.7 (6.8)	23.2 (4.5)	21 (11)	152.6 (5.4)	16.7 (2.9)
Total	280 (100)	147.8 (11.8)	20.5 (4.5)	190 (100)	141.3 (12.8)	16.7 (2.9)

BMI: Body Mass Index; SD: Standard Deviation.

WEB TABLE II Comparison of Height Standard Deviation Scores Among Children in Government and Private School Across all Age Groups and Both Sexes

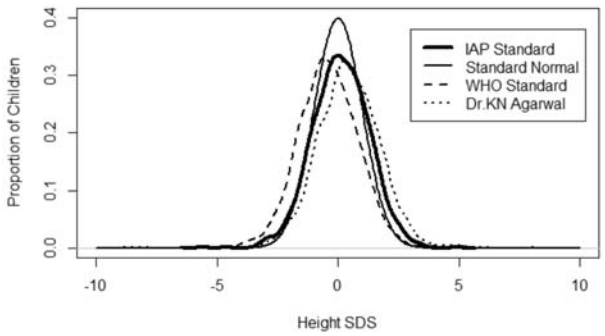
Gender	8-10 (n=275)		10-12 (n=330)		12-14 (n=358)		14-16 (n=274)	
	Pvt	Govt	Pvt	Govt	Pvt	Govt	Pvt	Govt
*WHO**								
Male	1.07 (0.97)	-0.47 (1.27)	0.98 (1.14)	-0.01 (1.11)	0.93 (1.04)	0.06 (1.22)	0.76 (1.21)	0.28 (1.04)
Female	1.01 (0.99)	-0.04 (1.26)	1.18 (1.72)	-0.88 (2.28)	0.79 (1.15)	-0.15 (1.27)	0.78 (1.21)	-0.28 (0.96)
Agrawal								
Male	1.07 (0.97)	-0.05 (1.27)	0.98 (1.14)	-0.01 (1.11)	0.93 (1.04)	0.06 (1.22)	0.78 (1.21)	-0.28 (0.96)
Female	1.01 (0.99)	-0.04 (1.26)	1.18 (1.72)	-0.87 (2.28)	0.79 (1.15)	-0.15 (1.27)	0.78 (1.21)	-0.28 (0.96)
*IAP**								
Mal	0.61 (0.88)	-0.45 (1.18)	0.52 (1.04)	-0.41 (1.05)	0.58 (1.07)	-0.36 (1.24)	0.60 (1.06)	-0.43 (0.98)
Female	0.60 (0.97)	-0.42 (1.19)	0.53 (1.03)	-0.74 (1.11)	0.60 (1.04)	-0.24 (1.13)	0.49 (1.02)	-0.38 (0.82)

*All values in mean (standard deviation scores); *P value <0.01; Pvt: Private school; Govt: Government school; males (n = 150), females (m=125).*

WEB TABLE III Comparison of BMI SD Score Scores Among Children in Government and Private School Across All Age Groups and Both Sexes

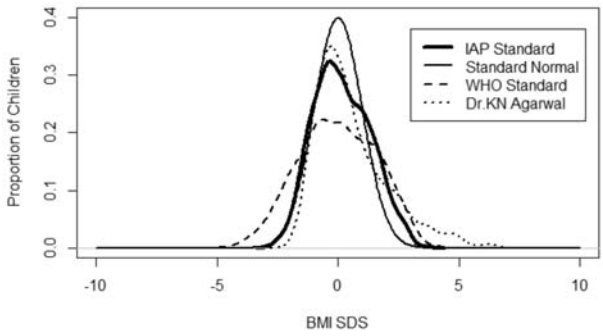
Gender	*8-10 (n=275)*		*10-12 (n=330)*		*12-14 (n=358)*		*14-16 (n=274)*	
	Pvt	*Govt*	*Pvt*	*Govt*	*Pvt*	*Govt*	*Pvt*	*Govt*
*WHO**								
Male	0.56 (1.51)	-0.61 (1.27)	1.08 (1.53)	-1.08 (1.27)	1.00 (1.39)	-0.92 (1.43)	0.61 (1.68)	-1.13 (1.21)
Female	0.66 (1.42)	-0.68 (1.05)	0.59 (1.33)	-1.01 (1.19)	0.64 (1.24)	-0.72 (1.22)	0.71 (1.25)	-0.78 (1.05)
*Agrawal**								
Male	1.27 (1.64)	0.04 (1.09)	1.63 (1.75)	-0.32 (0.73)	1.62 (1.54)	-0.12 (1.03)	1.45 (1.75)	-0.30 (0.87)
Female	1.17 (1.57)	-0.18 (1.43)	0.64 (1.15)	-0.36 (0.63)	0.73 (1.24)	-0.32 (0.83)	1.05 (1.40)	-0.45 (0.73)
*IAP**								
Male	0.56 (1.08)	-0.29 (0.86)	0.81 (1.09)	-0.65 (0.79)	0.82 (0.99)	-0.47 (0.90)	0.75 (1.17)	-0.53 (0.76)
Female	075 (1.14)	-0.34 (0.83)	0.64 (1.10)	-0.66 (0.87)	0.65 (1.08)	-0.38 (0.92)	0.86 (1.12)	-0.43 (0.79)

**P value <0.01; Pvt: Private school; Govt: Government school; males (n = 150), females (m=125).*



SDS: Standard deviation score.

WEB FIG. 1 *Comparison of distribution of height SDS among the different growth references with standard normal curve.*



SDS: Standard deviation score.

WEB FIG. 2 *Comparison of distribution of BMI SDS among the different growth references with standard normal curve.*

RESEARCH PAPER

Early Outcomes of Neonatal Cardiac Surgery in India

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Objective: To assess outcomes and factors influencing outcomes in neonates requiring cardiac surgery in India. **Methods:** This study reports on review of hospital data from a tertiary care cardiac surgical institute from January-2009 to December-2015. **Results:** A total of 200 neonates were included; of them, 5% of the cases were antenatally diagnosed and most of them had unmonitored transport (111, 55.5%). The overall mortality rate was 13.5%, (*n*=27) and 178 (89%) underwent complete defect repair. There was a significant association of mortality with shock, the number of inotropes, intra-operative procedure, residual lesion, aortic cross-clamp and deep hypothermic circulatory arrest time (all *P*<0.05). Logistic regression analysis showed ventilation duration, cardiac-bypass time, shock, and residual cardiac lesion as independent predictors of mortality. **Conclusion:** Cardiac defects were found to have late detection and most transports were unmonitored. Complete surgical repair and shorter cardiac bypass time can potentially improve neonatal cardiac surgical outcomes.

Key words: *Congenital heart disease, Management, Outcome.*

Neonatal cardiac surgical care is a relatively evolving subspecialty with a lack of outcome data from developing countries [1,2]. Cardiac surgical care is associated with significant gaps in terms of the availability of the services and the need in developing countries [3-6]. Additionally, poor referral and transport networks, delayed diagnosis, scarce insurance coverage, high attrition rates and poor patient affordability contribute to suboptimal outcomes [1,2,5]. There is limited data regarding outcomes after neonatal cardiac surgery from developing countries [3-5]. The aim of the present study patient to study was outcomes, and factors influencing outcomes in neonates requiring cardiac surgery in India.

METHODS

We conducted a retrospective review of data of all neonates (birth to 30 days of life) undergoing cardiac surgery at a tertiary level referral center situated in Western India. We report on data of all neonates, admitted to pediatric cardiac critical care unit of study institute from January 2009 to December 2015, pre-specified questionnaire was used for data collection based on electronic medical records which included demographic profile, cardiac defect characteristics, clinical presentation and hospital course, pre and post-operative risk factors, and early outcomes. Low cardiac output syndrome was defined based on existing literature as decrease in systemic perfusion transiently after cardiac surgery secondary to myocardial dysfunction [7]. Risk adjustment for congenital heart disease surgery (RACHS-1) score was used to categorize risk of individual surgeries [8]. Ethical approval with waiver of consent was obtained from institutional ethics committee.

Accompanying Editorial: Pages 117-118.

Statistical analysis: Mean (SD) and frequency (%) were used to depict baseline characteristics, demographic variables, short term morbidity, length of stay and mortality. Chi square test was used for categorical variables and independent sample t-test for continuous variables. Logistic regression with backward likelihood ratio method was done to find adjusted odds for independent predictors of mortality. The analysis was performed using STATA version 14.1.

RESULTS

A total of 200 neonates (male to female ratio 3.6:1) requiring cardiac surgery were included in the study. Mortality was 13.5%. Transport was mostly unmonitored (private vehicles: 111, 55.5%) compared to monitored (transport ambulance: 89, 44.4%), but was not significantly associated with mortality (*P*>0.05). Only 10 (5%) cases were antenatally diagnosed.

Primary cardiac defects necessitating surgery included TGA (transposition of great arteries) (*n*=88) (D-TGA, 85), TAPVC (total anomalous pulmonary venous circulation) (*n*=24) (supra-cardiac TAPVC, 10; infra-diaphragmatic TAPVC 11; and mixed TAPVC, 3), aortic

malformations (*n*=22) (aortopulmonary window, 3; coarctation of aorta; 14; interrupted aortic arch, 5), valvular malformations (*n*=17) (tricuspid atresia, 1; aortic stenosis/atresia, 8; pulmonic atresia/stenosis, 8), septal defects (*n*=15) (ventricular septal defect with outflow obstruction, 14; atrioventricular canal defect, 1), hypoplastic left heart syndrome (*n*=13), double outlet left ventricle (*n*=9), tetralogy of Fallot (*n*=7) and patent ductus arteriosus (*n*=5). Outcomes as per underlying cardiac defect are described in ***Table* I**.

Risk factors/complications at admission included invasive ventilation requirement 80, shock in 53, clinical sepsis in 33, prematurity in 22, blood culture-proven sepsis in 16, active resuscitation required at birth (intubation or chest compression) in 15. Peri-operative and in-hospital complications included culture-proven sepsis in 47 (blood, 33; ETT aspirate, 3; and urine cultures, 11), re-exploration in 18, seizures in 12, and antiepileptic medication requirement at discharge in 9. Nineteen neonates were extubated after the surgery before admission to the ICU, whereas, 181 neonates needed post-operative invasive ventilation.

On univariate analysis, there was a significant association between mortality and shock, intra-operative procedure, residual lesion, number of inotropes needed and urgency of surgery (***Table* II**). There was no statistically significant association of mortality with unmonitored/monitored transport, birth weight, initial arterial lactate, and clinical sepsis. There was no statistically significant difference in time between diagnosis and surgery, age at diagnosis, and weight for both groups (***Table* III**). Neonates requiring cardiopulmonary bypass (CPB) support during surgery were 134 (67%), aortic cross-clamp (ACC) were 129 (64.5%), and deep hypothermic circulatory arrest (DHCA) were 134 (67%). CPB, ACC, and DHCA times in participants who died was more as compared to survivors. While CPB time was not significantly different, the ACC and DHCA time were significantly different among both subgroups (***Table* III**). median RACHS-1 score for the study participants was 4 (interquartile range 3-4). On univariate analysis, there was a significant association between RACHS-1 score and mortality (*P*<0.001).

TABLE I Cardiac Defect and Outcome of Cardiac Surgery

Cardiac defect	*Mean RACHS 1 score*	Mortality *n* (%)
TOF (*n*=7)	3.5	0 (0)
TGA (*n*=88)	3.4	7 (7.9)
TAPVC (*n*=24)	3.8	5 (20.8)
DORV (*n*=9)	4	3 (33.3)
HLH (*n*=13)	6	2 (15.3)

TOF: Tetralogy of fallot; TGA: Transposition of great arteries; TAPVC: Total anomalous pulmonary venous return; DORV: Double outlet right ventricle; HLH: Hypoplastic Left Heart; Surgeries performed: TOF: Septal and RVOT repair; TGA: Arterial switch operation; TAPVC: TAPVC repair and re-anastomosis of PV to LA; DORV: Intracardiac channel repair; HLH: Norwood procedure.

Multivariable logistic regression done using mortality as outcome and neonatal variables and risk factors as independent variables, showed duration of ventilation [adjusted OR (95% CI) 2.19 (1.22,3.95), *P*=0.009], presence of residual lesion [adjusted OR (95% CI) 123.88 (9.43,1626.22), *P*=0.001], higher CPB time [adjusted OR (95% CI) 1.014, (1.005,1.024), *P*=0.003], and shock [adjusted OR (95% CI) 23.47 (1.95, 281.47), *P*=0.013] as independent predictors of mortality. This model had Nagelkerke R Square value of 0.67 with correct classification of 95.5%.

DISCUSSION

This review of hospital records was done to study

TABLE II Univariate Association Between Mortality and Categorical Variables (*N*=27)

Variable	*Category*	*Mortality, No. (%)*	*OR (95% CI)*	*P value*
*Inotropes	≤2 (106)	6 (5.6)	4.79 (1.84, 12.47)	0.001
	>2 (94)	21 (22.3)		
Shock	Yes (102)	19 (18.6)	2.57 (1.07, 6.19)	0.03
	No (98)	8 (7.2)		
Intraoperative procedure	Complete repair (178)	15 (8.4)	13.04 (4.83, 35.16)	<0.0001
	Staged repair (22)	12 (54)		
Urgency of surgery	Planned surgery (70)	4 (5.7)	3.55 (1.17, 10.71)	0.025
	Emergency surgery (130)	23 (17.7)		
Residual lesion	Yes (56)	19 (33.9)	8.73 (3.54 - 21.52)	<0.001
	No (144)	8 (5.6)		

**Number of inotropic medications required.*

What This Study Adds?

- Presence of shock, duration of ventilation, residual lesions, and cardiac bypass time were the variables independently associated with mortality in neonates undergoing cardiac surgery.

TABLE III Association of Various Patient and Surgical Factors with Mortality (*N*=200)

Variables	*Mortality, mean (SD)*	
	No (173)	*Yes (27)*
Weight, kg	2.7 (0.52)	2.8 (0.51)
*RACHS score	3.5 (0.9)	4.6 (1.07)
Age, d	7.5 (7.66)	6.2 (6.38)
Time between diagnosis and surgery, d	5.8 (5.13)	4.6 (5.38)
*ICU stay, d	9.7 (6.34)	4.7 (4.38)
*Hospital stay, d	14.9 (6.63)	4.5 (4.38)
CPB time, min	202.7 (75.19)	344.5 (361.41)
#DHCA time, min	26.4 (20.41)	61.9 (20.43)
‡ACC time, min	95.7 (43.94)	150.4 (70.28)
Ventilation, d	3.4 (2.19)	6.2 (5.95)
Cardiac support, d	3.9 (2.97)	5.8 (5.81)

*RACHS: Risk adjustment for congenital heart disease surgery; ACC: aortic cross-clamp; DHCA: deep hypothermic circulatory arrest; CPB: cardiopulmonary bypass; *P<0.001; #P=0.001; ‡P=0.01.*

outcomes and factors influencing outcomes in neonates requiring cardiac surgery in India. The variables that were found to be associated with mortality by multivariable logistic regression analysis were shock, duration of ventilation, residual lesion, and cardiopulmonary bypass time. We found that with every additional ventilation day, odds of mortality increased by 2.19 times and with every additional minute of cardiac bypass time, odds of mortality increased by 1.014. Neonates who died were having shorter duration of ICU and total hospital stay, which is possibly related to more unstable clinical status of those neonates.

Limitations of present study include retrospective study design and inherent possibility of selection bias. Additionally, as this was a single center study the generalizability of the results of the present study need to be explored further. Laboratory testing was delayed after admission in many cases to period after clinical stabilization, this precluded estimating admission illness severity scoring, which involves baseline laboratory tests. This also explains why mortality was related to presence of shock but not to initial lactate. The current study focuses only on short term outcomes, longer follow-up with neurodevelopmental and co-morbidities outcome would have been more informative.

Mortality rate (13.5%) seen in this study is higher than that reported in similar studies from developed countries (6-10%) [9,10], likely due to easier availability of cardiac surgical services and better diagnostic and referral services. Delayed diagnosis of congenital heart malformations [6] has been shown to impact outcomes adversely. However, in our study, we did not find a correlation between age at diagnosis and death, possibly due to death before hospitalization of those with critical cardiac defects. Mortality in cases undergoing complete repair was significantly lower than those who had residual lesion/staged repair. Similar reports of better outcomes with complete repair are seen in studies from developed [11-13] and developing countries [6]. Based on such data there is growing emphasis on performing early corrective operations in neonatal period [13,14].

The findings of this study are based on participants enrolled over a relatively long study period that would hopefully improve scope of generalizability of results. Early diagnosis, monitored transport, and corrective surgery with efforts to minimize aortic cross clamp time and deep hypothermic arrest time would likely reduce mortality burden. As intensive care is related to significant out-of-pocket expenses likely resulting in delayed diagnosis, poor healthcare seeking and worse patient outcomes [15], cardiac surgical care should be subsidized by the state for familiesunable to afford it. Larger scale studies from multiple centers from developing/underdeveloped countries with long-term outcome data would provide additional insight regarding this subject.

Contributors: VS: conceptualized and planned the study, drafted the proposal and manuscript, planned and conducted data collection, revised the manuscript; PB: planned the study design, conducted data collection, analyzed the data, and modified the manuscript for important intellectual points; SM,SR: planned the study design, modified the manuscript for important intellectual points; PJ: planned the study design, oversaw data collection, modified the manuscript for important intellectual points; VJ: conceptualized and devised the study, oversaw data collection, supervised the progress of the study, analyzed the data, provided important intellectual inputs to the manuscript.

He will be the guarantor for the study. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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RESEARCH PAPER

Peri- and Post-operative Amplitude-integrated Electroencephalography in Infants with Congenital Heart Disease

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Objective: To identify the factors influencing brain injury in infants with congenital heart disease (CHD) after cardiac surgery. **Methods:** This retrospective study investigated 103 infants with CHD undergoing cardiac surgery between January 2013 and February 2016. Pre- and postoperative amplitude-integrated electroencephalography (aEEG) recordings were assessed for background pattern, sleep-wake cycle pattern and seizure activity. Logistic regression model was used to determine the influencing factors of brain injury. **Results:** Pre-operatively, most infants in our study exhibited a normal background pattern, with 16.5% showing discontinuous normal voltage, whereas this pattern was observed in only 7.8% of infants postoperatively. The improvement in background pattern after surgery was significant (P<0.05) in infants at no more than 39 weeks of gestational age. Infants with postoperative sepsis or severe postoperative infection were prone to show a worse sleep-wake cycle pattern after heart surgery. **Conclusion:** The improvement in brain function of infants with CHD after cardiac surgery was associated with the gestational age and postoperative infection.

Keywords: *Cardiac surgery, Gestational age, Infection, Outcome*.

Congenital heart disease (CHD) is the most common birth defect, affecting approximately 1% of all live births [1]. With the tremendous improvement in treatment of CHD, the focus of attention has shifted toward managing brain injury, which is associated with neurodevelopment impairment affecting up to 50% of infants with CHD [2-4]. Because of the feasibility of continuous bedside monitoring brain activity, amplitude-integrated electroencephalography (aEEG) is increasing used to evaluate cerebral activity around infant cardiac surgery. Previously, aEEG was demonstrated as an early marker for brain injury in infants requiring cardiac surgery with CHD [5]. Although several factors including type of CHD, abnormalities of microstructural and metabolic brain development, and time of diagnosis have been identified as risk factors for brain injury [6,7], few studies have identified the predictors for brain function improvement or decline in infants with CHD undergoing cardiac surgery. Such predictors may help determine potential benefits or harm for brain function before operation.

METHODS

One hundred and three term infants who underwent surgery for CHD before 3 months of age between January 2013 and February 2016 at the NICU in our hospital were included in the study. Those infants who had any form of genetic or chromosomal abnormality independently associated with impaired neurodevelopment or were born before 37 weeks of gestational ages were excluded. The study was approved by the Ethics Committee of Guangdong General hospital, and written informed consent was obtained from all the parents.

Clinical data including Apgar scores, gestational age, birth weight, blood gas analysis, cardiovascular function, respiratory and multiorgan failure, neurological examination results, seizure occurrence, drug administration, neuroimaging data, infection, and surgical records were evaluated retrospectively for the study. Specifically, infection included postoperative sepsis diagnosed as bacterial infection by blood culture, and severe post-operative infection defined as postoperative infection (mainly pulmonary and urinary tract infections but not intracranial infection) that required antibiotics treatment, while excluding sepsis. Surgical procedures, cardiopulmonary bypass (CPB) time, and aortic cross-clamping (ACC) time were obtained from the surgical records.

aEEG was monitored 1 or 2 days before cardiac surgery and 3 or 7 days after surgery using an 8-channel EEG acquisition system (Nicolet One Monitor, Care Fusion, San Diego, California). The period of aEEG monitoring lasted for at least 24 hours each time and was extended when necessary. Eight disposable, self-adhesive EEG scalp electrodes (Blue Sensor BRS-50 K Ambu ECG electrode; Medicotest A/S, Ølstykke, Denmark) were applied in a reduced montage following the international 10-20 system. The 8-channel cross-brain aEEG trace was derived and displayed at 6 cm/hour on paper using a semi-logarithmic scale to assess and classify the aEEG background pattern. The channels were also used to record EEG data to describe episodes of EEG seizures in 10-second epochs. The 8-channel EEG recording was examined for the entire recording period when necessary. To ensure masking of evaluator, the expert who performed the main offline aEEG analyses was not involved in the clinical care of the infants.

The aEEG traces were classified by background voltage and descriptive pattern [8]. The aEEG recordings were categorized as continuous normal voltage (CNV) or discontinuous normal voltage (DNV). A combined third group called severe aEEG voltage pattern was defined, which included burst suppression, continuous low voltage, or a flat trace. We classified the Sleep-wake cycle (SWC) by occurrence into three types: normal SWC, immature SWC, and no SWC [9]. An electrographic seizure was defined as an evolving repetitive, stereotyped waveform with a definite onset, peak, and end that lasted for ≥10 seconds on raw EEG data [10]. Antiepileptic drugs were used to treat clinical seizures. Electrographic seizure activity was classified as no seizure, single attack (in which the amplitude of a single waveform appeared suddenly and showed persistent cerebral cortex activity) and recurrent attack (in which a recurring amplitude showed sudden and persistent cerebral cortex activity). Finally, we defined three types of pattern changes based on background pattern, SWC, and seizure activity by comparing to the preoperative traces: no change simply indicated the pattern did not alter, worse indicated the pattern shifted towards the abnormal type, and better denoted pattern shifted towards better type, e.g. from DNV to CNV. All reports were examined by qualified neonatal neurological experts.

Statistical analyses were performed using SPSS software, version 20 (IBM, Armonk,New York). Comparisons between groups were performed with the *t*-test, variance analysis or signed-rank test for continuous variables and with the x^2 test or Fisher's exact test for dichotomous variables. Comparisons of the ranked data were performed with the Wilcoxon sign-rank test. Logistic regression analysis was used to determine the influencing factors of aEEG. All values of *P* value <0.05 were considered statistically significant.

RESULTS

A total of 103 infants with CHD undergoing cardiac surgery were evaluated for the study. Demographic and clinical characteristics of all patients are shown in ***Table* I**. The mean (SD) gestational age at birth was 38.6 (2.4) weeks, while the mean age at surgery was 1.4 (1.2) months. The infants were classified into four types as previously defined, among which two-ventricle heart without arch obstruction was the predominant group (76, 73.8%), both two-ventricle heart with arch obstruction and single-ventricle heart without arch obstruction groups accounted for 12.6% of the total cases (*n*=13), and only one infant developed single-ventricle heart with arch obstruction. The comparison of pre- and postoperative aEEG results suggested that the background pattern was improved significantly after surgery (*P*=0.04) in infants of no more than 39 gestational weeks. The similar trends were observed for the SWC and seizure activity after surgery, but the differences were not statistically significant (***Table* II**). Since background patterns of only five infants turned worse after surgery, the changes in background pattern were classified as improved and not improved (including not changed and worse). Multivariate logistic regression analysis suggested that gestational age was the only factor affecting postoperative background pattern improvement (OR=0.20, 95% CI: 0.04-0.97; *P*=0.04), whereas bodyweight was not significant predictor for the improvement (***Table* III**). Infants with postoperative sepsis or severe postoperative infection were more likely to show a worsened SWC after heart surgery (OR=0.12, 95% CI: 0.02-0.67, *P*=0.02 and OR=6.77, 95% CI:1.60-28.68, *P*=0.01, respectively).

DISCUSSION

In the present study, background pattern of aEEG was improved in some infants after cardiac surgery, and the improvement was more likely to be identified in those with gestational age less than 39 weeks. Individuals with postoperative sepsis or severe infection were at increased risk of getting worse SWC after the operation. Our results demonstrate that gestational age and postoperative infection are predictive of benefits or harm after the surgery in terms of brain function.

