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