Heart surgery may improve brain function of infants with CHD, as is indicated by the improvement of background pattern in some individuals. Several studies have demonstrated that normal background pattern of aEEG was observed in most infants preoperatively [11,12],

TABLE I Demographic and Clinical Characteristics of the Study Population (*N* = 103)

Characteristics	*No.* (%)
Male sex	41 (39.8)
*Gestational age, wk	38.6 (2.4)
*Birthweight, g	2936.5 (595.4)
*Age at surgery, mo	1.4 (1.2)
*Length of intensive care stay, d	27.2 (12.4)
Emergency operation	14 (13.6)
Corrective surgery	94 (91.3)
*Duration of CPB, min	92.3 (59.9)
*Aortic cross-clamp time, min	51.6 (40.1)
Delayed sternal closure	29 (28.2)
*Mechanical ventilation, d	7.0 (6.9)
CHD categories	
Two-ventricle heart without arch obstruction	76 (73.8)
Two-ventricle heart with arch obstruction	13 (12.6)
Single-ventricle heart without arch obstruction	13 (12.6)
Single-ventricle heart with arch obstruction	1 (1)
Preoperative background	
Normal	86 (83.5)
Mildly abnormal	17 (16.5)
Preoperative SWC	
Developed SWC	62 (60.2)
Immature SWC	41 (39.8)
Absent SWC	0
Preoperative seizure	
None	100 (97.1)
Single attack	1 (1.0)
Recurrent attack	2 (1.9)

*Data in no. (%) or *mean (SD); SWC: sleep-wake cycle; SS: single attack; RS: recurrent attack; CPB: Cardiopulmonary bypass; CHD: Congenital heart disease.*

TABLE II Changes between Pre- and Postoperative aEEG (*N*=103)

Changes of aEEG		*n (%)*
*Background pattern		0.04
Better	14 (13.59)	
No change	84 (81.55)	
Worse	5 (4.85)	
Sleep-wake cycle		0.52
Better	16 (15.5)	
No change	70 (67.9)	
Worse	17 (16.5)	
Seizure		0.86
Better	3 (2.91)	
No change	96 (93.2)	
Worse	4 (3.9)	

TABLE III Logistic Regression Analysis for Influencing Factors of Changes of Background Pattern and SWC

Change of aEEG	*Influencing factors*	*OR (95% CI)*
Improved background pattern		
Gestational age[#]	0.04	0.20 (0.04, 0.97)
Bodyweight[$]	0.23	0.35 (0.12, 1.04)
SWC no change	(0.02, 0.70)	
Postoperative septicemia[‡]	0.12	
Postoperative severe infection[**]	0.01	6.77 (1.60, 28.68)

*Gestational age ≤39 wks group as the reference group; body weight ≤3000 g group as the reference group; [‡]no postoperative septicemia group as the reference group; **postoperative severe infection group as the reference group.*

which was in line with our study. However, few studies have reported the improvement of background pattern after surgery. In fact, the occurrence of abnormal background pattern was increased after surgery in one study [13]. The differences should be interpreted with caution as the time for conducting aEEG monitoring was different and the sample size of both studies is relatively small.

We did not perform intra-operative aEEG monitoring in the study due to the unstable quality and lack of predictive value. Gunn K, *et al*. [14] found that aEEG background pattern will recover to the normal in most cases and there was considerable variability in the intraoperative pattern. Furthermore, postoperative but not intraoperative aEEG proved effective in identifying cerebral injury in infants with CHD [15].

Our study identified two factors that may help infer which individual would gain benefits or harm regarding brain function from cardiac surgery. Multiple risk factors, of preoperative, intraoperative, or postoperative, have been identified. Petit, *et al*. [16] reported that preoperative low arterial hemoglobin saturation was associated with transposition of the great arteries [16]. Cardiac arrest before surgery was found to increase risk of developing brain injury [6]. Prolonged total circulatory arrest during the operation was reported to be related to white matter brain injury [17]. Another study suggested that single ventricle physiology after the surgery was likely to increase risk of brain injury [18]. Our research focused on the changes of aEEG patterns and pinpointed two novel variables, namely gestational age and postoperative infection, as influencing factors for brain function, which may provide valuable insights for clinical practices.

What This Study Adds?

- Gestational age and postoperative infection are associated with changes in amplitude-integrated electroencephalography in infants with congenital heart diseases requiring cardiac surgery.

Our study had several limitations. Most importantly, the retrospective character limits the level of evidence. Sample size was small, which requires further validation of the findings. We did not systematically record intraoperative anesthetic use or report the effects of these drugs on outcomes. Lastly, long-term neurodevelopmental outcomes were not investigated.

In conclusion, we retrospectively correlated clinical factors with brain function measured by aEEG, highlighting gestational age and postoperative infection as predictors for improvement of cerebral function. If this is confirmed in larger prospective studies, it would help optimize and personalize the perioperative procedures for CHD to achieve better neurodevelopmental outcome.

Contributors: JG: study design and manuscript preparation; SRH, JZ, JMC: guarantor of integrity of the entire study; YXS: study concepts; YML,SXL: clinical studies; CC: statistical analysis; YR: data acquisition; BW: data analysis. All authors are approved to this manuscript.

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Competing Interest: None stated.

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RESEARCH PAPER

Prevalence of Congenital Heart Disease Amongst Schoolchildren in Southwest China

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Objective: To investigate the prevalence and risk factors of congenital heart disease in Yunnan, China which has diverse ethnic groups. **Methods:** This cross-sectional study enrolled 244,023 children from 2010 to 2015. To diagnose CHD, a conventional physical examination was used to screen suspicious cases, which were further confirmed by echocardiography. **Results:** A total of 1695 children were diagnosed with CHD. The estimated prevalence was 6.94%. Atrial septal defects were the most common cardiac abnormalities. A higher prevalence of CHD was observed with preterm birth, low birth weight, maternal age ≥35 years, and high-altitude regions. The prevalence also showed differences between diverse ethnic groups. **Conclusion:** The prevalence of CHD in China may have ethnic differences.

Keywords: *Altitude, Epidemiology, Ethnic group, Risk factor.*

Congenital heart disease (CHD) is a major cause of non-infectious death among children [1]. CHD is a result of alterations of multifactorial origin that include genetic and environmental factors [2]. Since 2012, CHD has become the most frequent type of birth defect in China [3]. Yunnan is a remote and underdeveloped southwestern province of China with an area of 394,000 km2. Furthermore, it is one of the most geographically and ethnically diverse places in the world, with over 26 different ethnic groups, and approximately 90% of the area is mountainous with altitudes ranging from 40 to 6000 m. The study was conducted to collect epidemiological data and risk factors of CHD in schoolchildren (aged 3-18 years) in Yunnan.

METHODS

The study was conducted by Yan'an Affiliated Hospital of Kunming Medical University. We used a cluster sampling method to recruit children aged from 3 to 18 years in Yunnan. From October 2010 to March 2015, all the children in the 1309 schools and kindergartens of Yunnan were recruited in this study. The altitude of each school was measured to evaluate the altitude at which those children lived. This study was carried out after permission from the Ethics Committee of Yan'an Affiliated Hospital of Kunming Medical University (Yunnan, China), and informed written consent was obtained from the parents or legal guardians of each child.

Each participant completed a questionnaire, which included information such as birth date, gender, gestational age, birth weight, parent age, and the ethnic group. We used a two-step method to diagnose CHD. First, a primary screen consisting of a physical examination was performed on all participants, and children with signs of cyanosis, cardiac murmur, and splitting of the second heart sound were suspected as patients with CHD. Second, the subjects suspected to have CHD were further screened by echocardiography (Philips, CX50) to assess their parasternal long-axis, short-axis, apical four-chamber, and subcostal views (2D and Doppler) to confirm CHD by an expert in pediatric senior echocardiography. The classification of CHD was based on the International Classification of Diseases, Ninth Revision, and the Clinical Modification code. However, patent foramen ovale (defects <4 mm in diameter) was excluded from the inclusion criteria.

Statistical analyses: Analysis were done with SPSS version 17.0 software package (SPSS, Chicago, Illinois). Chi-square and Fisher's exact test were used compare rates. For the comparison of the prevalence of CHD in different altitude level regions, a Cochran-Armitage Trend Test was used. Odds ratios and 95% Confidence intervals were calculated. A *P* value <0.05 was considered statistically significant.

RESULTS

A total of 244,023 children (127, 295 boys) participated in the primary physical examination with a mean (SD) age of 9.8 (2.1) years. Furthermore, 24,646 children [13,122 girls, mean age of 9.2 (2.7) years] suspected to have CHD were further screened by echocardiography.

A total of 1695 children (877 girls) were diagnosed with CHD, giving an estimated prevalence of CHD of 6.9 (95% CI, 1.78-12.11) per 1000 live births in Yunnan. There was a clear sex difference in prevalence of CHD, with 7.5 per 1000 live births among 116,728 girls compared to 6.4 per 1000 live births among 127,295 boys (OR, 1.17; 95% CI, 1.06-1.29; $P<0.01$) higher prevalence of CHD was found in mothers aged over 35 years (OR, 1.36; 95% CI; 1.23-1.51; $P<0.001$), children with gestational age <37 weeks (OR, 1.74; 95% CI; 1.52-1.99; $P<0.001$), and birthweight <2500 g (OR: 2.23, 95% CI; 1.98-2.51; $P<0.001$) (***Table* I**).There was a significant difference between different altitudes ($P<0.001$), prevalence of CHD increasing with elevation.

Atrial septal defect was the most common acyanotic congenital heart lesions (***Table* II**). Fifteen diverse ethnic groups were enrolled. Compared with the Chinese Han population, many other ethnic groups, including Tibetan, Hani, Yi, Naxi, Lisu, Jingpo, and Achang ethnic groups showed a higher prevalence of confirmed CHD ($P<0.05$) (***Table* III**).

DISCUSSION

Our study observed that Yunnan has a higher CHD prevalence than other areas of China, and ASD is the most common subtype. The higher prevalence of CHD was found among children who were born in high-altitude regions. The prevalence of CHD in most of the minority ethnic groups was higher than that in Han Chinese. Meanwhile, some other risk factors such as advanced maternal age, low birth weight, and premature birth were associated with CHD.

Our study has some limitations. We did not perform echocardiography in all children; thus, some minor lesions without cardiac murmurs such as very small ASD, tiny PDA, and uncomplicated bicuspid aortic valve might have been missed on physical examination. Furthermore, some children with severe or complex malformations might have died at a younger age, so the prevalence of

TABLE I Characteristics of 244023 Schoolchildren With Congenital Heart Disease in Yunnan, China

Variable	*CHD*	*Prevalence*
*Sex**		
Boys (*n*=127295)	818	6.426
Girls (*n*=116728)	877	7.513
Maternal age (*y*)#		
<35 (*n*=183018)	1165	6.36
≥35 (*n*=61005)	530	8.69
Gestation age (*wk*)#		
<37 (*n*=22430)	253	11.3
≥37 (*n*=221593)	1442	6.51
Birthweight (*g*)#		
<2500 (*n*=24591)	337	13.7
≥2500 (*n*=219432)	1358	6.19

*CHD: Congenital heart disease; Prevalence: per 1000 live births; *P<0.01; #P<0.001.*

TABLE II Subtypes of Congenital Heart Disease Among Schoolchildren in Yunnan, China

Type of	*Male*		*Female*		*Total*	
CHD	*No.*	*Prevalence*	*No.*	*Prevalence*	*No.*	*Prevalence*
ASD	346 (42.2)	2.718	370	3.170	716	2.893
VSD	227 (27.6)	1.783	241	2.065	468	1.918
PDA	135 (16.9)	1.061	151	1.293	286	1.213
BAV	36 (4.1)	0.283	34	0.291	70	0.287
TOF	16 (1.8)	0.126	15	0.129	31	0.127
PS	15 (1.6)	0.118	13	0.111	28	0.115
AVSD	11 (1.5)	0.086	14	0.120	25	0.102
TGA	3 (0.3)	0.024	3	0.026	6	0.025
Ebstein	2 (0.3)	0.016	4	0.034	6	0.025
others	27 (3.5)	0.212	32	0.274	59	0.242

CHD: Congenital heart disease; Prevalence: per 1000 live births; ASD: atrial septal defect, VSD: ventricular septal defect, PDA: patent ductus arteriosus BAV: bicuspid aortic valve, TOF: Tetralogy of Fallot, PS: pulmonary valvular stenosis; AVSD: Atrioventricular septal defect; TGA: Transposition of the great arteries.

What This Study Adds?

- High-altitude levels, maternal age prematurity and ethnicity were associated with the prevalence of congenital heart disease in Southwest China.

CHD in our investigation may be underestimated. Secondly, we use the altitude of each school to represent the altitude at which the children were born and lived in, which may not be very accurate. Furthermore, the physical examination, such as auscultation to screen CHD, may differ depending on the doctor even though their medical training may be similar.

Some previous studies in China have shown that the prevalence of CHD to vary from 1.5 to more than 20 per 1000 live birth [4-6]; which might have been due to the varying use of echocardiography as a diagnosis tool. Our data indicated that ASD was the most frequent lesion, which was consistent with some previous reports [7]; though others found VSD to be the most common type [8]. Some altitude correlation studies have indicated that a higher prevalence of CHD is found in high-altitude regions [9,10], which was consistent with our results. Furthermore, decreased oxygen tension has been implicated as an extrinsic factor for the formation of CHD in high-altitude areas [11]. Previous authors have also shown that maternal age ≥35 years, preterm birth, and low birth weight are risk factors for CHD [12,13]. Meanwhile, these results were also consistent with some studies conducted in China [14], but the biological mechanism for these risk factors needs further exploration. As a multi-ethnic country, some previous studies have shown that the different ethnic groups in China have different a prevalence of CHD [14,15]. This may be associated with a unique genetic background, consanguineous marriage, or bad living environment.

Through this school-based, multiple-ethnic, and multiple altitude study with an enormous number of participants, we can conclude that a physical examination combined with echocardiography is a reliable, economical, and efficient method to screen CHD in remote areas. We obtained data on risk factors and the prevalence of CHD in Yunnan, which provides additional information on the epidemiology of CHD as well as additional support for the development of diagnostic and treatment plans in many high-altitude and poor minority areas of Yunnan, China.

TABLE III Prevalence of Congenital Heart Diseases by Different Ethnic Groups in Yunnan, China

Ethnic group	*No.*	*CHD*	*Prevalence*
Han	144132	890	6.17
Tibetan*	9443	85	9.00
Bai	37300	263	7.05
Dai	15590	98	6.2
Hani*	5570	54	9.69
Yi*	14383	123	8.55
Zhuang	3564	15	4.2
Lisu*	3219	58	18.0
Wa	2094	20	9.55
Jingpo*	1630	22	13.49
Jino	1172	8	6.83
Miao	851	8	9.40
Hui	1063	7	6.58
Achang*	323	5	15.48
Others	419	2	4.78

*CHD: Congenital heart disease; Prevalence: per 1000 live births; *P value<0.05 compared with Chinese Han population.*

Contributors: SH: drafting the work and revising it critically; CW: agreement to be accountable for all aspects; ZH: design of the work; YL: acquisition of data; YD: acquisition of data; XG: acquisition of data; DH: analysis of data; ZhN: analysis of data; WC: interpretation of data. LJ: final approval of the version to be published. All authors approved the final version of manuscript, and are accountable for all aspects related to the study.
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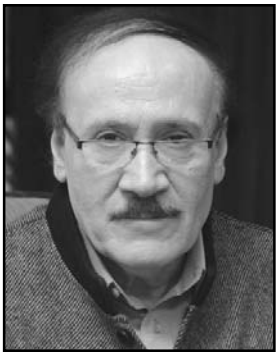
OBITUARY

Dr Maharaj Kishan Bhan



(1947-2020)

India and the biomedical science fraternity lost a jewel, Dr Maharaj Kishan Bhan on January 26, 2020, after battling for several months with malignancy at the age of 72 years.

He was born on November 9, 1947 in Srinagar. He completed his MBBS from Armed Forces Medical College, Pune in 1969 and MD (Pediatrics) from Delhi University in 1974. He was a registrar at Safdarjung Hospital (1974-76), senior consultant at Institute of Child Health, Kabul, Afghanistan (1976-78) and Lecturer at Post-graduate Institute of Medical Education and Research, Chandigarh (1978-79) before joining as a faculty in Pediatrics at AIIMS, New Delhi in 1979. At AIIMS, he pursued diarrhea and infectious disease research. His key research contributions with health impact on National and developing country programs include low osmolarity ORS, identification of enteroaggregative *E.coli* and its association with persistent diarrhea, and Zinc as treatment of diarrhea. Under his leadership, India adopted the Integrated Management of Neonatal and Childhood Illness (IMNCI) strategy.

Amidst all his achievements, the most important was the development of rotavirus vaccine, which is now saving thousands of children from diarrhea, a major cause of death in India and the world. In 1985-86, his team at AIIMS discovered and isolated the neonatal rotavirus strain, 116E, which was further pursued for development of the Indian rotavirus vaccine by Bharat Biotech International. This vaccine was introduced under the Universal Immunization Program in India in April, 2016 and now being used across several other countries. This was a game changer for India to be one the global vaccine research and development scenario.

He served as Secretary, Department of Biotechnology, Government of India, during 2004-12. During his tenure, he transformed the course of Indian biotechnology and biomedical science research and development through establishment of innovation support agencies, clusters and new Institutes. He conceived the Biotechnology Industry Research Assistance Council (BIRAC), which catalyzed academic and industry collaboration for product development and application. Translational Health Science and Technology Institute (THSTI) with centers dedicated to infectious diseases, pediatric biology, vaccines, bio-design and drug development was also one of his key initiatives during his tenure at DBT. He also steered several other programs to help foster innovation and promote the industry. He believed in big ideas and was all for a big expansion of the scientist pool and R&D activity in industry (small, medium, and large) and a smooth flow of ideas, people and knowledge.

He was a recipient of Padma Bhushan in 2013. He received numerous awards for his biomedical research including Shanti Swarup Bhatnagar Award (1990), National Ranbaxy Award (1990), ST Achar Gold Medal of the Indian Academy of Pediatrics (1984), SS Mishra Award of the National Academy of Medical Sciences (1986), Biotech Product and Process Development and Commercialization Award (2003), and Pollins Foundation Research Award (2003). He had been conferred with several fellowships including Fellow, Indian National Science Academy (FNA), Fellow, Academy of Sciences (FASc) and Fellow, Academy of Medical Sciences (FAMS) and Fellow, Third World Academy of Science (TWAS).

Professor Bhan was exceptionally compassionate with full of life and love. Despite being pulled in several directions, everyone wanted his time, and he was very accessible. His imagination was big and global while being rooted in India. He strived for excellence in science and scientific leadership in India. Two generations of biomedical researchers in India were mentored by him. He was a person with heart and mind always wanting to take India to next level of achievements and glory. According to his colleagues, whatever he did, he did with passion. He evolved from a clinician to a researcher pursuing research that changed the clinical practice, and developed new tools to save millions of lives. He shall always remain in minds and hearts of the pediatricians, clinicians, researchers and biotech innovators of India and the world.

Indian Guidelines for Indications and Timing of Intervention for Common Congenital Heart Diseases: Revised and Updated Consensus Statement of the Working Group on Management of Congenital Heart Diseases. Abridged Secondary Publication

WORKING GROUP ON MANAGEMENT OF CONGENITAL HEART DISEASE IN INDIA; ANITA SAXENA[1], JAY RELAN[1], RAVI AGARWAL[2], NEERAJ AWASTHY[3], SUSHIL AZAD[4], MANISHA CHAKRABARTY[5], KULBHUSHAN S DAGAR[3], VELAYOUDAM DEVAGOUROU[1], BAIJU S DHARAN[6], SAURABH K GUPTA[1], KRISHNA S IYER[4], M JAYRANGANATH[7], RAJA JOSHI[8], BRJ KANNAN[9], ASHISH KATEWA[10], VIKAS KOHLI[5], NAGESWARA RAO KONETI[11], SHYAM S KOTHARI[1], KM KRISHNAMOORTHY[6], SNEHAL KULKARNI[12], ROHIT MANOJ KUMAR[13], RAMAN KRISHNA KUMAR[14], SUNITA MAHESHWARI[15], KRISHNA MANOHAR[16], ASHUTOSH MARWAH[17], SMITA MISHRA[17], SMRUTI R MOHANTY[12], KONA SAMBA MURTHY, PV SURESH[19], S RADHAKRISHNAN[4], PALLETI RAJASHEKAR[1], SIVASUBRAMANIAN RAMAKRISHNAN[1], NITIN RAO[20], SURESH G RAO[12], CHINNASWAMY HM REDDY[15], RAJESH SHARMA[17], KRISHNANAIK SHIVAPRAKASHA[21], RAGHAVAN SUBRAMANYAN[22], R SURESH KUMAR[23], SACHIN TALWAR[1], MUNESH TOMAR[24], SUDEEP VERMA[25] AND VIJAYAKUMAR RAJU[26]

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(This is abridged secondary publication of a primary publication in Annals of Pediatric Cardiology: Saxena A, Relan J, Agarwal R, Awasthy N, Azad S, Chakrabarty M, et al. Indian guidelines for indications and timing of intervention for common congenital heart diseases: Revised and updated consensus statement of the Working group on management of congenital heart diseases. Ann Pediatr Cardiol. 2019;12:254-86)

Justification: A number of guidelines are available for management of congenital heart diseases from infancy to adult life. However, these guidelines are for patients living in high income countries. Separate guidelines, applicable to Indian children, are required when recommending an intervention for congenital heart diseases, as often these patients present late in the course of the disease and may have co-existing morbidities and malnutrition. **Process:** Guidelines emerged following expert deliberations at the National Consensus Meeting on Management of Congenital Heart Diseases in India, held on 10th and 11th of August 2018 at the All India Institute of Medical Sciences, New Delhi. The meeting was supported by Children's HeartLink, a non-governmental organization based in Minnesota, USA. **Objectives:** To frame evidence based guidelines for (i) indications and optimal timing of intervention in common congenital heart diseases; (ii) follow-up protocols for patients who have undergone cardiac surgery/catheter interventions for congenital heart diseases. **Recommendations:** Evidence based recommendations are provided for indications and timing of intervention in common congenital heart diseases, including left-to-right shunts (atrial septal defect, ventricular septal defect, atrioventricular septal defect, patent ductus arteriosus and others), obstructive lesions (pulmonary stenosis, aortic stenosis and coarctation of aorta) and cyanotic congenital heart diseases (tetralogy of Fallot, transposition of great arteries, univentricular hearts, total anomalous pulmonary venous connection, Ebstein anomaly and others). In addition, protocols for follow-up of post surgical patients are also described, disease wise.

Congenital heart diseases (CHDs) are the most common birth defects, responsible for nearly one-third of all congenital birth defects [1]. The birth prevalence of CHD is reported to be 8-12/1000 live births [2,3]. One-fifth of these babies have critical heart disease requiring very early intervention. Advances in pediatric cardiology and cardiac surgery have made it possible to repair or palliate most of the CHDs including the complex ones. If access to screening, early diagnosis and treatment is available, over 90% of patients born with CHD survive to adult life with good long-term outcome [4]. Most middle- and low-income countries lack such advanced level of care for children with CHD. Considering a birth prevalence of 9/1000, the estimated number of children born with CHD every year in India approximates 2,40,000, posing a tremendous challenge for the families, society and healthcare system. Approximately 10% of infant mortality in India may be accounted for, by CHDs.

JUSTIFICATION FOR DEVELOPING INDIAN GUIDELINES

Evidence based recommendations for management of CHD have been published by task force members from a number of national and international associations, but these are primarily meant for children born in high income countries. Applicability of these guidelines to Indian population with CHD is likely to be limited. Majority of patients with CHD are not diagnosed in antenatal period and often present late in the course of the disease. These patients are often underweight, malnourished and have comorbidities such as recurrent infections and anemia. Many of the late presenters have advanced level of pulmonary hypertension, ventricular dysfunction, hypoxia, polycythemia, etc. The outcome after surgery in such patients are expected to be suboptimal with longer periods of mechanical ventilation and stay in intensive care. Modifications in the treatment protocol may be required for optimizing the outcomes. All these factors justify the need for separate guidelines for management of CHDs in India, including the timing of intervention.

A statement on "consensus on timing of intervention for common congenital heart disease" which originated from a Meeting of Working Group on Management of Congenital Heart Disease in India, was published in the year 2008 [5]. This statement was revised and updated in a subsequent National Consensus Meeting, which was held in New Delhi after a gap of 10 years, in August 2018. In the intervening 10 years, a number of pediatric cardiac centres have been established and overall the numbers of interventions have increased by several folds. Considering the growing population of post-operative patients including those needing regular follow-up, we added guidelines and protocols for follow-up of these patients.

PREAMBLE

1. Every pediatrician/cardiologist/other healthcare provider must strive to get a complete diagnosis on a child suspected of having heart disease, with the help of a higher centre, if needed.
2. The proposed guidelines are meant to assist the health care provider (pediatrician, cardiologist, pediatric cardiologist) in managing cases of congenital heart diseases in their practice. While these may be applicable to the majority, each case needs individualized care, and exceptions may have to be made. Guidelines are intended to define practices, meeting the needs of patients in most, if not all circumstances, and should not replace clinical judgment.
3. These guidelines are in reference to current health care scenario prevalent in India. Subsequent modifications may be necessary in future as the pediatric cardiology practice evolves.
4. The recommendations are classified into three categories according to their strength of agreement:

Class I: Is recommended/is indicated. General agreement that the given treatment or procedure is beneficial, useful and effective.

Class II: Conflicting evidence and/or a divergence of opinion or both about the usefulness/efficacy of the given treatment or procedure. *IIa: Should be considered.* Weight of evidence/opinion is in favour of usefulness/efficacy. *IIb: May be considered.* Usefulness/efficacy is less well established.

Class III: Is not recommended. Evidence or general agreement that the given treatment or procedure is not useful/effective; and in some cases may be harmful.

AIMS AND OBJECTIVES

1. To outline the optimal timing of intervention in common CHDs.
2. To formulate guidelines and protocols for follow-up of patients who have undergone surgery/catheter interventions for CHD.

GUIDELINES FOR INDIVIDUAL CONGENITAL HEART DEFECTS

Atrial Septal Defect (*ASD*)

Diagnostic work-up: Physical examination, ECG, *X*-ray chest, echocardiography and cardiac catheterisation (in select cases).

Types of Atrial septal defect: Ostium secundum (~75%); Ostium primum (15%-20%); Sinus venosus (5%-10%); and Coronary sinus (<1%).

Patent foramen ovale: Small defect in fossa ovalis region with a flap with no evidence of right heart volume overload. Diagnosed on echocardiography, is a normal finding in newborns.

Indication for closure: ASD with left-to-right shunt associated with evidence of right ventricular volume overload without evidence of irreversible pulmonary vascular disease *(Class I)*. Indications for ASD closure remain the same irrespective of the method of closure.

Contraindications for closure: Severe pulmonary arterial hypertension or irreversible pulmonary vascular disease *(Class III)*.

Ideal Age of Closure

Asymptomatic child: 2-4 years *(Class I)*. For sinus venosus defect surgery may be delayed to 4-5 years *(Class IIa)*.

Symptomatic ASD: Rarely seen in infants. Present with congestive heart failure, pulmonary arterial hypertension. Early closure is recommended *(Class I)* after ruling out associated lesions such as left ventricular inflow obstruction, aortopulmonary window, total anomalous pulmonary venous drainage, etc.

If presenting beyond ideal age: Elective closure irrespective of age as long as there is left-to-right shunt with right heart volume overload and pulmonary vascular resistance is within operable range *(Class I)*.

Method of Closure

Surgical: Established mode *(Class I)*.

Device: For secundum ASDs with adequate rims and weight of child >15kg *(Class I)*.

Recommendations for Follow-up

Follow-up after surgical closure: Clinical and echo in the first year only. No further follow-up required if no residual disease, no pulmonary hypertension or arrhythmia. Patient/guardians should be explained about reporting to hospital in case of any cardiac symptoms, or symptoms suggestive of arrhythmias.

Follow-up after device closure: (*a*) Anti-platelet agents for total duration of 6 months (*b*) Echocardiography: - At discharge, 1 month, 6 months, 1 year, then every 3-5 years.

IE prophylaxis: It is recommended for 6 months after device or surgical closure. However, all patients are advised to maintain good oro-dental hygiene after this period also.

Isolated Ventricular Septal Defect (*VSD*)

Diagnostic Work-up: Physical examination, ECG, X-ray chest, echocardiography and cardiac catheterisation (in select cases).

Classification of Ventricular Septal Defect

Perimembranous: 80%; Outlet or sub-pulmonary (doubly committed): 5%-7%; Inlet: 5%-8%; and muscular: 5%-20%, these could be central (mid muscular), apical, marginal (anterior, septal-free wall area) or multiple, "swiss cheese" type.

Indications and Timing of Closure (All Class I recommendations)

Small VSD: (No symptoms, normal PA pressure, normal left heart chambers, no cusp prolapse): (*a*) Annual follow-up till 10 years of age, then every 2-3 years; (*b*) Closure indicated if patient has an episode of endocarditis or develops cusp prolapse with aortic regurgitation or develops progressive significant right ventricular outflow tract obstruction.

Moderate VSD: (*a*) Asymptomatic (normal pulmonary artery pressure with left heart dilation): Closure of VSD by 2-5 years of age; (*b*) Symptomatic: If controlled with medications, VSD closure by 1-2 years of age;

Large VSD: (*a*) Poor growth/congestive heart failure not controlled with medications (furosemide/spironolactone or enalapril +/- digoxin): As soon as possible; (*b*) Controlled heart failure: By 6 months of age.

VSD with aortic cusp prolapse: Any VSD with cusp prolapse and directly related aortic regurgitation that is more than trivial: Surgery whenever aortic regurgitation is detected.

Contraindications for Closure: Severe pulmonary arterial hypertension with irreversible pulmonary vascular disease *(Class III)*.

Method of Closure

Surgery: Conventionally patch closure is done. Pulmonary artery banding to be considered for patients with multiple VSDs, inaccessible VSDs and those with contraindications for cardio-pulmonary bypass.

Device closure: For VSDs with adequate rims around defect and weight of child >8kg.

Recommendations for Follow-up

Follow-up after surgery: Clinical, ECG and echo in the first year only. No further follow-up required if no residual defect or pulmonary hypertension. Patient/guardians should be explained about reporting to hospital

in case of any cardiac symptoms, or symptoms suggestive of arrhythmias.

Follow-up protocol for device closure: Anti-platelet agents for total duration of 6 months.

IE prophylaxis: It is recommended for 6 months after device or surgical closure. However, all patients are advised to maintain good oro-dental hygiene after this period also.

Atrioventricular Septal Defect (*AVSD*)

Diagnostic Work-up: Physical examination, ECG, *X*-ray chest, echocardiography and cardiac catheterisation (in select cases).

Types of AVSD

I. *Complete AVSD*: Large septal defect with an atrial component (ostium primum defect) and ventricular component (inlet septal defect), common atrioventricular valve ring and common atrioventricular valve. Generally associated with large left-to-right shunt, pulmonary arterial hypertension and congestive heart failure.

II. *Partial AVSD*: Two separate atrioventricular valves and primum atrial septal defect. Cleft of the anterior leaflet of atrioventricular valve is common with variable degree of regurgitation.

III. *Intermediate AVSD*: Two separate atrioventricular valves with primum atrial septal defect and small restrictive inlet ventricular septal defect.

IV. *Unbalanced AVSD*: One of the ventricles is hypoplastic. This form is usually associated with complex congenital heart defects such as heterotaxy syndrome (isomerism).

Varying degree of atrioventricular valve regurgitation may be associated with AVSD.

Ideal Age of Surgery

I. Complete AVSD

(*a*) Uncontrolled heart failure: Complete surgical repair as soon as possible *(Class I).*

(*b*) Controlled heart failure: Complete surgical repair by 3 months of age *(Class I).*

(*c*) Pulmonary artery banding: May be considered in select patients under 3 months of age *(Class IIb).*

II. Partial or intermediate AVSD, stable and with normal pulmonary artery pressures: Surgical repair at 2-3 years of age *(Class I).*

III. Associated moderate or severe atrioventricular valve regurgitation may necessitate early surgery in partial or intermediate forms.

IV. Pulmonary artery banding is reserved for complex cases and patients with contraindications for cardio-pulmonary bypass *(Class IIb).*

V. Surgery for moderate to severe left atrioventricular valve regurgitation is recommended as per the guidelines for mitral regurgitation, discussed later *(Class I).*

Recommendations for Follow-up

I. Lifelong follow-up is required.

II. In patients with no significant residual abnormality, annual follow-up is required till 10 years of age followed by 2-3 yearly follow-up.

III. IE prophylaxis recommended for 6 months after surgical closure. However, all patients are advised to maintain good oro-dental hygiene after this period also.

Patent Ductus Arteriosus (*PDA*)

Diagnostic Work-up: Clinical assessment, *X*-ray chest, ECG, Echocardiography. Cardiac catheterisation is usually performed for device closure.

Ideal Age of Closure

I. Large/moderate PDA (significant left heart volume overload, congestive heart failure, pulmonary arterial hypertension): Early closure (by 3 months) *(Class I).*

II. Moderate PDA (Some degree of left heart overload, mild to moderate pulmonary arterial hypertension, no/mild congestive heart failure): 6 months-1 year *(Class I).* If failure to thrive, closure can be accomplished earlier *(Class IIa).*

III. Small PDA (Minimal or no left heart overload. No pulmonary hypertension or congestive heart failure): Between 12-18 months *(Class I).*

IV. Silent PDA (Diagnosed only on echo Doppler. Hemodynamically insignificant, produce no murmur and there is no pulmonary hypertension): Closure not recommended *(Class III).*

Contraindication for closure: PDA associated with severe pulmonary arterial hypertension with irreversible pulmonary vascular disease, and silent PDA (*Class III).*

Method of Closure: Surgical: Established mode *(Class I)*. Device closure: Preferred for children >6kg as less invasive *(Class I).*

Recommendations for Follow-up

I. Clinical assessment, ECG and echo at one-year post

intervention. No further follow-up required if no residual defect or pulmonary hypertension. Patient/ guardians should be explained about reporting to a hospital in case of any cardiac symptoms.

II. IE prophylaxis recommended for 6 months after device or surgical closure. However, all patients are advised to maintain good oro-dental hygiene after this period also.

PDA in a Preterm Baby (Gestational age <37 weeks)

I. Intervene if baby is in heart failure (small PDAs may close spontaneously).

II. Approved drugs – Indomethacin/Ibuprofen/ Paracetamol (if no contraindication) *(Class I)*.

III. Mode of drug administration – Intravenous or oral. At least 2 courses of drug therapy should be tried before considering surgical intervention *(Class I)*.

IV. Surgical ligation, if above drugs fail or are contraindicated *(Class I).*

Prophylactic Indomethacin or Ibuprofen therapy: Not recommended *(Class III).*

Aortopulmonary Window

Diagnostic Work-up: Clinical assessment, *X*-ray chest, ECG, Echocardiography, Cardiac catheterisation and CT Angiography (select cases).

Ideal Age of Closure

I. Uncontrolled heart failure: Surgical repair as soon as possible *(Class I).*

II. Controlled heart failure: Elective surgical repair by 3 months of age *(Class I).*

III. In patients with associated anomalies, single stage repair of all defects is preferred *(Class I).*

***Contraindication for closure*:** Severe pulmonary arterial hypertension with irreversible pulmonary vascular disease *(Class III).*

***Method of Closure*:** Surgical patch repair *(Class I)*, transcatheter device closure in select cases with a restrictive defect.

Recommendations for Follow-up

I. Clinical evaluation, ECG and echo annually till 5 years. No further follow-up required if no residual defect or pulmonary hypertension. Patient/guardians should be explained about reporting to hospital in case of any cardiac symptoms.

II. IE prophylaxis recommended for 6 months after surgical or device closure. However, all patients are advised to maintain good oro-dental hygiene after this period also.

Coarctation of Aorta (*CoA*)

Diagnostic work up: Clinical assessment, X-ray chest, ECG, Echocardiography, CT angiography/cardiac MRI (in select cases when anatomy is unclear, and for follow-up in adults), cardiac catheterisation (if intervention is planned).

Indications for intervention

I. Patients with CoA gradient ≥20mmHg *(Class I).*

II. Patients of CoA presenting with left ventricular dysfunction, even though the gradient across is <20mmHg, where left ventricular dysfunction is considered to be due to tight CoA *(Class I).*

III. Patients with gradient <20mmHg but having upper limb hypertension, left ventricular hypertrophy or significant collateral formation *(Class IIa).*

IV. Patients with hypertension who have >50% narrowing at the site of CoA, relative to aortic diameter at diaphragm on CTA/cMRI/angiography, irrespective of pressure gradient *(Class IIa).*

V. Intervention is not indicated if Doppler gradient across coarctation segment is <20mmHg with normal left ventricular function and no upper limb hypertension *(Class III).*

Ideal Age for Intervention

I. With left ventricular dysfunction/congestive heart failure or severe upper limb hypertension (for age): Immediate intervention *(Class I).*

II. Normal left ventricular function, no congestive heart failure and mild upper limb hypertension: Intervention beyond 3-6 months of age *(Class I)*.

III. No hypertension, no heart failure, normal ventricular function: Intervention at 1-2 years of age *(Class I).*

Mode of Intervention

I. Neonatal presentation: Surgery *(Class I)*. Aortic arch hypoplasia, if associated, should also be repaired.

II. Critically ill neonate who are considered high risk for surgery (shock like syndrome, severe left ventricular dysfunction): Balloon angioplasty to tide over the crisis *(Class IIa).*

III. Infants with native coarctation: Surgery *(Class I)* or Balloon angioplasty *(Class IIa).*

IV. Infants with re-coarctation: Balloon angioplasty *(Class I).*

V. Children <25 kg with native coarctation: Balloon angioplasty *(Class I)* or Surgery *(Class IIa).*

VI. Children <25 kg with re-coarctation: Balloon angioplasty ± stenting *(Class I).*

VII. Children >25 kg and adults with native coarctation: Catheter based stenting *(Class IIa).*

VIII. Children >25 kg and adults with re-coarctation: Catheter based stenting *(Class I).*

IX. Elective endovascular stenting of aorta is contra-indicated in children < 10 years of age *(Class III).*

Follow-up Recommendations

I. Lifelong follow-up is required. Annual follow-up initially; later every 2-3 years if no residual lesions. Follow-up should include clinical assessment (upper and lower limb blood pressure) and echocardiography. Beyond 5 years of age, cMRI or CT angiography may be required.

II. Beta-blockers are the preferred drugs for control of hypertension.

III. IE prophylaxis is needed for 6 months after surgery and intervention. However, all patients are advised to maintain good oro-dental hygiene after this period also.

Aortic Stenosis (*AS*)

Diagnostic Work-up: Clinical assessment, *X*-ray chest, ECG, Echocardiography, CT Angiography/cardiac MRI (in select cases), cardiac catheterisation (primarily for therapeutic balloon valvuloplasty for valvar AS), Exercise test (in select cases).

Indications and Timing of Treatment

Valvar Aortic Stenosis

I. Immediate intervention required for:

(*a*) Newborns with severe AS who are duct dependent (balloon dilation or surgical valvotomy) *(Class I).*

(*b*) Infants or children with left ventricular dysfunction due to severe AS, regardless of the valve gradient *(Class I).*

II. Elective balloon dilation for:

(*a*) Asymptomatic or symptomatic patients with AS having gradient by echo-Doppler of >64mmHg peak or >40mmHg mean or peak to peak gradient of ≥50mmHg, measured invasively at cardiac catheterization *(Class I).*

(*b*) Patients with symptoms due to AS (angina, exercise intolerance) or ECG showing ST segment changes at rest or during exercise: balloon dilation should be considered for lower gradients (invasively measured) of ≥ 40mmHg *(Class I).*

(*c*) Asymptomatic child or adolescent with a peak systolic valve gradient (invasively measured) of ≥ 40mmHg but without ST–T-wave changes, if the patient wants to participate in strenuous competitive sports *(Class IIb).*

III. Intervention not indicated in asymptomatic children with normal ECG and AS gradient < 64 mmHg peak or < 40 mmHg mean, by echo-Doppler *(Class III).*

Subvalvar AS due to discrete membrane

Surgical intervention indicated in

I. Patients with a peak instantaneous gradient of ≥50 mmHg *(Class I).*

II. Patients with a peak instantaneous gradient of <50 mmHg associated with aortic regurgitation of more than mild severity *(Class I).*

III. Patients with a peak instantaneous gradient between 30 and 50 mmHg *(Class IIb).*

IV. Symptomatic patients with a peak instantaneous gradient < 50 mmHg in the following situations:

(*a*) Presence of left ventricular dysfunction attributable to obstruction *(Class I).*

(*b*) When pregnancy is being planned *(Class IIa).*

(*c*) When the patient plans to engage in strenuous/ competitive sports *(Class IIa).*

V. Intervention not indicated for asymptomatic patients with gradient of < 30 mmHg with no or trivial aortic regurgitation *(Class III).*

Supravalvar AS

Surgical intervention indicated in:

I. Symptomatic patients with peak instantaneous gradient ≥ 64 mmHg and/or mean gradient ≥ 50mmHg on echo-Doppler *(Class I).*

II. Patients with mean Doppler gradient <50 mmHg, if they have any of the following *(Class I)*:

(*a*) symptoms attributable to obstruction (exertional dyspnea, angina, syncope)

(*b*) left ventricular systolic dysfunction attributable to obstruction.

(*c*) severe left ventricular hypertrophy attributable to obstruction

(*d*) evidence of myocardial ischemia due to coronary ostial involvement

III. Asymptomatic patients with mean Doppler gradient ≥50mmHg may be considered for surgery when the surgical risk is low *(Class IIb).*

All patients with AS must be advised to maintain good oro-dental hygiene.

Recommendations for Follow-up

I. All patients with AS require life-long follow-up irrespective of the type of intervention.

II. Clinical assessment, ECG and echo are required; the interval depending on the severity of stenosis.

III. Patients who have significant AS and are planned for an intervention should refrain from any sporting activity. Those with asymptomatic moderate stenosis can participate in low- or moderate-intensity sports. Patients with mild degree of stenosis can participate in all sports.

IV. IE prophylaxis is recommended in patients with a prosthetic valve.

Pulmonic Stenosis (PS)

Diagnostic Work-up: Clinical assessment, X-ray chest, ECG, Echocardiography, cardiac catheterisation and angiography (primarily for therapeutic balloon valvuloplasty), CT Angiography/cardiac MRI (for peripheral pulmonic stenosis).

Indications and Timing of Treatment

Valvar pulmonic stenosis

I. Immediate intervention required for:

(*a*) Newborns with severe PS with duct dependent pulmonary blood flow *(Class I).*

(*b*) Infants or children with right ventricular dysfunction due to severe PS, regardless of the valve gradient *(Class I).*

II. Elective balloon dilation for:

(*a*) Asymptomatic or symptomatic patients with valvar PS having peak instantaneous gradient by echo-Doppler of >64mmHg *(Class I).*

(*b*) Neonates and infants with any degree of PS who have mild hypoxia due to mild hypoplasia of right ventricle, even if right ventricular function is normal *(Class IIa).*

(*c*) Patients with valvar pulmonic stenosis due to dysplastic valve, who meet the above criteria *(Class IIa).*

Mode of intervention: Balloon dilatation *(Class I)*; surgical intervention reserved for: subvalvar or supra-valvar PS with indications same as in valvar stenosis, Noonan syndrome (dysplastic valve) with hypoplastic annulus and failed balloon dilatation *(Class I).*

Recommendations for Follow-up

I. All patients with PS require life-long follow-up.

II. Clinical assessment, ECG and echo is required at each visit; the interval depending on the severity of stenosis.

III. IE prophylaxis is recommended in patients with a prosthetic valve. However, all patients with PS are advised to maintain good oro-dental hygiene.

Tetralogy of Fallot (TOF)

Diagnostic Work-up: Clinical assessment, pulse oximetry, ECG, X-ray chest, echocardiography, lab investigations (Hemoglobin/Packed cell volume, Fluorescence in situ hybridization for 22q11 deletion in some cases). CT Angiography, cardiac catheterization is performed prior to surgery in select cases.

Medical management *(Class I)*: Maintain Hb >14 g/dL (by oral iron or blood transfusion). Beta blockers to be given in highest tolerated doses (usual dose 1-4 mg/kg/day in 2 to 3 divided doses). Prostaglandin infusion for neonates with significant cyanosis.

Management of cyanotic spell: Oxygen administration, knee-chest position, intravenous fluid bolus of normal saline at the rate of 10-20 mL/kg, Morphine (0.1-0.2 mg/kg IV), IV Metoprolol (0.1 mg/kg over 5 minutes, can be repeated every 5 minutes provided no hypotension or bradycardia) or short acting Esmolol infusion (50-200 mg/kg/min), sodium bicarbonate 1-2 mEq/kg given IV, blood transfusion if required. For refractory spells, Phenylephrine infusion (2-5 µg/kg/min), IV Ketamine (0.25-1.0 mg/kg bolus dose), general anaesthesia may be needed. Severe refractory cyanotic spell is an indication for emergency surgery/intervention.

Timing of Surgery

I. Stable, minimally cyanosed: Total repair at 6-12 months of age or earlier according to the institutional policy *(Class I).*

II. Symptomatic children of <6 months of age with significant cyanosis or history of spells despite therapy: Palliation (by systemic to pulmonary artery shunt or stenting of the ductus arteriosus/right ventricular outflow tract, or pulmonary valve balloon valvuloplasty) or total repair depending on anatomy and centre's experience *(Class I).*

III. Patients having TOF with absent pulmonary valve who are stable: Medical management till 1 year of age followed by total correction with repair of pulmonary artery branch dilation/aneurysm *(Class I)*.

IV. Patients with anomalous left anterior descending artery from right coronary artery crossing the right ventricular outflow tract, who are likely to need right ventricle to pulmonary artery conduit *(Class I)*:

(*a*) <10 kg weight with significant cyanosis: Aorto-pulmonary shunt

(*b*) >10 kg weight: Total repair using conduit, or double barrel approach after two years of age, when the child weighs >10 kg.

Recommendations for Follow-up

I. Asymptomatic patients with no residual lesion but with free pulmonary regurgitation, not requiring intervention, should be followed up 1-2 yearly, life long.

II. Clinical assessment, ECG and echocardiogram is to be done at each visit. Holter monitoring is indicated in patients suspected to have arrhythmia.

III. Cardiac catheterization should be performed if any residual lesion is suspected. It may also be required for percutaneous intervention such as stenting of pulmonary artery branch for stenosis.

IV. Cardiac MRI is an important investigation for follow-up of these patients. In asymptomatic patients, baseline study should be performed 10 years after surgery with periodic follow-up.

V. Infective endocarditis prophylaxis is indicated in non-corrected patients, patients after surgical repair for 6 months, and patients with percutaneous or surgical pulmonary valve replacement. However, all patients with TOF are advised to maintain good oro-dental hygiene even after 6 months of surgical repair.

Ventricular Septal Defect with Pulmonary Atresia (*VSD-PA*)

Anatomical Types

Type A- Short segment valvar atresia, pulmonary arteries confluent and good sized, supplied by a PDA.

Type B- Long segment pulmonary atresia with absent main pulmonary artery. Branch pulmonary arteries confluent and good sized, supplied by a PDA.

Type C- Long segment pulmonary atresia with absent main pulmonary artery. Branch pulmonary arteries confluent but pulmonary blood flow dependent predominantly on MAPCAs.

Type D- Long segment pulmonary atresia with absent main pulmonary artery. Non-confluent branch pulmonary arteries with MAPCA dependent pulmonary blood flow.

Diagnostic Work-up: Clinical assessment, pulse oximetry, ECG, X-ray chest, echocardiography. Additional imaging in the form of cardiac catheterization, CT angiography/cardiac MRI or a combination of these is essential for planning definitive repair. Lab investigations (Hemoglobin/Packed cell volume, Fluorescence in situ hybridization for 22q11 deletion) in some cases.

Medical management same as outlined in section on Tetralogy of Fallot.

Indications and timing of intervention

Management depends on the type of VSD-PA, the institutional experience and the clinical presentation. Generally, this lesion requires a multistage management.

Type A (short segment VSD-PA with PDA):

I. Presentation with significant cyanosis at <1 year of age: Aorto-pulmonary shunt *(Class I)* or PDA stenting *(Class IIa)* depending on the institutional preference and feasibility.

II. After 1st intervention or those presenting at ≥1 year of age: Total correction at about 1 year of age, since a right ventricle (RV) to pulmonary artery (PA) conduit is not required *(Class I)*.

Type B (Long segment pulmonary atresia with PDA):

I. Presentation with significant cyanosis at < 1 year of age: Aorto-pulmonary shunt *(Class I)* or PDA stenting *(Class IIa)* depending on the institutional preference and feasibility.

II. After 1st intervention or in those presenting at ≥1 year of age *(Class I)*:

(*a*) Optimal pulmonary blood flow with good sized PAs – Total repair with RV to PA conduit at 3-4 years.

(*b*) Suboptimal pulmonary blood flow with small PAs – Additional shunt followed by total repair with RV to PA conduit at 3-4 years.

(*c*) Increased pulmonary blood flow with large PAs – Total repair with RV to PA conduit by 1 year.

Type C (Long segment pulmonary atresia with confluent branch pulmonary arteries supplied by MAPCAs) *(Class I)*:

(*a*) Neonatal presentation – Aorto-pulmonary shunt ± Unifocalisation of MAPCAs.

(*b*) After 1st intervention or late presentation: Total

repair with RV to PA conduit and VSD closure at 3-4 years of age.

Type D (Long segment pulmonary atresia with non-confluent branch pulmonary arteries supplied by MAPCAs) *(Class IIa)*: Aorto-pulmonary shunt + Unifocalisation of MAPCAs, followed by total repair with RV to PA conduit and VSD closure at 3-4 years of age.

Recommendations for Follow-up

I. All patients with VSD-PA require life-long follow-up. Clinical assessment, ECG and echocardiogram is required; the interval depending on the nature of repair, residual or additional lesions, symptoms and functional status.

II. Palliated patients need to be seen more frequently if their oxygen saturation is low and to decide for the next intervention.

III. Infective endocarditis prophylaxis is indicated in non-corrected or palliated patients with cyanosis, patients after surgical repair for 6 months, and patients with conduits and pulmonary valve replacement. All patients are advised to maintain good oro-dental hygiene even after 6 months of surgical repair.

Indications for pulmonary valve replacement are same as in Tetralogy of Fallot [6].

Transposition of Great Arteries (*TGA*)

Diagnostic Work-up: Clinical assessment, pulse oximetry, ECG, *X*-ray chest, echocardiography, cardiac catheterization (for balloon atrial septostomy or assessment of adequacy of left ventricle for an ASO or to assess pulmonary vascular resistance in late presenters), CT angiography and cardiac MRI (rarely required).

Indications and Timing of Surgery

Surgery is indicated for all patients with TGA except in those with irreversible pulmonary vascular disease.

Pre-surgical stabilization (Class I):

I. Start intravenous infusion of Prostaglandin E1 (PGE1), soon after delivery, if oxygen saturation is lower than 75% and/or lactic acidosis is present. Monitor respiration as PGE1 infusion may result in apnea. Use lowest maintenance dose once PDA is open.

II. Balloon atrial septostomy: This procedure is most successful in patients younger than 6 weeks, but can be tried in older infants also if the atrial septum is thin. Indications include:

(*a*) Low saturations despite PGE1 infusion and ASD is restrictive *(Class I)*.

(*b*) Those presenting with low saturation and a restrictive ASD beyond 3-4 weeks with a closed PDA where PGE1 is likely to be ineffective *(Class IIa)*.

(*c*) Patient with restrictive ASD, not fit for immediate surgery (e.g. having sepsis or respiratory infection) *(Class IIa)*.

(*d*) Restrictive ASD in TGA patients with large VSD or PDA: to decrease left atrial pressure and pulmonary venous hypertension *(Class IIa)*.

Timing and type of Surgery

I. TGA with intact ventricular septum presenting soon after birth: Arterial switch operation (ASO) is the best option *(Class I)*.

Timing of surgery: 7 days to 3 weeks, earlier if baby is unstable or has associated persistent pulmonary hypertension of the newborn. Exact timing based on institutional preference, but is best done before 4 weeks.

II. TGA with intact ventricular septum presenting beyond 3-4 weeks of life with regressed left ventricle:

(*a*) Presenting between 1 to 2 months: ASO; extracorporeal membrane oxygenator (ECMO) support may be required in some cases *(Class IIa)*.

(*b*) Presenting between 2 to 6 months: ASO with ECMO support or rapid two stage ASO* or an atrial switch (if rapid two stage or ECMO not feasible) *(Class IIa)*.

(*c*) Presenting between 6 months to 2 years: Atrial switch operation (Senning or Mustard operation) *(Class IIa)*. Rapid two stage ASO* to be considered in select cases after detailed evaluation *(Class IIb)*.

**The first stage of rapid two stage ASO involves retraining of regressed left ventricle by performing pulmonary artery banding along with the addition of a modified aorto-pulmonary shunt as the first stage. The same can also be achieved in select patients by stent placement in a patent ductus arteriosus (Class IIb). It must be noted that ASO with ECMO support and rapid two stage ASO have higher morbidity and mortality than primary ASO.*

III. TGA with a large VSD and/or a large PDA: ASO with VSD and/or PDA closure by 6 weeks of age *(Class I)*. These patients develop early pulmonary vascular disease and may become inoperable by 6 months to one year of age.

IV. TGA with VSD and coarctation of aorta: ASO with VSD closure and arch repair as soon as possible *(Class I)*. It is preferable to repair all lesions in a single stage.

V. TGA with VSD and significant left ventricular outflow obstruction *(Class I)*:

(*a*) Subvalvar pulmonary obstruction with normal or near-normal pulmonary valve and pulmonary annulus: ASO with resection of subvalvar stenosis.

(*b*) If obstruction involves pulmonary valve or is subpulmonary but not amenable to resection:

(*i*) Neonates and infants presenting with significant cyanosis: The options depend on patient's age and surgeon's preference:

a. Systemic to pulmonary shunt (at any age) followed by Rastelli type repair or root translocation (at 2-3 years of age, or when the child weighs >10kg).

b. Réparation à l'Etage Ventriculaire (REV) procedure (usually done at 4-6 months)

c. Pulmonary root translocation (usually done at 6-12 months)

d. Nikaidoh procedure (usually done beyond 6-9 months of age)

(*ii*) In older, stable patients, presenting beyond 2-3 years of age: One of the following surgeries: Rastelli type repair, Nikaidoh procedure or root translocation surgery.

(*c*) If the VSD is remote and not amenable to one of the biventricular repairs: Multistage palliative cavo-pulmonary connection *(Class IIa)*.

Recommendations for Follow-up

I. All patients need lifelong follow-up. Follow-up intervals depend on age, type of surgery and residual findings.

II. In operated patients with no residual defects: Follow-up visits should be at 1, 3 and 6 months after surgery, yearly after that till onset of adult life and every 2-3 years thereafter.

III. Follow-up visits should include clinical assessment, ECG and echocardiography.

IV. Infective endocarditis prophylaxis is recommended in patients with cyanosis, and for 6 months after definitive surgery, and in cases with conduits or other prosthetic material during surgery. However, all patients are advised to maintain good oro-dental hygiene even after 6 months of definitive surgery.

Double Outlet Right Ventricle (DORV)

Diagnostic Work-up: Clinical presentation, ECG, X-ray chest, pulse oximetry, echocardiography, cardiac catheterization (in select cases), CT angiography and cardiac MRI (when anatomy unclear).

Indication and Timing of Surgery

Surgery is indicated in all patients with DORV except in those with irreversible pulmonary vascular disease.

Timing and type of surgery depends on DORV variant (Class I)

I. DORV with subaortic VSD and pulmonary stenosis (TOF type DORV):

(*a*) Presenting with significant cyanosis at <3-4 months: Aorto-pulmonary shunt

(*b*) Presenting with significant cyanosis at >3-4 months: Total repair with closure of VSD and infundibular resection.

(*c*) Stable patients with no or minimal cyanosis: Total repair with closure of VSD and infundibular resection by 6-12 months.

II. DORV with large subaortic VSD and pulmonary hypertension (VSD type DORV):

(*a*) VSD closure by 6 months of age.

(*b*) Presenting beyond 6 months of age: assess for operability and close VSD if operable.

III. DORV with subpulmonary VSD and pulmonary hypertension (TGA type DORV):

(*a*) Arterial switch operation (ASO) with VSD closure by 6 weeks of age.

(*b*) If presenting beyond 3 months, should be evaluated for operability. ASO with VSD closure if operable.

(*c*) If associated with aortic arch abnormality, arch repair should be done in same sitting.

IV. DORV with subpulmonary VSD and pulmonary stenosis:

(*a*) If pulmonary obstruction is localized *e.g.* subvalvar fibrous membrane or ridge: ASO with resection of subvalvar stenosis.

(*b*) If pulmonary obstruction is tubular or valvar: One of the following complex surgeries required: Rastelli type repair, REV procedure, Nikaidoh procedure or root translocation. A systemic to pulmonary artery shunt may be required before these procedures in those presenting early with significant cyanosis. Please refer to section on "TGA with VSD and left ventricular outflow tract obstruction" for more details.

V. DORV with remote VSD or associated with other complex anatomy: One should strive to perform biventricular repair by intraventricular baffling of left ventricular connection to aorta. Univentricular palliation is done in cases where biventricular repair is not possible.

Recommendations for Follow-up

I. All patients need lifelong follow-up, frequency to be individualized depending on the type of surgery, presence or absence of residual lesions and functional status.

II. Follow-up visits should include clinical assessment, ECG and echocardiography.

III. Infective endocarditis prophylaxis recommended in patients with cyanosis, and in cases with conduits or other prosthetic material in the heart. Prophylaxis is also required for 6 months after definitive surgery. However, all patients with DORV are advised to maintain good oro-dental hygiene even after 6 months of definitive surgery.

Congenitally Corrected Transposition of Great Arteries (ccTGA)

Diagnostic Work-up: Clinical assessment, pulse oximetry, ECG, *X*-ray chest, echocardiography, cardiac catheterization (in select cases), cardiac MRI (in adults or after surgery), electrophysiological testing (selected patients, who have arrhythmias/blocks).

Indications and Timing of Surgery [7,8]

General recommendations:

I. Tricuspid valve (systemic atrioventricular valve) surgery for severe regurgitation should be considered before systemic ventricular failure (ejection fraction <45%) sets in *(Class IIa)*.

II. Anatomic repair (double switch operation - atrial switch plus arterial switch or Rastelli) may be considered when left ventricle is functioning at systemic pressure and when such surgery is feasible *(Class IIa)*.

Indications and Timing for Specific Groups of ccTGA

I. No associated anomalies: Medical follow-up to look for any development of tricuspid regurgitation or right ventricular dysfunction *(Class I)*. Neonatal double switch operation may be considered *(Class IIb)*.

II. Associated with large VSD

(*a*) <3 months: Pulmonary artery banding followed later by double switch operation (atrial plus arterial switch) *(Class I)*.

(*b*) >6 months: Double switch (atrial plus arterial switch), provided that patient has not developed irreversible pulmonary vascular disease *(Class I)*.

(*c*) 3-6 months: Pulmonary artery banding followed by double switch operation or direct double switch operation depending on institutional policy *(Class IIa)*.

III. Associated with Large VSD and left ventricular outflow obstruction (pulmonary stenosis): Double switch (atrial switch plus Rastelli) *(Class I)* or univentricular repair pathway *(Class IIa)*. If the saturation is good, medical follow-up may be considered after discussion with the family.

IV. Associated with complete heart block: Permanent, dual chamber pacemaker implantation *(Class I)*.

Recommendations for Follow-up

I. All patients with ccTGA require lifelong follow-up, usually every year.

II. Infective endocarditis prophylaxis is recommended for all patients with cyanosis and in cases with conduits or other prosthetic material in the heart. It is also advised for 6 months after a definitive surgery. However, all patients with ccTGA are advised to maintain good oro-dental hygiene.

Univentricular Hearts (*Single ventricles*)

Diagnostic Work-up: Clinical assessment, ECG, *X*-ray chest, pulse oximetry, echocardiography, cardiac catheterisation, CT angiography, cardiac MRI.

Timing and Type of Intervention

Preamble: Surgery for univentricular heart is a palliative procedure. The life expectancy is less than normal (exact age cannot be predicted), and is interposed by interventions over these years [9]. Treating physician must inform and discuss the details with the parent/ guardian prior to surgery.

The timing and type of intervention depends on age at presentation and presence or absence of obstruction to pulmonary blood flow.

I. Those presenting in neonatal period, or within 2-3 months of life *(Class I)*:

(*a*) With increased pulmonary blood flow:

(*i*) Type of surgery: Pulmonary artery banding at 4-6 weeks of age, preferably before 3 months.

(*ii*) Additional procedures may be required if systemic outflow obstruction is present.

(*b*) With decreased pulmonary blood flow (pulmonary stenosis group): Systemic to pulmonary artery shunt or stenting of ductus arteriosus if systemic arterial saturation is consistently below 70%-75%.

(*c*) With balanced pulmonary circulation: The baby usually maintains saturations above 80% and is not in failure. Such infants should be followed up closely. Surgery if saturation falls below 70%. *(Class I)*.

II. Those presenting later in life or have undergone first surgery earlier:

(*a*) With pulmonary hypertension and no pulmonary stenosis: Most patients who present beyond 3-4 months would become unsuitable for pulmonary artery banding or any definitive repair in the future due to irreversible increase in pulmonary vascular resistance.

(*b*) With normal pulmonary pressure and resistance due to pulmonary stenosis/previous pulmonary artery banding/previous aorto-pulmonary shunt:

(*i*) Bidirectional Glenn procedure between 4-12 months of age *(Class I)*.

(*ii*) Total cavo-pulmonary connection or completion of Fontan procedure (preferably extracardiac): Between 4-7 years of age when the child weighs 15-20 kg. Fenestration of Fontan circuit is indicated in high-risk cases.

Recommendations for Follow-up

I. All patients with univentricular heart (operated or unoperated) require lifelong follow-up. Frequency should be individualised, but should be at least once a year in stable cases.

II. Drugs after surgery: Aspirin (3-5 mg/kg/day) for all patients. Oral anticoagulants (warfarin) and sildenafil in select group, or as per institution policy [9].

III. The threshold for performing cardiac catheterisation during follow-up should be low as a number of complications can be successfully treated if diagnosed in time.

IV. Infective endocarditis prophylaxis recommended in patients with cyanosis and in cases with conduits or other prosthetic material in the heart. However, all patients with univentricular heart are advised to maintain good oro-dental hygiene.

Persistent Truncus Arteriosus

Classification of truncus arteriosus (Van Praagh and Van Praagh's) [10]

I. Type A1 - Aorta and main pulmonary artery originate from a single large common trunk.

II. Type A2 - Both pulmonary arteries arise separately and directly from the truncus.

III. Type A3 - One pulmonary artery arises from the truncus and the other is supplied by the patent ductus arteriosus or collaterals from the aorta.

IV. Type A4 - There is associated obstructive lesion of the aortic arch.

Diagnostic Work-up: Clinical assessment, pulse oximetry, *X*-ray chest, ECG, echocardiography, CT angiography/cardiac MRI (select cases), cardiac catheterisation (when operability is in doubt).

Ideal Age for Surgery: Surgery indicated in all, unless patient is inoperable.

I. Uncontrolled heart failure: Surgical repair as soon as possible *(Class I)*.

II. Controlled heart failure: Surgical repair by 3-6 weeks of age *(Class I)*.

Type of surgery

Total repair using right ventricle to pulmonary artery conduit. The prospects of repeat surgeries in future for conduit obstruction should be discussed with parents. Truncal valve is repaired if it is regurgitant.

Contraindication for Surgery

Severe pulmonary arterial hypertension with irreversible pulmonary vascular disease *(Class III)*.

Recommendations for Follow-up after Surgery

I. Lifelong follow-up is required in view of above listed postoperative issues.

II. Follow-up after surgery with clinical assessment, *X*-ray chest, ECG and echocardiography at 1, 6 and 12 months, and yearly thereafter in stable cases.

Infective endocarditis prophylaxis is recommended after surgical repair due to presence of conduit. All patients are advised to maintain good oro-dental hygiene.

Total Anomalous Pulmonary Venous Connection (TAPVC)

Types of TAPVC

Type I: Anomalous connection at supracardiac level (to innominate vein or right superior vena cava)

Type II: Anomalous connection at cardiac level (to coronary sinus or right atrium)

Type III: Anomalous connection at infradiaphragmatic level (to portal vein or inferior vena cava)

Type IV: Anomalous connection at two or more of the above levels.

Diagnostic Work-up: Clinical assessment, pulse oximetry, ECG, *X*-ray chest, echocardiography, cardiac catheterization (Rarely performed when operability is in doubt), CT angiography/cardiac MRI (select cases).

Indications and Timing of Surgery (all are *Class I* recommendations)

I. Patients with obstructive TAPVC should undergo emergency surgery.

II. Surgery should be performed as early as possible in non-obstructive TAPVC, even if they are asymptomatic.

III. Those presenting late should be evaluated for onset of pulmonary vascular disease and operated if the data suggests operable status.

Recommendations for Follow-up

I. After surgery, patients should be followed up at one month, 6 months and then annually for 5 years if there is no residual defect.

II. Since arrhythmias can occur long after TAPVC surgery, parents/patients should be informed to report if any symptom suggestive of arrhythmia develops.

Infective endocarditis prophylaxis is indicated in non-corrected patients and in patients after surgical repair for 6 months. However, all patients with TAPVC are advised to maintain good oro-dental hygiene after this period also.

Ebstein's Anomaly of the Tricuspid Valve

Diagnostic Work-up: Clinical assessment, pulse oximetry, ECG, *X*-ray chest, echocardiography, cardiac catheterization (in select cases), cardiac MRI (important when planning surgical repair), electrophysiological studies (select cases).

Indications and Timing for Treatment

Presentation in neonatal period: Significant cyanosis: IV Prostaglandin infusion; Heart failure: Anti-failure therapy including diuretics; Tachyarrhythmias: Antiarrhythmic drugs; Surgery for neonates not stabilized with medical therapy *(Class IIa).*

Presentation in older children and adults: Surgery is indicated *(Class I)* in those with symptoms or deteriorating exercise capacity, cyanosis (oxygen saturation <90%), paradoxical embolism, progressive cardiomegaly on chest *X*-ray (cardiothoracic ratio >0.65), progressive dilation or dysfunction of the right ventricle on echocardiography.

Types of Surgery: Depends on the underlying anatomy and size of the functional ventricle. Options include tricuspid valve repair (Cone repair, best done at about 2 years of age)/replacement (if repair not possible), and one and a half ventricle repair.

Recommendations for Follow-up

I. ECG, *X*-ray chest and echocardiography should be done at each visit. Holter, exercise testing and cardiac MRI may be required in select patients.

II. Asymptomatic patients who are not candidates for surgery can be followed up every 2-3 years.

III. Infective endocarditis prophylaxis is indicated in patients who have undergone tricuspid valve replacement, have previous history of endocarditis or have cyanosis. However, all patients with Ebstein's anomaly are advised to maintain good oro-dental hygiene.

Mitral and Aortic Regurgitation

Background: Mitral (MR) and aortic regurgitation (AR) occur most commonly secondary to acute or chronic rheumatic heart disease, and they may co-exist in some. Congenital MR is uncommon, however congenital AR due to a congenitally bicuspid aortic valve is not rare.

Diagnostic Work-up: Clinical assessment, ECG, *X*-ray chest, echocardiography, exercise test (in select cases), CT angiography or cardiac MRI (in select cases).

Medical Therapy

I. Angiotensin converting enzyme inhibitors are indicated in patients with severe MR and severe AR. Diuretics to be used in those with dyspnea due to heart failure.

II. Sodium nitroprusside infusion is recommended for treatment of acute MR; invasive BP monitoring is required for these cases.

III. Anticoagulants (oral) if atrial fibrillation is present.

IV. Secondary prophylaxis, preferably with long acting Benzathine penicillin injection, is required for patients who have underlying rheumatic heart disease as the etiology of MR or AR.

Indications and Timing of Surgery

Mitral regurgitation [11,12]

I. Symptomatic patients with moderate to severe MR

with left ventricular ejection fraction >30% *(Class I)*.

II. Asymptomatic patients with severe MR: Surgery indicated if any of the following present *(Class IIa)*:

(*a*) Left ventricular ejection fraction <60%.

(*b*) Left ventricular end systolic dimension Z score >3 for mitral valve replacement; and >2.5 if likelihood of mitral valve repair is >95%.

(*c*) Pulmonary artery systolic pressure >50mmHg.

III. Asymptomatic patients with moderate or severe MR undergoing cardiac surgery for another indication *(Class IIa)*.

Aortic regurgitation [11]

I. Symptomatic patients with moderate to severe AR *(Class I)*.

II. Asymptomatic patients with severe AR: Surgery indicated if any of the following present *(Class I)*:

(*a*) Left ventricular ejection fraction <50%.

(*b*) Left ventricular end systolic dimension Z score >4.

III. Asymptomatic patient with moderate or severe AR undergoing cardiac surgery for another indication *(Class I)*.

All patients with valvular regurgitation must be advised to maintain good oro-dental hygiene.

Type of Valve Surgery [13]

I. Valve repairs are preferable to valve replacements *(Class I)*.

II. Valve replacement in those in whom valve cannot be repaired *(Class IIa)*:

(*a*) Ross procedure for young patients with non rheumatic AR (if expertise available).

(*b*) Bioprosthetic valve for: female patients planning pregnancy in future, or if compliance with oral anticoagulation is dubious.

(*c*) Prosthetic metallic valve replacements for the rest of patients.

Anticoagulation after Valve Surgery [14]

I. Oral anticoagulant drug: Warfarin or other anticoumarin drug

(*a*) Desired INR (International Normalized Ratio):

(*i*) After mitral valve replacement: 3.0 (±0.5)

(*ii*) After aortic valve replacement: 2.5 (±0.5)

(*iii*) After valve repair, bioprosthetic valve: 2.5 (±0.5)

(*b*) Patients should be educated about the importance of maintaining INR in therapeutic range, the effect of diet, medicines, etc. on INR and the warning signs of overdose of warfarin. These patients should be advised to avoid contact sports; otherwise normal activities are allowed. Regular intramuscular immunization can be given while on oral anticoagulant drugs. Dental surgery is safe with therapeutic levels of INR.

(*c*) Duration of anticoagulation:

(*i*) Valve repair, bioprosthetic valve: For 3 months after surgery

(*ii*) Prosthetic metallic valve: Lifelong

(*d*) Oral anticoagulants are also indicated for patients with atrial fibrillation.

II. Aspirin: Dose - 3 to 5 mg/kg/day given in addition to anticoagulation *(Class I)*.

(*a*) Duration: Valve repair, bioprosthetic valve: For 6 months after surgery

(*a*) Prosthetic metallic valve: Lifelong

Recommendations for Follow-up

I. Patients with valve lesions require lifelong follow-up.

II. Asymptomatic patients with MR or AR: Clinical assessment, ECG and echocardiography at periodic intervals.

III. Operated patients with no residual abnormality: Clinical assessment, ECG and echocardiography. Patients with prosthetic metallic valve require frequent monitoring of INR and fluoroscopy (for valve motion).

Infective endocarditis prophylaxis [14]: All patients must be advised to maintain good oro-dental hygiene after valve surgery. Prophylaxis is reasonable before dental procedures that involve manipulation of gingival tissue or periapical region of teeth, or perforation of the oral mucosa, in patients with prosthetic valve and also in those where prosthetic material is used for valve repair (*e.g.* annuloplasty rings).

These guidelines originated from a National Consensus Meeting on "Management of Congenital Heart Diseases in India" held on 10th and 11th of August, 2018 at the All India Institute of Medical Sciences, New Delhi, India.

Contributors: All authors were part of the National Consensus Meeting that formulated these Guidelines. All authors reviewed the literature and drafted recommendations of respective sections assigned to them. The final document was drafted and

compiled by AS and JR. All authors provided critical inputs at every stage to finalize the draft recommendations. All authors approved the final document.

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ANNEXURE List of Participants with Affiliations

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OBITUARY

Prof. Lata Kumar

(1940-2020)

Professor Lata Kumar, who was born in Jaipur, did her initial education from MGD College. Later she graduated from SMS Medical College Jaipur in 1963 and did her postgraduation in Pediatrics from AIIMS in 1966.

Then she went to Denver, Colorado (USA) for Fulbright Scholarship for training in Allergy. She was associated with Professor Ishizaka (the discoverer of IgE). She joined PGIMER Chandigarh in 1971 and laid the foundation of Allergy and Asthma Clinic. Her contribution to this field is invaluable. She was a mentor to several internationally renowned pediatricians and super-specialists in Pediatrics. Her motherly attitude and guidance went a long way in shaping the career of her students.

She was the President of the Indian College of Allergy and Clinical Immunology. She was married to Prof. Vijay Kumar who is the founder of Department of Community Medicine in PGIMER, Chandigarh and is a renowned public health expert. Her demise has been a great loss to the Pediatric fraternity.

She passed away on 24th January, 2020 in the presence of her loving family. She will always remains in our hearts not just for her vast knowledge, administrative skills, and passion for teaching, but also for her calming and pleasant personality.

REVIEW ARTICLE

Management of Infants with Congenital Adrenal Hyperplasia

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Treatment of congenital adrenal hyperplasia (CAH) requires lifelong replacement of glucocorticoids with regular follow up to manage associated morbidities. The current review focuses on follow-up and management of infants diagnosed with classical CAH pertinent to Indian context. Early initiation of oral hydrocortisone in divided doses is recommended after diagnosis in newborn period, infancy and childhood. Fludrocortisone is recommended for all infants with classical CAH. All infants should be monitored as per protocol for disease and treatment related complications. The role of prenatal steroids to pregnant women with previous history of CAH affected infant for prevention of virilization of female fetus is controversial.

Keywords: *Adrenal crisis, Complication, Glucocorticoid, 17OHP, Mineralocorticoid*.

Congenital Adrenal Hyperplasia (CAH) due to 21-hydroxylase deficiency is a potentially life-threatening endocrine disorder if not diagnosed and treated timely. The disorder has variable phenotypic expressions ranging from overt symptomatic disease with signs of acute adrenal insufficiency and virilization at birth in female infants [salt-wasting (SW) CAH], to only virilization in female babies and precocious puberty in boys without features of adrenal insufficiency [simple-virilizing (SV) CAH], to non-classical CAH which may remain asymptomatic or present during adolescence with features of hyper-androgenism.

Newborn screening for CAH has emerged as a useful and practical tool to detect affected babies at birth. The prevalence of CAH in India is reported 1 in 5762 babies as per newborn screening data [1]. This data may not be a true incidence figure in India due to regional variations across different study centres and absence of confirmatory testing available for all screen positives. Newborn screening helps in early diagnosis, correct gender assignment and timely initiation of corticosteroid therapy thereby reducing mortality. The treatment of classical CAH is lifelong with steroids. Patients with CAH may develop complications as part of their disease and as side-effects of long term steroid therapy. The most significant of these are the ill-effects on linear and pubertal growth. Therefore, it is essential to initiate appropriate and early therapy and formulate a plan of regular follow-up.

We, herein, discuss the strategies for treatment and follow-up of infants with classical CAH (21-hydroxylase deficiency; SW and SV-CAH), applicable in the Indian context. The scope of this review is limited to management after diagnosis in newborn period till early childhood and does not cover details of management of other endocrine morbidities in CAH like precocious puberty or growth failure.

METHODS

A group of experts in Pediatric endocrinology and newborn screening (Delhi Pediatric Endocrinology Newborn Screening Group) met in September, 2017 and decided to carry-out this review to guide CAH management in the country. The present review is limited to management of infants with classical CAH with 21 hydroxylase deficiency. A semi-structured literature search strategy was used. The primary database used to search information was Medline through PubMed. The search was performed in September 2017 and repeated in January 2019 to include data from Indian subcontinent. Both MeSH and keyword-based inputs were searched for articles pertaining to management of CAH in childhood. Systematic reviews, meta-analysis and randomized controlled trials were given priority. Articles pertaining to the management of advanced endocrinal issues like precocious puberty, short stature and adulthood problems were not included.

Drug-therapy

Oral Hydrocortisone is recommended as the first line replacement therapy in classical CAH during childhood.

Agent- Glucocorticoid replacement is the cornerstone of replacement therapy in CAH. The drug of choice in children is hydrocortisone. This drug should be administered in tablet form which can be crushed and mixed with milk or liquid as fresh preparation before administration. The medicine should not be left dissolved or suspended in liquid for later use as there may be uneven drug delivery [2]. Other potent forms of glucocorticoids like prednisolone and dexamethasone are not recommended for use in early childhood years but can be used in post-pubertal and adult patients. Young patients with CAH who were administered prednisolone showed poor suppression in morning serum 17OHP levels and short adult height, suggesting overdosing and poor clinical outcomes [2,3].

Route - Oral hydrocortisone is effective with high bioavailability. The absolute bioavailability after oral dose was 94% after morning dose in CAH subjects [4].

Hydrocortisone should be administered in physiological doses of 10-15mg/m^2/day during infancy.

Dosage of hydrocortisone is chosen to simulate normal physiological cortisol production rate. Normally, this rate is higher during neonatal period and infancy. The endogenous cortisol production rate is estimated to be approximately 5.7-7.4 mg/m^2/day. Thus, a recommended dose of 10-15 mg/m^2/day would achieve the physiological cortisol production after accounting for first pass metabolism and bioavailability [5]. Physiological doses would promote attainment of normal growth potential without adverse effect on growth [6]. The use of more potent alternative glucocorticoids like prednisolone (4-6 mg/day) or dexamethasone (0.25-0.5 mg/day) is reserved for post-pubertal patients to permit once- or twice-daily administration [7].

Hydrocortisone should be supplemented in thrice daily schedule. The morning dose should be given as early as possible in the morning.

Hydrocortisone has a short half-life of 1.8-2 hour with extensive protein binding (90-95%), which contributes to the non-linear pharmacokinetics of the drug. The maximum suppression of adrenal hormones occurs after 2-4 hours of morning or afternoon dose and till 6-8 hours of evening dose of hydrocortisone [8]. The best time to administer hydrocortisone to achieve adrenal suppression is morning, which corresponds to the body's circadian rhythm. Delaying the evening dose till night time does not improve suppression of morning serum 17OHP levels and is not recommended [8]. The attainment of normal serum cortisol levels with twice daily and thrice daily hydrocortisone was 15% and 60%, respectively [5]. It is recommended to administer hydrocortisone in three divided doses with morning dose administered as early as possible. Modified/ extended release hydrocortisone preparations are not advisable for pediatric use [9].

Stress doses of steroids to be continued during illness and stressful situations in all patients of CAH.

Patients with classical CAH fail to produce adequate endogenous steroids, thus requiring supplemental doses of steroids during periods of stress. Data from 2298 visits of 156 patients with CAH showed incidence of adrenal crisis at 7.55 per 100 patient-years [10]. Gastrointestinal and upper respiratory tract infections were the commonest triggers with lower age, lower hydrocortisone dose and higher fludrocortisones dose as risk factors for total illness episodes [10]. All patients with CAH should be administered higher doses of hydrocortisone at 50-75 mg/m^2/day during stress (approximately 3-5 times of daily oral dose). This may be given in intravenous form in sick children or may be given orally in those who are less sick and can take orally. The usual stress dose varies from 25 mg during infancy to 50 mg in childhood [2]. All children should be given a disease card (***Web* Box I)**, which mentions about their condition and should be produced by the parents anywhere they take the affected child for treatment. The card should ideally always accompany the child, such as at school, home, picnic etc.

The diagnosis of adrenal crisis is based on clinical suspicion as symptoms are nonspecific and include weakness, lethargy, abdominal pain, nausea, vomiting, shock, and rarely seizures. Management of adrenal crisis is a medical emergency, and should receive protocolized management ***(Box I)***.

Fludrocortisone should be supplemented in all infants with classical CAH irrespective of genotype/ phenotype. All infants with salt losing should be prescribed oral salt supplements 1-3 g day.

Fludrocortisone should be supplemented in all babies with classical CAH including those with SV-CAH (lower doses required in SV-CAH) [6,7]. Supplementation of fludrocorticsone reduces requirement of corticosteroid and optimizes final height outcomes. The doses prescribed are not dependent upon weight of the infant. The requirement for mineralocorticoids is higher during infancy at 0.05-0.2 mg/day and decreases as the child grows. The drug should be started at a lower dose initially and titrated according to serum electrolytes and blood pressure. A higher dose of fludrocortisone carries the risk of hypertension, edema and hypokalemia. Fludro-cortisone has a long half-life thus a single daily administration suffices [11].

A salt intake of 1-3 g/day (5-10 mmol/kg/day) is recommended in SW-CAH to replace the hyponatremia

Box I Protocol for Management of Adrenal Crisis

Clinical features

- Non-specific- lethargy, poor feeding, vomiting, abdominal pain, shock.
- Diagnosis based on high index of clinical suspicion.
- May obtain history of preceding viral disease, minor illness.

Management

i. Maintain airway, breathing and circulation.
ii. Restore intravenous hydration by intravenous route using a wide bore needle.Infuse isotonic saline at 20 mL/kg over 10 minutes if signs of shock are present (maximum upto 60 mL/kg).
iii. Further fluid replacement to be guided by clinical signs of shock or over-hydration. Newborns should be continued on 1.5-2 times fluid as maintenance therapy (half normal saline in 5% dextrose solution).
iv. Check and correct hypoglycaemia. Administer 5 mL/kg of 10% dextrose if low blood sugar is detected.
v. Administer Intravenous hydrocortisone at 50-100 mg/m^2 bolus followed by 50-100 mg/m^2/d in four divided doses (6 hourly). Usual dose in newborn babies is approximately 25 mg bolus followedby 5-6 mg every 6 hourly.
vi. Continue intravenous route till patient is fit to consume orally.
vii. Check and correct any dyselectrolytemia.
viii. Monitor vitals, intake, output and sensorium.
ix. Mineralocorticoid replacement may be resumed when patient is stable and shifted to oral hydrocortisone maintenance doses.

which results from steroid deficiency. A recent study reported similar dose requirement of fludrocortisone and hydrocortisone, height SDS and BMI SDS in salt supplemented (27%) and un-supplemented (72.7%) children with CAH, questioning the role of routine salt supplementation in CAH [12]. However, most clinicians prefer to supplement salt in SW-CAH during first year of life when fludrocortisone requirements are also high [11]. The normal family pot diet usually suffices for the sodium requirement after infancy.

Monitoring

All children with CAH should be monitored for steroid excess clinically. Physical examination should look for hyperpigmentation, cushingoid features, growth, distribution of body fat, presence of pigmented striae and blood pressure for hypertension.

The goal of glucocorticoid supplementation in CAH is to achieve physiological replacement with maximal height potential and prevention of adrenal crisis and virilization. There is no single indicator to optimally monitor the glucocorticoid dose. Physical indicators like weight, height, growth velocity, signs of virilization and degree of skeletal maturation are the key parameters for monitoring a child with CAH. Skin pigmentation decreases in patients once optimally controlled with suppression of serum ACTH levels. There should be no progression of virilization with good control. The follow-up visits are usually monthly for first three months, and then 3-4 monthly for first two years of life. The parameters to be evaluated at every follow up visit are highlighted in ***Table* I.** Annual skeletal age computation must be done after the age of two years.

TABLE I Monitoring of Children with Classical Congenital Adrenal Hyperplasia

Age, frequency	*Investigations*
First three mo,	Serum electrolytes*
monthly	Baseline serum 17-hydroxyprogesterone recorded
3-12 mo,	Serum electrolytes*
3-monthly	Serum 17-hydroxy progesterone** Serum androstenedione, total testosterone, ACTH[#] Plasma renin activity and aldosterone:renin ratio – optional
12 -30 mo	Serum electrolytes*
4-monthly	Skeletal age assessment annually after 24 mo of age Serum 17-hydroxy progesterone** Serum androstenedione, total testosterone, ACTH[#] Plasma renin activity and aldosterone:renin ratio – optional

*Clinical parameters to be performed at all visits: Weight, length, blood pressure, Genitalia, signs of virilization, Skin pigmentation, Cushingoid features; *Performed at all visits for all patients with classical CAH or those on mineralocorticoid supplementation; **Sample for serum 17OHP should be taken before the morning dose of glucocorticoid; [#]Serum androstenedione, total testosterone, ACTH (adrenocorticotropin hormone)- to be performed if feasible.*

A sudden spurt in growth velocity along with an accelerated bone age is an indicator of under-treatment even without other signs of androgen excess. This is related to increase in adrenal hormones that cause premature bone maturation [5,6]. In contrast, weight-gain, cushingoid features and poor growth velocity are pointers of steroid overdose that warrant a dose adjustment. Timely initiation of therapy during newborn period, use of physiological doses of steroids, and lower steroid doses during puberty have shown to optimize height outcomes in children [13]. Data on 81 Indian children with CAH (mean age 6.7 y) showed a mean height SDS as -0.6 on glucocorticoid replacement (hydrocortisone mean dose 14.6 mg/m^2/d) [14]. Height was most affected in SW-CAH than SV-CAH and in children less than two years than in older age [14]. Similar data was reported in 18/30 classical CAH Indian subjects with final height SDS at -2.06 (1.1) at mean age of 14.2 y [15].

In males, high levels of ACTH can also stimulate formation of testicular adrenal rest tumors (TARTs), which impair testicular function and can cause oligospermia [5]. Beyond five years of age, affected males should be screened for development of any TARTs by serial ultrasonography of testis to detect hypoechoic lesions. Usually these lesions are small, not clinically discernible, and regress with better titration of steroid therapy. Five out of 21 boys (age >5 y) in an Indian study [14] had TARTs on ultrasonography, which regressed in three boys on follow-up.

Hormonal profile for serum 17OHP should be done 3-monthly during infancy and subsequently every 6-12 month interval.

Amongst the adrenal steroids, the three most commonly used markers for monitoring the adequacy of glucocorticoid treatment in CAH are 17-OHP, androstenedione and/or testosterone. The hormone evaluation can be performed in urine, blood, saliva or dried blood filter paper. The measurement of adrenal steroids is subject to wide variation as it depends upon time of sampling and interval from glucocorticoid administration. The diurnal variability is most marked for 17-OHP levels and relatively less for androstenedione and testosterone. Moreover, intra-individual divergence in measurement of 17-OHP can occur up to 40 folds. The single random hormone levels are difficult to interpret in isolation as there is considerable degree of overlap between the normal and poorly-controlled patients [16]. The use of consistently timed serum estimation of hormones is recommended for routine monitoring of children with CAH [7]. The serum levels of 17-OHP are usually maintained between 5-10 ng/mL. It is undesirable to achieve normal age appropriate 17-OHP levels with replacement doses of corticosteroids as that often leads to over-treatment. The dose adjustments of gluco-corticoids should be done in relation to the overall clinical context coupled with adrenal hormone measurements [2,7].

Measurement of serum androstenedione and serum testosterone add to the hormonal profile assessment in CAH and should be maintained in near normal range. Serum testosterone (total) levels can be used to monitor CAH in patients aged 6 month (beyond-minipuberty) to prepubertal age to maintain a level below 20 ng/dL [17]. Routine measurement of serum cortisol for monitoring therapy is not indicated. The plasma levels of ACTH are highest in the morning and fall abruptly after morning steroid dose. The goal of therapy is seldom to suppress ACTH production as that would lead to excess steroid dosing and side-effects of therapy. Thus, plasma ACTH values may not serve any benefit in monitoring adequacy of therapy.

The adequacy of mineralocorticoid therapy can be adjudged by monitoring blood pressure and serum electrolytes. Plasma renin activity (PRA) and aldosterone-to-PRA ratio are useful adjuncts to clinical monitoring where resources permit.

The mineralocorticoid axis can be monitored by measuring serum electrolytes (sodium and potassium) and blood pressure (***Table* I**).The aim of therapy is to maintain serum electrolytes and blood pressure in normal range. Inadequate mineralocorticoid dosing can manifest as salt craving and result in hyponatremia and hyperkalemia. Hypertension is usually asymptomatic and detected on examination. Monitoring of blood pressure should be done as per age, and gender, specific charts to detect hypertension, which can develop with overdosing of steroids. Plasma renin activity (PRA) is a sensitive marker of volume depletion. A high PRA level even with normal serum electrolyte concentrations is suggestive of inadequate replacement dose of fludrocortisone [18]. However, the logistics of sample collection, processing and measurement of PRA level preclude for its estimation in routine clinical practice.

Genital Surgery

Early genital surgery during infancy is recommended for severely virilized (≥ Prader stage 3) female babies.

Surgical correction of female genitalia is often indicated in extreme virilized states. The goals of corrective surgery are (*i*) improving the appearance of external genitalia to resemble normal female genitalia, (*ii*) conserve sexual and reproductive functions, (*iii*) achieve adequate urinary stream without incontinence. The decision for corrective surgery should never be taken in haste during early

newborn period. There is evidence to show that there may be partial regression of mild clitoromegaly after starting hydrocortisone replacement, thus averting the need of extensive surgical correction [19]. Genital surgery should be performed at a tertiary-level center, where expertise for genital surgery, urosurgery and endocrinology are available. Surgery must be conducted by experienced surgeons taking care to achieve as normal anatomical reconstruction with preservation of neurovascular bundle. Corrective surgery is indicated when patient has a high proximal junction between the vagina and urethra (^{3}Prader 3 stage) [2]. Corrective genital surgery includes vaginoplasty, clitoroplasty and labial surgery. Clitoroplasty done during infancy provides advantage of using phallic skin for vaginal reconstruction. Most children will need a staged repair [20]. There is no role of bilateral adrenalectomy in children with CAH.

Prenatal Steroids

Prenatal dexamethasone administration to pregnant woman with a prior CAH affected child for prevention of virilization of a female fetus should be considered experimental and offered after a complete discussion with the family about possible maternal adverse effects, variable genital outcome and unknown long-term side effects of dexamethasone therapy

Prenatal steroids (oral dexamethasone) may be administered to a mother having an earlier baby with CAH to prevent virilization of an affected female fetus in current pregnancy. Oral dexamethasone is not metabolized by the placenta and has shown to significantly decrease virilization in 75-85% cases if started before 9 weeks of gestation. The criteria for considering prenatal steroids are (*i*) history of previously affected sibling or first degree relative with known mutations, (*ii*) period of gestation less than 9 weeks, and (*iii*) aim to continue pregnancy till term with good drug compliance [2,7].

Diagnosis of CAH in fetus may be made preferably by molecular genetic testing of *CYP21A2* gene in chorionic villus cells. Genetic testing includes sequencing followed by deletion/duplication analysis, if no variant is identified. The aim of prenatal diagnosis is to start treatment early to prevent virilization of female fetus. Hence, pending confirmation of affected fetus, all high-risk pregnancies where prenatal therapy has been agreed upon after counseling are started on prenatal steroids by 5-6th week of gestation. Confirmation is done by chorionic villus sampling (CVS) or amniocentesis. CVS is advantageous over amniocentesis as it can be performed early around 9 weeks of gestation. As CAH is inherited as an autosomal recessive disease, the risk of affected fetus is 25%. Prenatal steroids, are beneficial only for affected homozygous or compound heterozygous females, hence 7/8 fetuses (boys and unaffected females) would unnecessarily be exposed to prenatal steroids raising ethical concerns [7,19]. The use of prenatal steroids is postulated to be associated with maternal complications like higher weight gain, edema and abdominal striae but not hypertension and gestational diabetes. The adverse fetal outcomes reported are spontaneous abortion, fetal demise, intrauterine growth retardation, liver steatosis and congenital malformations. Mild cognitive and behavioral abnormalities have been reported in children who received prenatal steroids.

A meta-analysis based on four observational studies, which included total 325 pregnancies, reported significant reduction in virilization in female babies who received prenatal dexamethasone. An increased incidence of edema and striae were found in mothers but no increased risk of stillbirths, spontaneous abortions, fetal malformations, neuropsychological or develop-mental outcomes were seen. However, as these studies were only observational and lacked long-term follow-up, the use of prenatal steroids is not recommended at present and may be started only after detailed discussion with the family [21].

Gender Assignment

Gender assignment should be done after expert opinion and appropriate counseling and discussion with the parents. Most babies with 46XX DSD with CAH should be assigned female gender at birth

Gender assignment may be difficult, and not always possible, immediately after birth. The parents should be appropriately counseled by the pediatrician regarding the nature of disease, including the need of karyotype and additional biochemical tests for confirmation of diagnosis. A recent review of 52 cases of CAH (42 simple virilizing, 10 salt-wasting) from India reported male gender assignment in one-fourth of simple virlizing CAH (median age 2 mo). All babies with SW-CAH presented earlier at median age at 0.4 mo, and were reared as females [22]. Similar data from Northern India showed male gender assignment in 17/49 (35%) of CAH, affected girls [14].

In patients with 46 XX DSD due to 21-hydroxylase deficiency, gender identity is generally female and fertility is possible. Hence, according to an International consensus guideline, female gender assignment is advised [23]. Appropriate pediatric surgery referral should be made for severely virilized females (Prader stage ≥3) for genital surgery in infancy [24].

CONCLUSIONS

Congenital adrenal hyperplasia is an endocrine disorder amenable to newborn screening and treatment. Early diagnosis and treatment have shown to improve growth,

final adult height, fertility, bone health and metabolic parameters in both girls and boys. Patients and parents must be educated about the appropriate use of steroids and the possibility of adrenal crisis. Treatment of CAH is lifelong and should be supported by a dedicated team of endocrinologists, geneticists, psychologists, surgeons and social workers.

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WEB BOX I Identification Card for Patients Affected with Congenital Adrenal Hyperplasia

- Name
- Date of birth
- Gender:
  Male
  Female
  Unassigned
- Father's name:
- Emergency contact number
- Diagnosis:
  CONGENITAL
  ADRENAL
  HYPERPLASIA
- Management if sick:
  - Check blood glucose, serum electrolytes
  - Check hydration, blood pressure, perfusion. Start Intravenous fluids if in doubt.
  - At home: Do not stop hydrocortisone or fludrocortisone.
  - Minor illness (like upper respiratory tract infection, acute diarrhea or mild fever): Double the dose of oral hydrocortisone in minor illness.
  - Moderate to severe illness (vomiting, fever >38.5 ^{o}C, lethargy, poor feeding, dehydration, surgery, trauma): Take 3-5 times the dose of oral hydrocortisone. May need intravenous steroids if hospitalized or poor oral acceptance.
  - Withhold oral fludrocortisone till taking increased dose of hydrocortisone. Continue increased dose of hydrocortisone till illness subsides.
  - Hospitalization: Administer intravenous hydrocortisone at 50-75 mg/m^2 stat if patient needs hospitalization.
  - Contact your doctor immediately after stabilization.

Antisense Oligonucleotides: A Unique Treatment Approach

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Synthetic Antisense oligonucleotides (ASOs) are novel and efficient laboratory tools to regulate the expression of specific genes, and have only recently come into clinical use. These are synthetic single-stranded DNA analogs, whose sequence is complementary to a target nucleotide and alter protein synthesis by several mechanisms. We herein provide a primer on the topic for pediatricians, as this group of drugs is likely to see many more drugs for previously incurable diseases.

Keywords: *Duchenne muscular dystrophy, Eteplirsen, Nusinersen, Spinal muscular atrophy, Treatment.*

Nucleic acids come in two forms: deoxyribonucleic acids (DNA) and ribonucleic acids (RNA). RNA has much structural variety with subtypes like messenger RNA (mRNA, that codes for protein) non-coding RNAs, transfer RNA (tRNA), ribosomal RNA (rRNA), and long-noncoding RNAs (lncRNAs) – DNA is a much more stable molecule [1]. Genetic information from DNA encodes to RNA, *ie*, transcription, which is then translated into proteins. Most of the available drugs, such as small molecules and antibodies target mainly proteins due to their mechanisms of action and chemical properties. In recent years, the use of compounds that can bind messenger RNAs (mRNAs) has gained increasing interest, as inhibition of protein expression can be helpful for controlling the course of inflammatory and neoplastic diseases. The two major therapeutic approaches in this field are the antisense oligo-nucleotides (ASOs) that inhibit mRNA translation, and the oligonucleotides, which function *via* RNA inter-ference (RNAi) pathway [2].

Synthetic antisense oligonucleotides are a novel and efficient laboratory tool to regulate the expression of specific genes. These are synthetic single-stranded DNA analogs; usually 15-30 base pairs in length, whose sequence (3' to 5') is antisense and complementary to the sense sequence of the target nucleotide (mRNA) hence called antisense oligonucleotides [2]. They selectively bind to specific pre-messenger ribonucleic acid (pre-mRNA)/mRNA sequences and alter protein synthesis by several mechanisms. First studied in the late 1970s to inhibit oncogenic viral production [3], further research led to designing of highly modified ASOs with more targeted delivery, tolerability, safety, with a prominent role in treating life-threatening diseases that were previously incurable [4].

MECHANISM OF ACTION

The mechanism of action of ASOs may briefly be summarized in three sequential steps, as follows [5]:

Pre-hybridization phase is the phase in which the ASO enters the cell, distributes within the cell, to achieve sufficient concentrations at the target RNA site. The internalization of the ASO within the cell by carrier protein-mediated endocytosis is a complex process – further, the ASO needs to escape the cellular endosomal pathway to reach the target site, which is a rate-limiting process [6].

Hybridization phase is the phase in which ASO sorts through the cellular nucleic acid sequence space to hybridize to its target RNA site. This is a complex process that involves interactions with proteins, such as Ago2, or other cellular components [5].

Post hybridization phase: After binding to the mRNA site depending on the chemical design of the ASO, a variety of events may be induced that alter the target RNA to achieve the desired pharmacological outcome. There are two main mechanisms: the common mechanism is by induction of endogenous RNAse H activity (ASO-RNase H) that cleaves the mRNA-ASO hetero-duplex which leads to degradation of the target toxic mRNA and leaves the ASO intact. The second mechanism includes binding to the RNA and causing translational inhibition by steric hindrance, exon skipping, exon inclusion, destabilization of pre-mRNA in the nucleus, or targeting the destruction of microsomal RNAs that control the expression of other genes [2,7]. For example, ASOs can bind to mRNA

structures and prevent the 5'-mRNA cap formation or, alternatively, they modify the polyadenylation site to prevent mRNA translation or alter RNA stability. Moreover, ASOs can directly stick to the mRNA and sterically block the 40S and 60S ribosomal subunits from attaching or running along the mRNA transcript during translation. Other ASOs bind on pre-mRNA intron/exon junctions and directly modulate splicing by masking splicing enhancers and repressor sequences, skipping exons, or forcing the inclusion of otherwise alternatively spliced exons. These actions are independent of RNase activity, as with Eteplirsen.

The mechanism of ASO action is shown in ***Fig.* 1**. There are many hurdles to incorporating ASOs in therapeutic use, because of their mechanism of cellular uptake and action (***Box* 1**). Thus, modifications are needed on the native ASOs to overcome these disadvantages, and this has led to various versions for clinical use.

First Generation ASOs

These are obtained by replacing one of the non-bridging oxygen atoms in the phosphate group of nucleotide with either sulfur groups (phosphorothioates), methyl groups (methylphosphonates) or amines (posphoroamidates). Phosphorothioate substitution was the earliest and the most commonly used modification that renders the inter-nucleotide linkage resistant to nuclease degradation, supports endogenous RNAse H activity to degrade the target mRNA, improves the pharmacokinetic characteristics by their binding with plasma proteins which alter the half-life and increases the availability of ASO to the target site. The other type is thiophosphoramidate substitution, though it had many side-effects in animal models and *in vitro* experiments [2,8].

Box I Hurdles to Using Anti-sense Oligonucleotides for Therapeutic Purposes

- Nucleic acids are inherently susceptible to degradation by endogenous nucleases: ASOs in their native forms have a very short half-life, even before they are filtered out through the kidney.
- Unfavorable bio-distribution and pharmacokinetic properties: Synthetic ASOs are large (approximately 30 kD) and highly negatively charged molecules and thus do not cross vascular endothelium, dense extracellular matrix and cell and nuclear membranes in order to reach their intracellular DNA or mRNA targets.
- Off-target effects of ASO may lead to a devastating adverse reaction.
- Synthetic ASOs can be immunogenic.
- Sub-optimal binding affinity for complementary sequences.

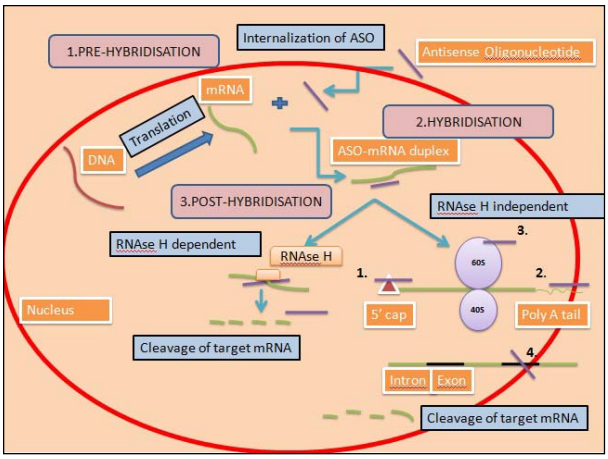

FIG. 1 *RNAse H independent mechanisms to prevent mRNA translation by ASO. Step 1. Binds to 5' cap; Step 2. Binds to poly A tail; Step 3. Stearic hindrance; and Step 4. Modifies exon splicing.*

Second Generation ASOs

Second generation ASOs were developed to overcome the shortcomings of first-generation ASOs. These second-generation antisense agents, contain a Phosphorothioate backbone and replacement of the 2-hydroxyl by many different groups but most commonly by 2'-O-methoxy (OMe), 2'-O-methoxyethyl (MOE), and locked nucleic acid (LNA). 2'-OMe modifications are commonly used in a 'gapmer' design, which is a chimeric oligo nucleotide comprising a DNA sequence core with flanking 2'-MOEnucleotides.2-Methoxyethyl is probably the most common one used in trials. Their mechanism of action is RNAse independent. The advantages of these ASOs are improved nuclease resistance, target-binding affinity, increased thermal stability of complementary hybridization, encourages tighter binding and allowing use of shorter oligonucleotides [2,4,7].

Third Generation ASOs

These are modified ASOs which help in their intracellular uptake and effective delivery to the target. These ASOs are covalently bound to a carrier or ligand, such as lipid particles, liposomes, nanoparticles, and, more recently, the sugar N-acetyl galactosamine to enhance safer delivery to the target site [2,9,10].

PHARMACOKINETICS

The rationale for understanding the pharmacokinetics of ASOs is to correlate effective dose with clearance rates to

optimize effectiveness while reducing potentially harmful side-effects [6]. The route of administration of these drugs is parenteral – intravenous, subcutaneous and intrathecal because oral bioavailability is less than 1% [11].

Absorption: The pharmacokinetic properties of oligonucleotides following parenteral administration are predominantly studied in phosphorothioate oligonucleotides, which after parenteral administration, bind to plasma proteins at >90% and transfer rapidly from blood to tissues with a distribution half-life of 1-2 hour. By 12 hour after dosing, <1% of the administered dose remains in circulation. At the same time, <5% of the administered dose is recovered in urine and feces over the first day, and this broad distribution to tissues causes the rapid disappearance of compound from blood. The highest tissue accumulation has been observed in kidney, liver, spleen, lymph nodes, adipocytes and bone marrow. In marked contrast, those oligonucleotides lacking charge and/or binding to plasma proteins (peptide nucleic acids, morpholinos) are rapidly cleared from plasma, with substantially higher excretion in urine in the first day resulting in lower overall tissue accumulation and ultimate target bioavailability [12].These drugs do not cross the blood-brain barrier and poorly distribute in skeletal muscle, heart, and lung.

Distribution: Although distribution out of plasma to tissue is rapid, the ultimate distribution to the active site within cells following a single dose is maximally realized at 24-48 h. Thus, the onset of action for antisense oligonucleotides is slower than the distribution out of plasma, which is explained due to the intracellular uptake and the kinetics for transport from the cell surface to the nucleus. Once distributed to cells, they are slowly cleared with tissue half-life ranging from 2-4 weeks [11,13].

Metabolism: These drugs are metabolized by endonucleases, which are expressed in most tissues hence liver dysfunction does not appear to affect their action. These drugs are not substrates for cytochrome P450 enzymes, and hence a very low drug-drug interaction is known [11].

Excretion: Excretion is predominantly renal and fecal; biliary uptake is minimal.

CLINICAL USE

Chemically modified 1st and 2nd generation ASOs have generated a new hope in the management of devastating neuromuscular and few other diseases such as Duchenne Muscular Dystrophy (DMD), Spinal Muscular atrophy (SMA), Myotonic dystrophy, familial hypercholesterolemia, Amyotrophic lateral sclerosis, factor IX thrombosis, Huntington chorea and peripheral neuropathies [6,14,15]. Nearly two decades after their advent, the US FDA approved the first ASO for therapeutic use in 1998 (Fomiversan). We have come a long way since then (**Box II**), with approvals coming for two oligonucleotides in 2016 for use in DMD and SMA [16]. These modify the disease make-up and progression by an effect at the gene (mRNA) level, hence provide immense scope for complete cure or at least a better quality of life. A multitude of other drugs is under development or in trials for the treatment for various other diseases, including cancers.

Individual Drugs

Fomiversan: This was the first ASO to be approved by the FDA in 1998, used clinically in CMV retinitis secondary to AIDS [17]. At that time, there was a high unmet need for anti-cytomegalovirus retinitis drugs; however, subsequently, due to the development of high-activity antiretroviral therapy (HAART), the number of CMV cases dramatically decreased [16], and its use has declined.

Pegabtinib: It was approved by the FDA in 2004 to treat Age-related macular degeneration (AMD) of the retina [16,18]. This is caused by the VEGF-stimulated growth of blood vessels (neovascularization)of the choroid of the eye leading to macular blindness. This molecule prevents the binding of VEGF to VEGFR receptors. However, with the advent of cheaper and better alternatives like bevazimumab, its use is on the downswing [16].

Eteplirsen: It was approved by the FDA for DMD in 2016, which was a remarkable step in the future of treatment for this disease. DMD is caused by mutations within the dystrophin gene that disrupt the reading frame or cause premature termination of protein synthesis [19].This was

BOX II Available Anti-sense Oligonucleotides for Clinical Application

Nusinersen:	Spinal muscular atrophy
Eteplirsen:	Duchenne Muscular Dystrophy
Fomiversan:	Cytomegalovirus retinitis secondary to AIDS
Pegabtinib:	Age-related macular degeneration of the retina
Mipomersen:	Familial hypercholesterolemia
Defibrotide:	Severe HVOD following high-dose chemotherapy and autologous BMT
Patisiran:	Transthyretin amyloidosis

HVOD: hepatic veno-occlusive disease; BMT: bone marrow transplantation

also the first approved exon skipping ASO to be used in humans [14]. This molecule is a 30-nucleotide phosphoro-diamidatemorpholino oligomer type third-generation ASO that hybridizes to exon 51 of DMD Pre-mRNA and causes it to be skipped during splicing; this corrects the translational reading frame in certain DMD gene deletions, resulting in the production of shortened but functional dystrophin protein similar to what is found in Becker's muscular dystrophy. It is effective only in DMD caused by exon 51 deletion (13%), which, however, is supported by a limited trial including 12 patients. High costs limit its widespread use [16].

The FDA approval of eteplirsen has been controversial due to the poor generalizability of the trial. Mendell, *et al*. [20] compared the three-year progression of the disease and its effect on ambulation in those receiving Eteplirsen and compared them to historic controls (*n*=13). Ambulatory DMD patients aged between 7-13 years, amenable to exon 51 skipping who were able to walk between 180-440 m on 6-Minute Walk Test and on stable corticosteroids for 24 weeks were randomized into three cohorts (each *n*=4) *viz*, placebo, Eteplirsen 30 mg/kg/week and 50 mg/kg/week. Later all received the drug in an open labeled trial. Six minute walk test and pulmonary function tests were done at baseline, 6, 1 and 24 months. A significant advantage on the walk test and a lower incidence of loss of ambulation (16%) were seen in the eteliprisen group in comparison to matched historic controls (46.2%).

Nusinersen: This is the other ASO approved by FDA in 2016 for spinal muscular atrophy (SMA). SMA is most frequently caused by a homozygous deletion or mutation within the *Survival motor neuron1 (SMN1)* gene located on chromosome 5. Homozygous deletion of *SMN1* exon 7 is confirmatory for the diagnosis of SMA. *SMN1* gene codes for the ubiquitously expressed 'survival motor neuron' (SMN) protein, which is essential for the maintenance of motor neurons. Humans have one more paralogous *SMN1* gene copy, referred to as *SMN2*, which differs from *SMN1* only by a cytosine-to-thymine mutation in exon 7 of the *SMN2* gene,which leads to alternative splicing processes with the consequence that exon 7 is omitted from the majority of *SMN2* transcripts [6,14,21]. Yet a small amount (approximately 10%) of functional SMN protein is expressed *via* the *SMN2* gene. This allows for partial compensation of the lost SMN1 exon 7 by SMN2 synthesis. Clinical phenotype is hence related to the number of *SMN2* copies [21]. Nusinersen is a 2'-OMe phosphorothioate ASO that induces the inclusion of exon 7 in the *SMN1* and *SMN2* mRNA by targeting and blocking an intron 7 internal splice site and producing functional SMN protein [16]. Nusinersen is now indicated in infants with types 1, 2, and 3 SMA. Nusinersen has to be given intrathecally as it does not cross the blood-brain barrier. The mean plasma terminal elimination half-life is 63-87 days, and the mean CNS terminal elimination half-life is 135-177 days. A fixed-dose is recommended because dose-related toxicity has not been demonstrated. The renal route of elimination is applicable for nusinersen and its inactive metabolites [22]. It is supplied as 12 mg/5 mL preservative-free solution and given in a standard dose of 12 mg on days 0, 14, 28, and 63 in two-weekly intervals followed by repeated applications in 4-month intervals [22,23].

Nusinersen is probably the most promising ASO manufactured which could modify the outcome and mortality in infants with SMA. A randomized, double-blind, sham-controlled trial by Finkel, *et al*. [23] in 2017 proved the same. In this trial 122 infants who were less than 7 months of age at the time of screening, having onset of symptoms from less than 6months of age with a confirmed mutation in the *SMN1* gene with two copies of *SMN2* gene were randomized in 2:1 ratio. 81 were to receive the drug and 41 the sham injections. Nusirensen was injected intrathecally 12 mg/ adjusted according to CSF volume on days on days 1, 15, 29, and 64 and maintenance doses on days 183 and 302. The primary endpoints were the motor-milestone response defined according to results on the Hammersmith infant neurological examination and event-free survival which was the time to death or the use of permanent assisted ventilation. Secondary end-points were overall survival and subgroup analyses of event-free survival according to disease duration at screening. Due to a very significant result during the interim analysis which showed a motor milestone response of 41% in test and 0 in control, the trial was prematurely terminated and everyone received the drug. In the final analysis, 51% in the test group showed a motor response. Risk of death or use of permanent assisted ventilation was lower in nusinersen group 47% [hazard ratio (95% CI) 0.53 (0.32-0.89), $P = 0.005$]. Also the likelihood of event-free survival and overall survival were significantly more in the test group – infants with the shortest disease duration prior to drug administered had the highest likelihood of event-free survival [23].

In another multi-center, double-blind, sham-controlled phase 3 trial by Mercuri, *et al*. [24] in 2018, 126 children with SMA who had symptom onset after 6 months of age were randomly assigned in a 2:1 ratio, to undergo intrathecal administration of nusinersen at a dose of 12 mg (nusinersen group) or a sham procedure (control group) on days 1, 29, 85, and 274. The primary endpoint was the least squares mean change from baseline in the Hammersmith functional motor scale-

expanded (HFMSE) score at 15 months of treatment; Secondary endpoints included the percentage of children with a clinically meaningful increase from baseline in the HFMSE score (≥3 points), an outcome that indicates improvement in at least two motor skills. This trial was also prematurely terminated as the pre-specified interim analysis showed a least-squares mean increase (by 4.0 points) from baseline to month 15 in the HFMSE score in the nusinersen group and a least-squares mean decrease in the control group (by-1.9 points) with a significant between-group difference favoring nusinersen (least-squares mean difference in change, 5.9 points; 95% confidence interval, 3.7 to 8.1; $P<0.001$). Results of the final analysis were consistent with results of the interim analysis in which 57% of the children in the nusinersen group as compared with 26% in the control group had a significant increase from baseline to month 15 in the HFMSE score of at least 3 points, and the overall incidence of adverse events was similar in the nusinersen group and the control group (93% and 100%, respectively) [24]. Patients from both the above trials were later enrolled in SHINE, an open-label extension trial. SHINE is structured to evaluate the effects of longer treatment with nusinersen with respect to motor function and quality of life which is still ongoing [25]. The results from the above studies infer that nusinersen could produce positive changes in the SMA patient's clinical course however the results may not be generalizable to all patients with SMA because only patients with types 1, 2, and 3 were included in the trials. Additionally, the long-term benefit and safety is not known at this time. It appears that nusinersen may have more benefit in patients who are younger with less severe disease or less comorbidity.

The most common adverse reactions of nusinersen are (>10%) upper and lower-respiratory tract infections (39%-43%), atelectasis (14%), constipation (30%), headache (50%), back pain (41%), and post-lumbar puncture syndrome (41%). Its high cost and route of administration are its major limitations [22,26].

Mipomersen: Mipomersen is the first FDA-approved systemically-delivered ASO in 2013 for familial hypercholesterolemia [16]. This is a disease caused loss of function mutations in both LDL-receptor genes which results in the reduced liver uptake of plasma LDL cholesterol leading to a very high plasma concentration of low-density lipoprotein. The core protein of the LDL particle is apolipoprotein B [27]. Mipomersen is targeted to the coding region of the apoB mRNA which effectively reduces plasma LDL and cholesterol levels with less deleterious effects on HDL. Side effects are injection site reactions and liver toxicity [28].

Other drugs include Defibrotide for severe hepatic veno-occlusive disease occurring after high dose chemotherapy and autologous bone marrow transplantation [29], and Revusiran, Patisiran and Inotersen for Transthyretin amyloidosis [30-32].

Adverse Drug Reactions

Oligonucleotides are prone to a diverse array of off-target interactions because of their size, negative charge, and potential to be synthetic [4]. Thus, despite a good overall safety profile, a few adverse reactions are encountered due to their off-target effects [33]. However, the number of studies and the sample size included are too small to determine the general side effect profile, the dose relationship and class effect for these drugs.

Binding of nucleic acid to cell surface proteins or to proteins inside cells -oligonucleotides can bind serine/threonine protein kinase PKR or Toll-like receptors (TLRs) and activate the innate immune response/alternate complement pathway. These can also bind to dRNA and DNA by complementary base-pairing. Vasculitis or glomerulonephritis are rare manifestations of immune activation [9]. All ASOs and dsRNAs will be at least partially complementary to DNA or RNA sequences inside cells that are not their intended targets and thus can modify the actions of genes on these mRNA/DNA, which could be harmful [4].

Thrombocytopenia is one of the most common side-effects seen [34]. Two forms of thrombocytopenia are studied. The more common form is milder, transient and dose-dependent wherein bleeding episodes are very rare. In humans, thrombocytopenia has been reported in cancer studies with a number of first-generation ASOs and occasionally with second-generation ASOs such as Mipomersen [35]. Other is rarer and severe form with bleeding episodes [36].

Cost

Despite remarkable progress in the development of ASOs for clinical use, the cost remains a major limitation for widespread use. For Eteplirsen, the costs were estimated at US$ 57,600 (INR 38,59,000) per month [37]. For Nusinersen, the cost of treatment of a patient with SMA amounts to US$ 750,000 (INR 5,02,50,000) for the first year, and half of that every year afterward [38,39].Thus the high costs are a major setback to any healthcare system plus the poor validity of the clinical trials in showing efficacy and adverse effects do not give a definitive risk-benefit advantage.

CONCLUSIONS

The invention of ASOs represents a therapeutic

milestone in those diseases for which we do not have a definitive cure by modifying the disease pathways. ASOs are under development or have already been tested in clinical trials for the treatment of many other diseases like myotonic dystrophy, Huntington chorea, Amyotrophic lateral sclerosis, Hemophilia A, Hereditary neuropathies. There have been some demands from individual patients and patient-support groups in LMICs (including India) to permit use of these drugs through publicly-funded programs. Although these drugs have good safety and tolerability, their high cost, route of administration, localized target (not applicable to all variants of disease), and lack of significant clinical trials describing mechanism of action, target sites, efficacy, and side effects are the major limitations. Hence, further research is required to better elucidate these important aspects, before widespread use would be a possibility.

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INDIAN PEDIATRICS

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Vaccine Response With OPV: Should We Worry?

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Polio infection plagued children all over the globe and resulted in significant mortality and neuro-morbidity till eradication was achieved with effective vaccination strategies using oral (Sabin) and or killed (Salk)/ inactivated polio vaccines (IPV). India was declared Polio free in March, 2014 for which oral polio vaccine (OPV) played an instrumental role. However, efficacy, immunogenicity and safety data with OPV had been under purview. The present study,published in February 1970, documents an early report about the immunogenicity of OPV vaccine in Indian children. This landmark paper paved the way for further research on immunization strategies against polio to outline the present revised National immunization strategy.

THE PAST

The reviewed paper reported antibody responses to oral polio vaccine (OPV) in 87 infants (29 babies less than three mo) from Delhi who received three doses of OPV[1]. The study was done to assess the seroconversion rates with OPV in Indian children and if concurrent prevalence of enteroviruses affected the uptake of OPV. All enrolled children received three doses of trivalent OPV at 4-6 weeks interval and antibody titers were compared between baseline and a second sample drawn 4-8 weeks after third OPV dose. Positive transferred maternal antibodies were present at baseline in 17.4%, 26.5% and 16.1% of infants against serotype 1, 2 and 3 respectively. The post-immunization seroconversion rate was 40.2%, 74.7% and 50.5% for seroptype 1, 2 and 3, respectively. Around 16% children were negative for all three antibodies post-immunization while only 27.6% tested positive for antibodies against all three seroptypes. The enterovirus isolation rate was 7.8% out of 296 rectal swabs and similar in pre and post-immunization samples. The study showed poor seroconversion rates following OPV in Indian infants and suggested for alternatives like increasing the dose or frequency of OPV or an additional dose of killed polio vaccine.

Historical Background

Polio continued to afflict lakhs of children despite the OPV being given as per Universal immunization schedule ever since 1985. Therefore, to decrease the paralysis related to polio, Government of India rolled out the Pulse polio program in 1995 in India so as to achieve polio elimination. OPV was provided as mandatory pulses in addition to routine immunization services and further the house to house campaign was done to leave no child unprotected. However, OPV scored over IPV as a vaccination strategy in developing countries as it was effective in providing local gut immunity and herd immunity, was cheaper, easily made available and easier to administer. Seroconversion rates were known to be superior with IPV than OPV with best protection against serotype 2 of polio virus [2]. The seroconversion rates with OPV were poorer in tropics possibly due to concurrent malnutrition and altered gut microbiota, feeding patterns, diarrhea and repeated gut inflammation with poor sanitation [3]. Additional possible dangers of neuro-virulence seen as vaccine-associated paralytic polio and vaccine-derived poliovirus with live attenuated polio strains in OPV had emerged.

THE PRESENT

Initial Indian data of effectiveness on IPV showed intramuscular dose to be most effective than intradermal dose or OPV in infants 6-9 months of age, with maximum seroprotection against serotype 2 of virus which is the most neuro-virulent strain [4]. This suggested for the need to introduce IPV with OPV to improve seroconversion. WHO launched the 'Polio Eradication and Endgame Strategic Plan 2013-2018' [5,6] which recommended switching of trivalent OPV to bivalent OPV and introduction of IPV with OPV. IPV has now been introduced

in the National Immunization schedule of India [7]. The seroconversion rates were higher with IPV when administered as a single intramuscular dose [8]or as fractional dose [9]. The continuation of OPV during PPI visits maintains mucosal immunity and is recommended [7]. A recent community survey in infants in post-polio eradication era across high risk areas for polio virus transmission in India, reported high seroprotection rates (>95%) for type 1 and 2 poliovirus and >88-90% for type 3 poliovirus. All enrolled children had received three routine doses of OPV and median four additional doses during polio campaigns [10]. Rotavirus vaccine has also been introduced in National Immunization schedule to decrease the burden of diarrheal infections. The co-administration of rotavirus vaccine has not shown to affect the seroprotection provided by OPV vaccines [11].

A trial from Southern India evaluated the effect of bacterial and viral intestinal microbiota on immunogenicity of OPV in 704 infants. Non-polio enterovirus and recently acquired enteroviral diarrheal infection were associated with a lower OPV response (OR 0.45, 95% CI 0.35,0.67 and OR 0.38, 95% CI 0.25, 0.59, respectively). Bacterial microbiota did not have any effect on seroconversion [12]. Recent data on poor antibody responses to different oral vaccines has been analyzed. A systematic review [13] analyzed the risk factors with poor performance of vaccines in low-middle income countries. Among 46 studies (25 Asian) on 8838 participants, there was no advantage of supplementation of vitamin A, zinc or probiotic or of withholding breastfeeding on seroconversion with OPV. There was no advantage either with addition of buffer or increasing vaccine inoculums of OPV. However, the seroconversion was higher with use of monovalent or bivalent vaccine instead of a trivalent vaccine (RR 1·51, 95% CI 1·20–1·91) and with use of additional birth dose of OPV (RR 1.1.2, 95% CI 0·96–1·30) [13].

THE FUTURE

The Government of India has been successful to roll out fractional IPV throughout the country. However, the challenges which stay ahead are need to maintain quality polio surveillance, improving injectable vaccine delivery systems, development of indigenous vaccines, newer research for IPV valence and composition and ensuring quality and accountability of services for safety of the masses [14]. A bigger unconquered problem remains poor water, sanitary and hygiene services and practices, which if persistent will further compound the problem of poor vaccine efficacy in Indian children.

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Congenital Heart Disease in the Pediatric Population in Eastern India: *A Descriptive Study*

This cross-sectional study assessed distribution and pattern of echocardiography confirmed congenital heart disease, among 593 pediatric patients in outpatient departments of a tertiary care hospital in eastern India. Commonest defects were ventricular septal defect (43, 40.7%), atrial septal defect (241, 31.7%), and tetralogy of Fallot (125, 21%).

Keywords: *Birth defects, Congenital heart failure, Cyanosis.*

Congenital heart disease (CHD), a common developmental defect among pediatric population, contributes to significant morbidity and mortality [1]. Epidemiological studies show CHD prevalence varying from 4/1000 to 50/1000 live-births [2,3]. This variation is attributed to genetic, environmental and socioeconomic differences**.** In India, prevalence of CHD ranges from 0.8-26.4/1000 children [4]. However, most studies have been conducted in northern and western parts of India among school children (5–15 years age), and under-represent children from eastern India and those <5 years age [4]. This study aimed to assess proportion and pattern of CHD among pediatric patients attending outpatient department (OPD) of a tertiary care hospital in eastern India.

This cross-sectional study was conducted at Neonatology, Pediatric Medicine, Pediatric Cardiology and Cardiovascular Surgery OPDs of Seth Sukhlal Karnani Memorial (SSKM) Hospital, Kolkata, India, between December, 2016 to June, 2018. Ethical approval was obtained from the Institutional Ethics Committee of SSKM Hospital. Assent and informed consent were obtained from the participants' and participant's guardian wherever applicable, prior to study enrollment. All patients (age 0-14 year) attending relevant OPDs were included. The diagnoses were confirmed by echocardiography, and classified according to Q20-Q28 of tenth revision of International Classification of Diseases (ICD) [5], and International Pediatric and Congenital Cardiac Code (IPCCC) [6]. Major CHDs included atrial septal defect (ASD), ventricular septal defect (VSD), patent ductus arteriosus (PDA), pulmonary stenosis (PS) and tetralogy of Fallot (TOF). ASD <4.0 mm diameter was not considered as a cardiac defect. If a patient had more than one lesion, the defect that required treatment or caused hemodynamic effect was considered the main malformation. Standardized, validated questionnaires administered by trained research assistants were used for collecting data. Age-at-diagnosis was considered 0 day if CHD was reported from maternity ward, or age-at-first hospitalization for CHD, or age-at-cardiac procedure.

Proportion of CHD was calculated as number of pediatric patients affected with CHD out of total attendance of pediatric OPDs in hospital. Chi square tests were used to test difference in proportions among categorical variables. Analysis was done using PC-SAS program (V9.2, SAS institute, Cary, NC, USA).

Of 41,236 patients attending pediatric OPDs during study period, 593 (1.4%) had CHD; 51.9% were males. The mean (SD) age was 4 (3.2) years; 225 (37.9%) patients more than one CHD. The commonest types were: VSD (241, 40.7%), ASD (188, 31.7%) and TOF (125, 21%). Others included PDA (44, 7.5%), PS (43, 7.3%) and double outlet right ventricle (DORV) (27, 4.5%). Isolated VSD accounted for 23.2%, both ASD and VSD 7.3%, and VSD combined with other cardiac defects (PS, PDA, DORV) 6.5% of all CHD cases. There was no significant difference in age-group (≤5 years and >5 years) (P=0.9) and sex distribution (P=0.3) of CHD. Proportion of CHD did not differ significantly among birth-weight groups (≤2.5 kg and >2.5 kg) (P=0.5), gestational age (full-term *vs.* premature) (P=0.09), maternal age (<18, 18-29 and >29 years) (P=0.9) and maternal weight (normal *vs.* overweight) (P=0.5). CHD proportion also did not significantly differ with presence/absence of history of spontaneous abortion, maternal co-morbidities, infection and smoking.

The high proportion of VSD in our study is in agreement with reported range of 21-53% from other studies [4,7,8]. ASD was the second most common CHD (31.7%), and was higher compared to reported figures of 10-23% in Indian studies [4,7]. TOF was the most common cyanotic heart disease and its proportion (21%) was higher compared to reported figures of 4.6-18.3% [9]. Though our study did not document detailed history on socioeconomic and nutritional background of mothers, our study population comprised mostly middle- and low socioeconomic class, and our findings seem consistent with studies that report premature birth, low socio-economic status and poor nutrition as important factors associated with CHDs among Asian population [10].

Most studies state that 50% of all cases of CHD are detected by 1 month, 75% by 3 months and 100% by 3-4 years age [9]. This variation at CHD detection occurs due to hemodynamic alterations occurring after birth. Our study showed that about 5% of cases were detected by 1 month, majority (83.1%) by 5 years and diagnosis was delayed beyond 10 years in 11.7% of cases. The delay in diagnosis of CHD can be explained by lack of awareness, and less health facilities and pediatric cardiac care programs in India.

The nature of survey only provided us with an estimation of proportion and pattern of CHD and no conclusions can be drawn on prevalence and causality of CHD from this study. Nevertheless, this is the first survey from eastern India providing an up-to-date data on CHD, and filling some gaps in knowledge of CHD from this geographical region.

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Antibiotic Prescription Quality in Group A β-hemolytic Streptococcal Pharyngitis

Antibiotic prescriptions in 227 patients with acute group A β-hemolytic streptococcal pharyngitis in the emergency department were studied. Antibiotic prescription was inappropriate in 42% of the cases, especially due to errors in the prescription of amoxicillin. Probably the use of low-spectrum penicillins would improve this percentage.

Keywords: *Amoxicillin, Prescription error, Treatment*.

Excessive use of antibiotics is one of the main factors associated with antibiotic resistance [1]. The administration of inappropriate antibiotics represents an unnecessary healthcare expense and likelihood of unwanted side effects [1-3]. Incorrect prescription of antibiotics in terms of dosage and administration is another factor related with antibiotic resistance guidelines. Spain is one of the European countries with the highest rates of antimicrobial prescription and antibiotic resistance [2]. Presently, rational use of antibiotic must be a priority and quality assessment and control are essential to detect deficient areas that are ripe for improvement [4,5]. In a review [6] of acute group A β-hemolytic streptococcal (GABHS) pharyngitis treated in our pediatric emergency department (ED) in 2008, a prescription rate of penicillin V <5% and errors in the posology of the prescribed antibiotic were evidenced [6].

Subsequently, annual sensitization sessions on antibiotic prescription were held. The aim of the study was to determine the appropriateness of the antibiotic prescribed in GABHS pharyngitis following the implementation of these measures.

Clinical records of patients for whom a rapid diagnostic test (RDT) was ordered in the ED for *Streptococcus pyogenes* in May-June 2016 were reviewed. Patients diagnosed with GABHS pharyngitis with positive RDT were included. A prescription was considered inconsistent if there was a mismatch or error with the existing ED protocol; type of antibiotic, dose, frequency of administration, and duration of treatment.

Two hundred twenty-seven cases were included. A first line antibiotic was prescribed for 217 (93.5%) patients [penicillin V for 74 (32.6%) and amoxicillin for 143 (63%)]. The prescription was consistent with legal guideline in 132 (58.1%) cases, 69 (93.2%) cases of penicillin V, 56 (39.2%) cases of amoxicillin and 7 (70%) cases of other antibiotics. The reasons for inconsistent prescription were type of antibiotic (5, 2.2%), dose (51, 22.5%), interval (72, 31.7%), and duration (33, 14.5%). Prescription consistency was significantly better (P=0.004) among physicians within the hospital (61.2%) than external physicians (28.6%).

The present study revealed an increase in the prescription of penicillin V administered to one-third patients with GABHS pharyngitis after introduction of sensitization sessions. The inconsistency in antibiotic prescription in the present study was similar to other studies which report prescription inconsistency between 22 and 51% [6,7]. The main reason for inconsistency in the present study was related to dosing frequency of amoxicillin advised eight hourly instead of twelve hourly as per standard guidelines [8-10]. This error may be explained by the greater familiarity with eight hourly dosing of amoxicillin for other infections [5,10]. Nevertheless, this dosing interval is not only inconsistent, but could additionally lead to lower patient adherence to treatment. The degree of consistency for the four assessed factors was high with penicillin V, unlike amoxicillin. Also, the quality of the prescription was poorer when the prescribing physician was external to the hospital. Therefore, better training of external professionals working in the ED should be a prerequisite to the optimization of antibiotic prescription.

In conclusion, this study corroborates the usefulness of observational studies in the assessment of compliance to antibiotic policy. Knowledge of the prescription and its critical analysis allows for identification and improvement in the use of the antibiotics. Antibiotic prescription was inconsistent in a significant percentage of patients with GABHS pharyngitis, mainly for amoxicillin. Given the easy guidelines for penicillin V administration and its narrow spectrum, it should be the main prescribed antibiotic for patients with GABHS pharyngitis.

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Factors Associated with Nutritional Status of Adolescent Schoolchildren in Tripura

Among 893 adolescent school children from 31 schools, 78.9% were found to have normal body weight; prevalence of thinness and overweight were 8.1% and 13%, respectively. Compared to the National reference, 95th percentile value of Body Mass Index was higher; while both weight and height were lower. Literacy, economic and physical activity status were the most significant predictors influencing nutritional status.

Keyword: *Obesity, Ethnic, Overweight, Thinness*.

The existence of ethnic differences between different tribes of India in regards to their nutritional health is well reported [1]. Hence, in the present study, nutritional status and its correlates among both ethnic (Tripuri) and non-ethnic (Bengali) adolescent of Tripura was assessed.

Subjects (14-18 y) were selected using random numbers, from 31 different government schools of Tripura (3-4 school per district selected randomly). Only the students whose parents agreed to sign the informed consent were included in the study. Ethical clearance was obtained from Institutional Human Ethical Committee of Tripura University. A prevalence of 30% for malnutrition was taken to calculate the sample size with 95% confidence interval and absolute precision of 5% [2]. The sample size was 893. History of nutritional and socioeconomic status was obtained by questioning the parents using a pre-validated questionnaire. Weight and height were recorded. Frequent calibration of the scale was done. Subjects were grouped into thinness, overweight and normal weight categories based on CDC criteria [3]. Student t test, chi-square test, and logistic regression were applied for statistical analyses.

A total of 893 students (54.8% males) were evaluated. Prevalence of thinness, overweight and normal weight was found to be 8.1%, 12.9%, and 78.9%, respectively. Highest (14.61%) and lowest (2.07%) prevalence of thinness was seen in 14 years age group of Bengali and Tripuri male subjects, respectively. On the other hand 18 years and 14 years age group of Bengali female was found to have highest and lowest prevalence for overweight (20% and 11.2%, respectively) compared to other groups (***Table* I**). Compared to ICMR reference, 95th percentile value of weight and height were found to be lower and BMI was higher in both sexes of our subjects.

On multiple logistic regression analysis, only literacy status of parents, socioeconomic class, and physical activity level were found to be significantly related to being overweight or being thin (***Table* II**).

Ethnic Tripuri subjects showed equal and in many cases better physical characteristics compared to non-ethnic Bengali subjects, which contradicts the findings from other studies [4,5]. Another significant observation of the study was a non-significant urban and rural difference in nutritional status of adolescents from both the communities of Tripura [6]. Overall prevalence of thinness found in study was much lesser than the prevalence reported from other Indian studies [7]. Similar to our findings, previous studies reported that early adolescence was more vulnerable period for malnutrition [8].

TABLE I Association Between Nutritional Status and Socio-Demographic Status (*N*=893)

Demographic factors	*% No.(%)*	*Nutritional status(%)*	
		Thinness	*Overweight*
Female gender	404 (45.24)	8.66	12.87
Community			
Tripuri	530 (59.35)	6.72	12.86
Bengali	363 (40.65)	9.95	13.17
Study area			
Rural	419 (46.92)	9.07	12.17
Urban	474 (53.08)	7.17	13.71
Age group			
14 y	398 (44.57)	6.78	12.06
15 y	223 (24.97)	7.62	13.01
16 y	118 (13.21)	9.32	13.56
17 y	90 (10.08)	11.11	14.44
18 y	64 (7.17)	10.94	15.62

TABLE II Logistic Regression Analysis of Factors Used With Nutritional Status

Factor	*Thinness OR (95% CI)*	*Overweight OR (95% CI)*
*Literacy status**		
Elementary	3.10 (1.59-6.42)	1.84 (0.60-5.11)
High School	4.98 (2.66-9.33)	3.06 (1.09-8.65)
College	7.77 (2.78-21.61)	6.11 (2.06-18.07)
Socioeconomic class[#]		
Middle	1.15 (0.66-2.01)	2.52 (1.53-4.17)
Upper Middle	1.77 (0.77-4.04)	3.09 (1.74-5.49)
Upper	2.77 (0.97-7.91)	3.64 (2.03-6.52)
Physical activity[‡]		
Low	2.58 (1.23-5.42)	2.43 (1.49-3.96)
Moderate	1.66 (0.84-3.26)	3.04 (1.78-5.19)
High	0.79 (0.43-1.46)	5.45 (2.69-11.09)

*[#]P<0.001 for all classes as compared to lower socioeconomic class; [‡]P<0.001 for high and moderate physical activity and P=0.01 for low physical activity, as compared to none; *P<0.001 for college educated and P=0.02 for high school educated, as compared to illiterate group.*

Nutritional status of subjects was significantly influenced by educational status and literacy status of their parents. Similar influence of parental education in raising the nutritional status of children is well reported [9]. Similar to our study, Kotian, *et al*. [10] also showed that the risk of overweight was two-times higher among the adolescents of high socio-economic status [10]. It has been shown previously an established fact that no or low level of physical activity is associated with overweight and obesity, which was also evident in our study.

The present study suggests that literacy, economic and physical activity status plays determinant role in nutritional status of adults. Overall, there is little difference in nutritional status between Tripuri and Bengali adolescents; as well as among urban and rural subjects from both the groups.

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Cardiac Rhabdomyoma Causing Progressive Dynamic Severe Right Ventricular Outflow Tract Obstruction in an Infant

Multiple cardiac masses were incidentally detected in a neonate on twelve day of life. Failure to thrive, feeding difficulty and severe dynamic right ventricular outflow tract obstruction developed at 7 months of age. Surgical resection of intracardiac masses relieved symptoms and histological studies confirmed rhabdomyoma. Progressive increase in the size of rhabdomyoma during infancy is an uncommon presentation and surgery can be life-saving.

Keywords: *Cardiac tumor, Echocardiography, Tuberous sclerosis.*

A 12-day-old asymptomatic neonate was detected to have multiple cardiac masses during evaluation of a cardiac murmur. There were multiple lobulated cardiac masses in the left ventricular apical region and interventricular septum (largest 10 x 8 mm) and pedunculated mass (14 × 9 mm) in right ventricular outflow tract (RVOT) **(*Fig.* 1)**. The baby did not have other features of tuberous sclerosis and was kept on close medical follow-up.

At 7 months of life, parents reported failure to thrive and new onset feeding difficulty. The right ventricular mass had increased in size (19×19 mm) and was causing severe RVOT obstruction (peak gradient 86 mmHg) without increase in size of left ventricular masses. In view of symptomatic severe RVOT obstruction, surgical resection of all the masses was done. The largest mass (20×15 mm) was firm in consistency, gray-white and glistening, arising from right ventricular free wall partly attached to the chordae of septal leaflet of tricuspid valve (***Web Fig.* 1a**). Histopathology showed vacuolated tumor cells with clear cytoplasm and characteristic spider cells on Haematoxylin and Eosin staining (***Web Fig.* 1b**) and Desmin expression (***Web Fig.* 1c**) suggestive of cardiac rhabdomyoma.

Neonatal cardiac tumours are rare, rhabdomyomas being commonest among them. Tuberous sclerosis is associated with cardiac rhabdomyomas in 50-60% patients and conversely, rhabomyomas are associated with tuberous sclerosis in 59-80% [1,2]. Rhabdomyomas are generally multiple, well-circumscribed, intramural or pedunculated tumours seen most commonly in the ventricles. They are hamartomas with no malignant potential. Their presentation varies from asymptomatic incidentally detected cardiac murmur, congestive cardiac failure, arrhythmias or sudden infant death depending on the size, number and location of the tumour.

Cardiac rhabdomyomas have a propensity for spontaneous regression [3,4]. Most of them have a benign course and remain static or regress with age, higher chances of spontaneous regression seen at younger age. Complete regression is common in the ûrst 4 years of life [3,4]. Mammalian targets for rapamycin inhibitors have been used to treat large, inoperable or residual rhabdomyomas [5]. Surgical intervention is indicated with haemodynamic compromise or intractable arrhythmia. Progressive severe dynamic outflow tract obstruction is an uncommon presentation and surgery can be life-saving.

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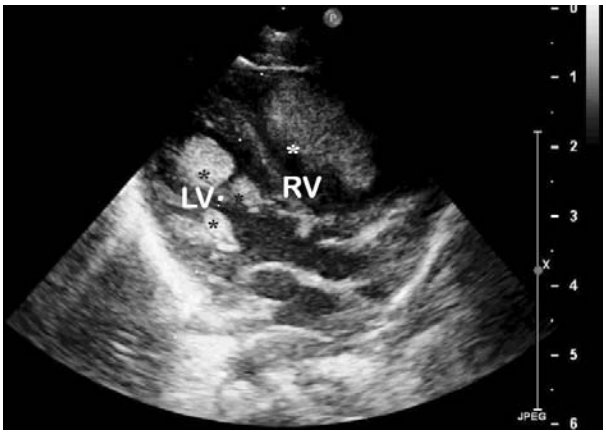

FIG. 1 *Echocardiogr am (parasternal long-axis view) showing multiple cardiac masss in left ventricle (LV) and right ventricle (RV).*

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Mevalonate Kinase Deficiency as Cause of Periodic Fever in Two Siblings

Mevalonate kinase deficiency (MKD) is a rare autosomal recessive autoinflammatory disease caused by mutations in *MVK*. We report two siblings with MKD, presenting with recurrent febrile illnesses, detected to have compound heterozygous variants in *MVK*. MKD mimics common pediatric conditions and should be considered as a differential diagnosis.

Keywords: *Hyper-IgD syndrome, Pyrexia of unknown origin, Neonatal hepatitis, Periodic fever.*

Fever of unknown origin is often a diagnostic challenge in children. Etiology includes infections, malignancy, autoimmune and autoinflammatory diseases. Autoinflammatory diseases are multisystem disorders characterized by periodic attacks of fever and systemic inflammation. Mevalonate kinase deficiency (MKD) is an autosomal recessive autoinflammatory disease caused by mutations in the *mevalonate kinase* (*MVK*) gene which encodes for mevalonate kinase, a key enzyme in the mevalonic acid pathway [1]. The clinical spectrum ranges from Hyper-IgD syndrome (HIDS) (MIM 260920) to the more severe mevalonic aciduria (MIM 610377). This paper reports two siblings with MKD.

A five-year-old male child born to nonconsanguineous parents was symptomatic from 2 months of age with history of recurrent febrile illnesses associated with diarrhea, icterus, hepatosplenomegaly, along with thrombocytopenia and severe anemia requiring repeated blood and platelet transfusions. From 3 months of age he developed febrile episodes recurring weekly without any systemic focus, which subsided by 8 months of age. At 1.5 years of age, he developed frequent constipation with abdominal distention and pain which continued till 2.5 years of age. He developed recurrent tonsillitis and lymphadenopathy from four years of age. At five years, his height was 92 cm (-3.95 SD), weight 11.5 kg (-3.55 SD) and head circumference 46cm (-3.19 SD). He had a triangular face, open anterior fontanelle, blue sclera, cervical lymphadenopathy and hepatosplenomegaly (liver 4.5 cm and spleen tip palpable). Investigative work-up detected raised C-reactive protein (CRP) but other tests for infectious etiologies, immunodeficiency, chronic liver disease and storage disorders were negative. The proband's younger brother was also symptomatic at 1 month of age with fever, neonatal hepatitis, cholestasis and severe anemia. He also had elevated CRP levels even during asymptomatic periods. At 1 year of age he developed episodes of subacute intestinal obstruction and one episode of acute lymphadenitis. At 18 months of age his length was 68 cm (-5.3 SD), weight 6.5kg (-4.4 SD) and head circumference 43.5cm (-2.9 SD). He had a facial phenotype resumbling his brother's, cervical lymphadenopathy, hepatosplenomegaly (liver 5.5 cm and spleen 3.5 cm below costal margin) and motor and speech delay.

Repeated febrile episodes with elevated inflammatory markers raised the possibility of periodic fever syndrome. Urine organic acid analysis using gas chromatography and mass spectrometry (GCMS) showed elevated levels of mevalonolactone. Genetic testing using clinical exome panel by next generation sequencing in the proband revealed previously reported compound heterozygous variants, c.803T>C (p.Ile268Thr) on exon 9 and c.976G>A (p.Gly326Arg) on exon 10 in *MVK* gene (***Web Fig.* 1a**). Both the variants were confirmed in the second sibling (***Web Fig.* 1b**). Segregation analysis in parents could not be done. Both siblings were treated with tocilizumab. There was reduction in frequency of febrile episodes and normalization of CRP levels. Tocilizumab was discontinued due to adverse drug reactions and patients were shifted to nonsteroidal anti-inflammatory drugs (NSAID) and corticosteroids.

Approximately 300 cases of MKD have been reported with the vast majority having European ancestry (median age at diagnosis, 8 to 10 years) [2]. HIDS is characterized by recurrent febrile inflammatory episodes associated with diarrhea, abdominal pain, vomiting, lymphadenopathy, splenomegaly, macular papular rash, and arthritis. Additionally patients with mevalonic aciduria have intrauterine growth reduction, failure to thrive, facial

dysmorphism, and neurologic involvement [2]. Loss of function mutations in the *MVK* block the mevalonic acid pathway affecting protein prenylation and thereby decreasing geranylgeranyl pyrophosphate which leads to increased production of inflammatory cytokines [3,4].

Our patients initially had features of neonatal hepatitis with cholestasis followed by subacute intestinal obstruction probably caused by adhesions secondary to sterile peritonitis [1]. Elevated serum levels of polyclonal immunoglobulin D (IgD) is not diagnostic of MKD as it may be raised in tuberculosis, sarcoidosis, Hodgkin lymphoma and acquired immunodeficiency, or normal in 20% of cases [3]. IgD does not correlate with diseases severity or pathogenesis. IgD levels could not be measured in index case. Excretion of mevalonic acid in urine supports the diagnosis of MKD [1,3]. In mevalonic aciduria, mevalonolactone is significant and continuously observed unlike HIDS where it is mildly elevated or even normal in asymptomatic periods. Confirmatory diagnosis is possible by detecting homozygous or compound heterozygous mutations in *MVK* or decreased mevalonate kinase enzyme activity in lymphocytes or cultured fibroblasts. A strong clinical suspicion, urinary GCMS and genetic testing led to the confirmation of diagnosis at an early age in index patients. Both detected variants have been reported in patients with European and Arab ancestry [5,6]. The p.Ile268Thr variant is the second most common of over 200 variants found in patients with both MA and HIDS phenotypes [6]. This is the first report of these variants from India.

Acute exacerbations may be treated with NSAID and short course corticosteroids. Drugs like interleukin (IL) 1 blocking agents, anakinra and canakinumab, and anti TNF-α agent etanercept and IL-6 receptor antibody, tocilizumab, have also been successful in reducing the frequency of exacerbations [4]. However, cost and lack of availability of these medications limit their use in resource limited setting such as India.

HIDS is a self-limiting illness with poor quality of life but not associated with decreased life expectancy unlike severe form of mevalonic aciduria [2]. Prenatal genetic testing can be used to detect affected fetuses as there is 25 percent chance of recurrence in subsequent pregnancies.

This report highlights the fact that MKD is a disorder with constellation of commonly encountered symptoms and signs. Despite being rare, autoinflammatory disorders should be considered in the differential diagnosis of patients with recurrent febrile attacks associated with raised inflammatory markers. Genetic testing is a gold standard modality to confirm the diagnosis and end the diagnostic odyssey.

Contributors: AREC: case management, draft the initial and revised manuscript; NG: data collection, diagnosis, case management and conceptualization of the study, manuscript review and revision; NB,PV,SA: case management and manuscript review and revision; SY: case diagnosis and manuscript review. All authors approved the manuscript as submitted and agree to be accountable for all aspects of the work.

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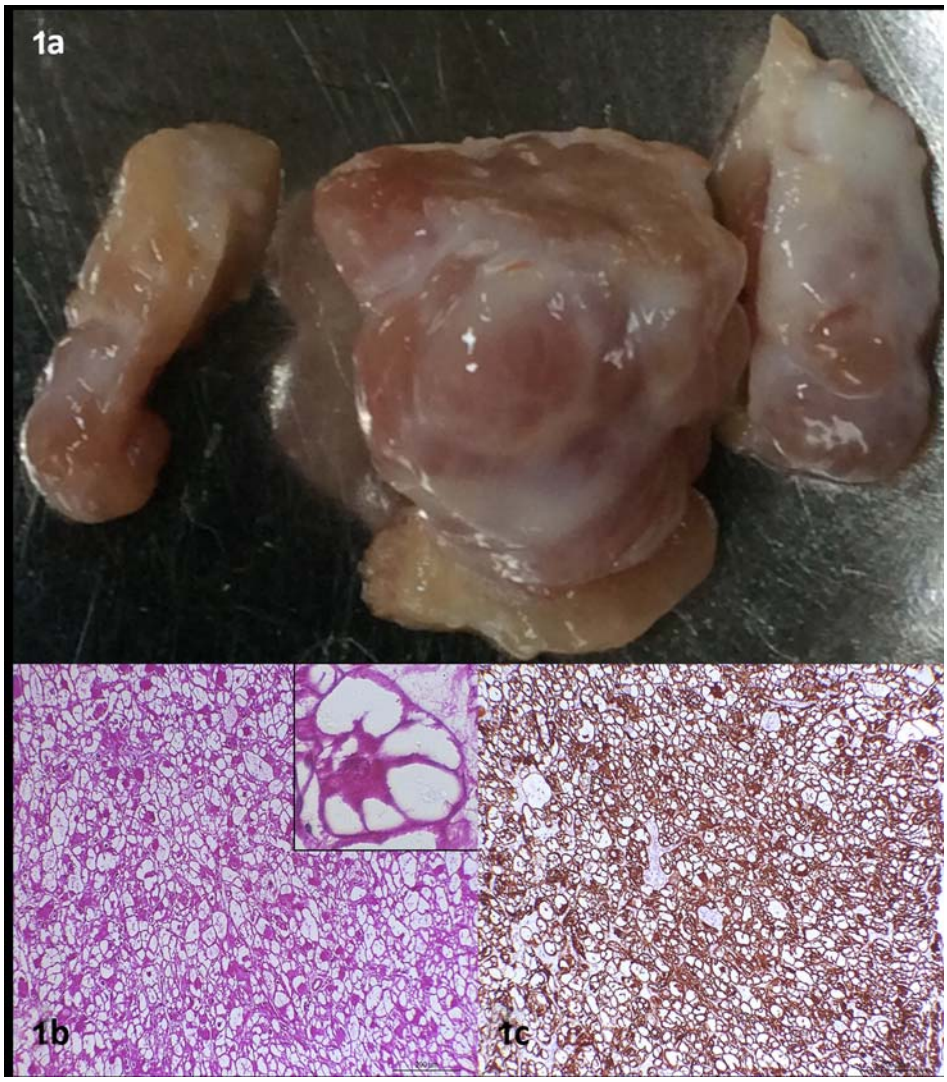
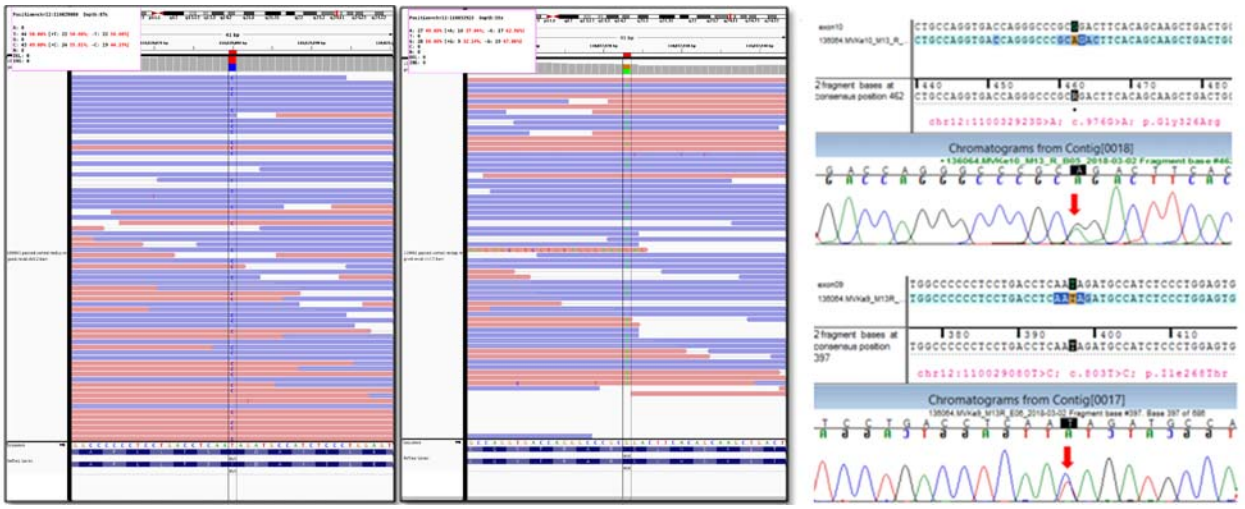


WEB FIG. 1 *(a) Gross specimen of the cardiac mass. (b) Histopathology showing vacuolated tumour cells with clear cytoplasm and characteristic spider cells on Haematoxylin and Eosin staining (spider cell in inset). (c) Immunohistochemistry demonstrating desmin expression by rhabdomyoma cells.*



(*a*) (*b*)

WEB FIG. 1 *(a) Integrated genome viewer images of clinical exome sequencing showing compound heterozygous c.803T>C and c.976G>A variants for sibling 1 and (b) Electropherogram of respective variants for sibling 2.*

Indian Academy of Pediatrics Releases Uniform Learning Objectives for Competency Based Curriculum in Undergraduate Pediatric Education

The Medical Council of India (MCI) has introduced competency based medical education curriculum [1] with effect from the admission year 2019. They have come out with a list of competencies expected in a medical student at the end of undergraduate training. These competencies cover a wide range of areas, with inclusion of knowledge, attitudes, skills and communication. Suggestions on teaching methods and assessment have also been provided [1].

At the operational level, the competencies must be translated into specific learning objectives (SLOs), which allow the teachers to use them as a framework for teaching and assessment. The task of converting competencies into objectives has been left to the teachers/departments/ institutions. While this allows flexibility in teaching and assessment, it is also likely to bring a lot of variability across medical institution and universities across the country, with more than 500 medical colleges trying to carry this task independently.

Professional associations can play an important role in ensuring uniformity of teaching throughout the country. With this background, the Indian Academy of Pediatrics undertook the task of developing SLOs out of competencies listed in the MCI document. Under the leadership of the IAP President-2019, a task force comprising of two experts was created. A total of 20 teachers at various levels from across the country were enlisted. One of them was designated to collect and compile the suggestions. An orientation and training session for the task force members and contributors was organized at Delhi on 6 July, 2019. The methodology was discussed, and topics were allotted to individual members for framing the SLOs.

The members created SLOs as per standard methodology. These were shared within the group and comments were invited and discussed. Modifications, where appropriate, were made and the first draft was circulated at the National Conference of Pediatric Education at Jodhpur in October, 2019. The draft was further revised in the light of the comments which were received. This draft was then circulated to around 100 Departmental heads of pediatric departments in various colleges in India for comments/ modifications and suggestions. The final version was released during the National Conference of IAP in January, 2020 at Indore. The document is available at the Indian Academy of Pediatrics website (*www.iapindia.org/iap-recommendations-on-competency/*), and is in the public domain. All medical colleges in India are encouraged to use it as the base document for implementation of teaching of pediatrics in the new competency based MBBS curriculum. We believe that this unique initiative by IAP, the first of its kind by any professional society in India, will go a long way in setting the standards and serve as an example for others to follow.

The next phase of this activity will be to train teachers into using appropriate teaching learning methods and assessment, with emphasis on direct observation and feedback. Maintaining the logbook and assessment of competencies will also be included in the plan.

Acknowledgments: We acknowledge the leadership of Dr Digant Shastri, President, IAP 2019 for creating this taskforce and continued patronage to the Taskforce. Dr Santosh Soans, Dr Bakul Parekh and Dr R Remesh provided all logistics support from Central IAP in carrying out this mammoth task. We are grateful to Prof Jugesh Chhatwal and Dr Shashikant Dhir for compiling the document. Above all, all the contributors and members of the taskforce deserve special thanks for making it possible.

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Annexure I

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Protocol Driven Extubation in Neonates- A Quality Improvement Initiative

We read with interest the study on a quality improvement (QI) initiative for extubation in newborns [1]. Failed extubation is a common problem faced by healthcare workers across all neonatal intensive care units [2,3] and a QI initiative designed to improve this is a welcome step. We have two observations regarding this reasonably well-conducted study.

Authors have stated that ethical approval was not obtained as this study was a quality improvement initiative. Multiple articles have questioned this approach of not obtaining ethics approval for QI studies [4,5]. We feel ethics committee approval should be sought for all QI studies when it directly impacts patient care.

Secondly, authors have not specified if they have calculated sample size, as primary objective was to reduce extubation failure rates by 25% from baseline.

In Table I of the article, extubation failure in PDCA-1 is mentioned as 23.8% (5/21) while in figure 2 it is mentioned as 10/21. The other two categories *ie*, baseline and PDCA-2 figures are appropriate.

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AUTHOR'S REPLY

We thank the readers for their queries - their concern is justifiable. Quality improvement (QI) projects are being widely used to improve quality of care in patient management. In fact several government-supported QI projects are underway *eg*, LaQshya program. These projects do not need any ethical approval as they intend to implement already established evidence-based recommendations in clinical practice. We also implemented evidence-based practices and recommendations modified to our needs and available resources in this project. As long as no new intervention of questionable efficacy is introduced, QI projects do not need any ethical approval. Taking ethical approval in such cases would just hamper rapid progress in delivering quality care.

We did not calculate sample size for the study. The targets in QI projects are usually not based on sample size. There are many ways to set targets *eg*, benchmarks, percentiles, best achieved elsewhere etc. In our project, there is no benchmark or we can say that there should be theoretically zero extubation failures. Setting zero extubation failures as target would be unrealistic. So, a realistic target is set depending on our current performance and feasibility.

We did not find any discrepancy in Fig. 2 and table I of the article.

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Nasopharyngeal Flora in Children on Inhaled Corticosteroid Therapy

We read with interest the recent article by Nirmal, *et al*. [1]. We congratulate the authors for carrying out this study, which definitively clearified some issues related to the long-term use of inhaled corticosteroid (ICS) in children. However, we want to highlight some points related to this article.

In this study, the ratio of the case (*n*=75) to control (*n*=25) was only 3:1, which may decrease the statistical power of the study and make a comparison between the groups difficult. For optimal statistical power, at least a 1:1 ratio is suggested. The number of controls rather than cases increase the statistical power, but this effect is negligible after the case to control ratio 1:4 [2].

Allthough it was not the objective of this study to look at fungal colonization, but fungi also form an important component of nasopharyngeal flora. ICS is well known to enhance fungal colonization in naso-oropharynx [3]. Hoarseness of voice and oropharyngeal candidiasis are known side effects of ICS as a result of fungal colonization [4]. Therefore, it would have been interesting if the authors had also considered fungal colonization in this study.

It is essential to look at adherence to ICS therapy since poor adherence might have a nasopharyngeal flora similar to control group. Authors should have given information on adherence to therapy in the study participants.

Authors had mentioned low, moderate and high doses of ICS in children ≥ 6 y; however, they did not describe the same in children < 5 y of age (28 % of the cases).

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AUTHOR'S REPLY

We would like to thank the reviewer for taking interest in our study. In our study, the ratio of the case to control was 3:1. Wacholder, *et al.* [1] have reported that the best way to increase precision in a case-control study is to increase the number of cases by widening the base geographically or temporally rather than by increasing the number of controls because the marginal increase in precision from an additional case is greater than from an additional control.

In a metanalysis done by Rachelefsky, *et al.* [2] ICS metered-dose inhaler (MDI) device was associated with a 5-fold greater risk of oral candidiasis as compared to placebo. Increased risk of fungal colonization has been demonstrated in numerous studies as suggested by the reviewer. As we could not find much literature on the colonization pattern of bacterial flora in asthmatic children on ICS, our study mainly focused on bacterial colonization.

In our study, except three, all the asthmatic children were compliant with the prescribed medicines. None of these three children had colonization of nasopharynx by the pathogenic organisms.

According to GINA guidelines, for children less than 5 years, a low dose of inhaled budesonide with spacer was 200μg and 400μg were considered as double low dose ICS [3]. In asthmatic children younger than 5 y, colonization with pathogenic organism was found in 31% of asthmatic children who were taking low dose ICS as compared to 40% of asthmatic children who were taking double low dose ICS, which was not statistically significant ($P = 0.72$), but for maintaining uniformity, we considered Double low dose ICS as the medium dose of ICS in our analysis.

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NEWS IN BRIEF

THE GENETIC MAP OF ASIA

Science from Asia was on the cover of Nature in December 2020. An ambitious project called Genome Asia 100K is behind this. The project was launched in 2016 to fill the gap in genetic data from Asia. Though Asians comprise 40% of the world population, only 6% of the worlds recorded genetic data is from here.

The goal of the project is to sequence the genomes of 100,000 Asians. Genome Asia 100K is a non-profit organization which has shown remarkable cooperative effort between academia and industry. It is being hosted by Nanyang Technological University, Singapore while the industrial support has come from MedGenome in India, Macrogen from South Korea and Genentech from the US.

The pilot study published in Nature details the genetics of 1739 people from across Asia. And the findings are interesting. It appears that while the genetic data from Europe points towards a single ancestry, the Asian data suggests at least 10 different lineages.

Genomic data was sequenced in people from India, Malaysia, China, Mongolia, Korea, Philippines, Pakistan, Papua New Guinea, Japan and Russia. Further data crunching was conducted in powerful supercomputers in Singapore. A hold on genetic big data will be the gateway to innovation in newer drugs and personalized medical therapies.
(Nature 4 December 2019)

SNAKE BITES – A FRESH LOOK

The anti-venoms available in India are against the 'Big Four' - the spectacled cobra, the common krait, Russell's viper and the saw scaled viper. The manufacturing protocols have not changed an iota over the past 100 years. The various other species which cause serious envenomation have been completely neglected.

Kartik Sunagar, an evolutionary biologist from Indian Institute of Science Bangalore, along with herpetologists in Chennai and Mysore recently published important data about the venom composition of the neglected yet medically important Indian snakes. They found that the currently available anti-venoms had poor efficacy against many neglected snakes. They also found large inter-species differences in venom composition depending on the area where they were found. The group is now working with anti-venom manufacturers to develop region specific anti-venoms.

Globally many innovative products are also in the pipeline. Presently only 15% of the antibodies in commercial anti-venoms actually target snake toxins. So scientists are trying to develop specific antitoxins in the laboratory, which can be used as and when required. Another new molecule is Varespladib, which targets phospholipase A2 found in a wide range of snake venom. This could fill a critical gap in the prehospital treatment of snake bites. It is refreshing to see ground level research into important neglected medical problems of India.
(*PLoS Negl Trop Dis 2019*)

WHERE IS ALL OUR HEALTH DATA GOING?

Data is the new oil. Large companies like Amazon and Google mine it to further economic interests. But what happens to all the health care data collected at the national level by the government? Health Information analyst Arunima Mukherjee and colleagues have written an eye opening article in the Economic and Political Weekly.

We are just beginning our entry into the data collection era. It behooves us to understand the intricacies of what data is being collected, who gets to see it, what the implications are and what action results from all this data which gets collected using public money.While ministries of health are primary users of data, there are increasingly major corporate interests involved in the development and management of data systems, for example, in the health insurance sector.

Around 2006 when the National Rural Health Mission analyzed its data from three states, they found that less than 3% of the data collected was used to generate health indicators. Unnecessary data collection added a huge burden on the health worker reducing their time for actual health care. They then decided that no data must be collected more than once (eg, under more than one health program) and only pertinent data may be collected.

Currently almost no data is made public to citizens. Another cause for concern is the individual data collected without adequate privacy standards and regulation. Are the gargantuan investments in information technology in healthcare rewarded by justifiable gains? We need a systematic evaluation,review and self-improvement strategy.
(*Economic & Political Weekly 4 January 2020*)

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CLIPPINGS

Association between neck circumference and non-alcoholic fatty liver disease in children and adolescents with obesity(*J Pediatr Endocrinol Metab. 2019 Dec 16*)

Non-alcoholic fatty liver disease (NAFLD) is the commonest chronic hepatic disorder in children. This authors studied if there was an association between neck circumference and NAFLD, and to establish cut-off values based on gender and pubertal staging. Mexican children and adolescents (*n*=112) between the ages of 6-18 y were included and presence of NAFLD determined by hepatic ultrasound.The neck circumference was larger in NAFLD pediatric patients as compared to those without NAFLD (*P* = 0.001). Moreover, neck circumference was associated with NAFLD as an independent risk factor [OR (95%CI) =1.172 (1.008-1.362); *P* = 0.038). In male adolescents, Tanner 2-3 = 35cm and Tanner 4-5 = 38 cm were established as risk cut-off values to develop NAFLD.

The effect of overweight and obesity on liver biochemical markers in children and adolescents (*J Clin Endocrinol Metab. 2019 Dec 16*)

Age- and sex-specific percentile curves were calculated for liver biochemical markers in two cohorts of Danish children and adolescents (between 6-18 years of age, 1858 from a population based cohort and 2155 with overweight and obesity).Children with overweight and obesity had a higher level of alanine aminotransferase (ALT) in all age groups. Optimal ALT cut-points for diagnosis of hepatic steatosis (liver fat content >5%) was 24.5 U/L for girls (sensitivity: 55.6%, specificity: 84.0%) and 34.5 U/L for boys (sensitivity: 83.7%, specificity: 68.2%).

Thus obesity is associated with liver damage, underscoring the importance of its prevention in the pediatric age group.

A randomized clinical trial to evaluate sitagliptin in pediatric patients with type-2 diabetes (*Pediatr Diab.2019;20:48-56*)

A randomized, placebo-controlled, double-blind evaluation of sitagliptin in 35 patients 10-17 years old with T2DM at seven clinical research sites was conducted.It was found that single doses of 50, 100, and 200 mg sitagliptin inhibited 67.2%, 73.8%, and 81.2% of plasma DPP-4 (dipeptidyl-peptidase IV) activity over 24 hours, respectively. The least squares (LS) mean glucose concentrations two hours after an oral glucose tolerance test or a meal tolerance test decreased in patients treated with sitagliptin compared to placebo, while active LS mean glucagon-like peptide 1 concentrations increased significantly at all sitagliptin doses in both tests. Adverse effects of mild intensity were reported in eight study participants; only one had intravenous site pain of moderate intensity. It was thus concluded that a single dose of 200mg was well tolerated in all the study participants.

There is now a need for further phase III safety and efficacy studies in pediatric patients with type-2 diabetes using a single dose of 100 mg of sitagliptin.

Findings from the dsd-LIFE study on bone mineral density and fractures in congenital adrenal hyperplasia (*Clin Endocrinol (Oxf). 2019 Dec 30*).

Congenital adrenal hyperplasia (CAH) patients (*n* = 244) from dsd-LIFE cohort (women, 147; men, 97; salt-wasters, 148; simple virilizing, 71; non-classical-CAH, 25) were chosen.It was found that prednisolone-only treated patients had more detrimental effects on BMD than hydrocortisone (*P*<0.05).The androstenedione/testosterone ratio at the age of 16 years had a positive correlation with lumbar spine *Z* score in women (r^2=0.284, *P* = 0.024) and trochanter *Z* score in men (r^2 = 0.60, *P* = 0.025), thus showing that higher glucocorticoid doses have lower bone mineral density in adulthood.

Prevalence of TG and TPO mutations in Sudanese children with Congenital Hypothyroidism (*J Clin Endocrinol Metab. 2019 Dec 23*)

Congenital hypothyroidism (CH) is due to thyroid dyshormonogenesis in 10-15% of subjects worldwide and 60% of CH cases in the Sudan.With the aim of investigating the molecular basis of CH, clinical evaluation, thyroid function tests, genetic sequencing and analysis was performed on 26 Sudanese families with CH.Mutations were found in *DUOX1, DUOX2, IYD, SLC26A4, SLC26A7, SLC5A5, TG,* and *TPO* genes, and all occurred in domains important for protein structure and function, predicting the CH phenotype. *TG* mutations were significantly higher on average in the Sudanese compared to other populations.

Long term methimazole therapy in pediatric Grave's disease (*Pediatrics. 2019;143:e20183034*)

This randomized parallel-group controlled trial was performed on 66 children with Grave's disease in Tehran, an iodine replete area, to evaluate if long term methimazole therapy (>4 y) was associated with lower relapse rate than shorter therapy, thus abating the need for ablative therapy. Fifty six patients were randomized after daily methimazole intake of 0.25 to 0.5 mg/kg for 18-24 mo, to discontinue the drug or continue low dose methimazole for 96-120 mo, and reassessed after 48 mo of stopping the drug in each group. The study reported lower relapse rate in long term therapy group than shorter therapy group (*P*<0.001) with no side effects in the former group. Methimazole treatment duration was the only significant factor on multivariate analysis to affect the outcome.

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PRESENTS

MENVEO
Meningococcal Group A,C,W135 & Y
Conjugate Vaccine Ph. Eur.

High efficacy*
with a clinically
acceptable safety profile[1]

Robust immune response
across age groups (>2 years)
against all four serogroups[1,2]

~10 years
of global real world experience[3]

Approved in US & EU
only MCV licensed
in both regions[4,5]

Safety Information:
Most common adverse events in clinical trials:
Injection site pain, erythema, induration, sleepiness, headache, irritability, malaise, eating disorder, nausea, vomiting, diarrhea, rash, myalgia, arthralgia, fever and chills.

* The efficacy of MENVEO has been inferred by measuring the production of serogroup-specific anti-capsular antibodies with bactericidal activity[6]

^ Meningococcal Vxs global IMS data

Reference : 1. S.A. Halperin et al., Vaccine 28 (2010), 7865–7872 2. Lalwani S, et al. Int J Infect Dis. 2015;38:36-42 3. GSK data on file- Sales summary- May 2019 4. ECDC factsheet about meningococcal disease, available at https://www.ecdc.europa.eu/en/meningococcal-disease/factsheet (Accessed Nov, 2019) 5. Meningococcal Vaccine Safety, available at https://www.cdc.gov/vaccinessafety/vaccines/meningococcal-vaccine.html (Accessed Nov, 2019) 6. Menveo India Prescribing information Version MNV/PI/IN/2019/03 dated 21 August 2019

For the use only of Registered Medical Practitioners or a Hospital or a Laboratory

Abbreviated Prescribing information of MENVEO [Meningococcal Group A, C, W-135 and Y Conjugate Vaccine Ph. Eur.]

ACTIVE INGREDIENT: Each reconstituted dose (0.5 ml) contains: 10 µg Meningococcal group A oligosaccharide conjugated to 16.7-33.3 µg CRM197, 5 µg Meningococcal group C oligosaccharide conjugated to 7.1-12.5 µg CRM197, 5 µg Meningococcal group W-135 oligosaccharide conjugated to 3.3-8.3 µg CRM 197, 5 µg Meningococcal group Y oligosaccharide conjugated to 5.6-10 µg CRM197. Therapeutic Indication: Active immunization of children (from 2 year of age), adolescents and adults to prevent invasive meningococcal disease caused by Neisseria Meningitidis groups A, C, W-135 and Y. Posology: Children (> 2 years of age), adolescents and adults administered as a single dose (0.5 ml). Older people: Limited data in age d 56-65. No data in age d >65 years. Booster vaccination: May be given in subjects vaccinated with same, other conjugated or unconjugated polysaccharide meningococcal vaccine. Need and timing of booster dose to be based on national recommendations. Children under 2 years of age: Safety and efficacy not established. Method of Administration: Intramuscular injection, preferably in deltoid muscle. Contraindications: Hypersensitivity to any active substance, excipient or diphtheria toxoid (CRM197), or life-threatening reaction after administration of vaccine with similar components. Postpone in acute severe febrile illness. Minor infection not a contraindication. Special Warnings and Precautions: Take all precautions for prevention of allergic or other reaction. Appropriate medical treatment and supervision should be readily available in case of rare anaphylactic reaction. Anxiety-related reactions (vasovagal reactions, syncope, hyperventilation or stress-related reactions) may occur; ensure procedure to avoid injury from fainting. Should not be administered intravascularly. Not protect against serogroups of N. meningitidis not included in vaccine. May not elicit protective immune response in all vaccinees. Waning of serum bactericidal antibody titers against serogroup A seen in studies; clinical relevance unknown. If individual at risk of exposure to Men A; consider booster dose. No data on use as post-exposure prophylaxis. Vaccination in immunocompromised individuals may not result appropriate protective antibody response. Increased risk of invasive disease in individual with familial complement deficiencies and treatment that inhibit terminal complement activation (for example, eculizumab). Evaluate risk-benefit in person at risk of haematoma following intramuscular injection. Interaction with Other Medicinal Products and Other Forms of Interaction: Can be given concomitantly with hepatitis A and/or B, yellow fever, typhoid fever (Vi polysaccharide), Japanese encephalitis and rabies. Administer concomitant vaccines at separate injection site (preferably contralateral). Adolescents (11-18 years of age): Can be co-administered with Tetanus Reduced Diphtheria and Acellular Pertussis Vaccine, Adsorbed (Tdap) alone for Human Papilloma virus Quadrivalent (Types 6, 11, 16 and 18) Vaccine, Recombinant (HPV). Lower W-135 seroresponse on administration of MENVEO one month after Tdap; clinical relevance unknown. Children (2-10 years of age): No data on concomitantly administration with other childhood vaccines. Co-administration with other vaccines not studied. Administer concomitant vaccines at separate injection sites, preferably contralateral. Effects on Ability to Drive and Use Machines: Dizziness very rarely reported, may temporarily affect ability to drive or use machines. Undesirable Effects: Clinical Trial Data: a) Subjects aged 2 - 10 years: Very common (≥ 1/10): sleepiness, headache, irritability, malaise, injection site pain, erythema (≤50 mm), induration (≤50 mm) Common (≥1/100 to <1/10): eating disorder, nausea, vomiting, diarrhea, rash, myalgia, arthralgia, injection site erythema (>50 mm), induration (>50 mm), chills, fever ≥38°C Uncommon (≥1/1,000 to <1/100): injection site pruritus b) Subjects aged 11 to 65 years: Very common (≥ 1/10): headache, nausea, myalgia, injection site pain, erythema (≤50 mm), induration (≤50 mm); malaise Common (≥1/100 to <1/10): rash, arthralgia, injection site erythema (>50 mm), induration (>50 mm), fever ≥38°C, chills Uncommon (≥1/1,000 to <1/100): dizziness, injection site pruritis Post-marketing experience (all age groups): hypersensitivity including anaphylaxis, tonic convulsion, febrile convulsion, syncope, vertigo, injection site cellulitis, injection site swelling, including extensive swelling of the injected limb.

Version: MENVEOPI/IN updated 6-Sep-2019

Registered medical practitioners can refer company website http://india-pharma.gsk.com/en-in/products/prescribing-information/ for full Product Information

Please report adverse events with any GSK product to the company at indiapharmacovigilance@gsk.com.

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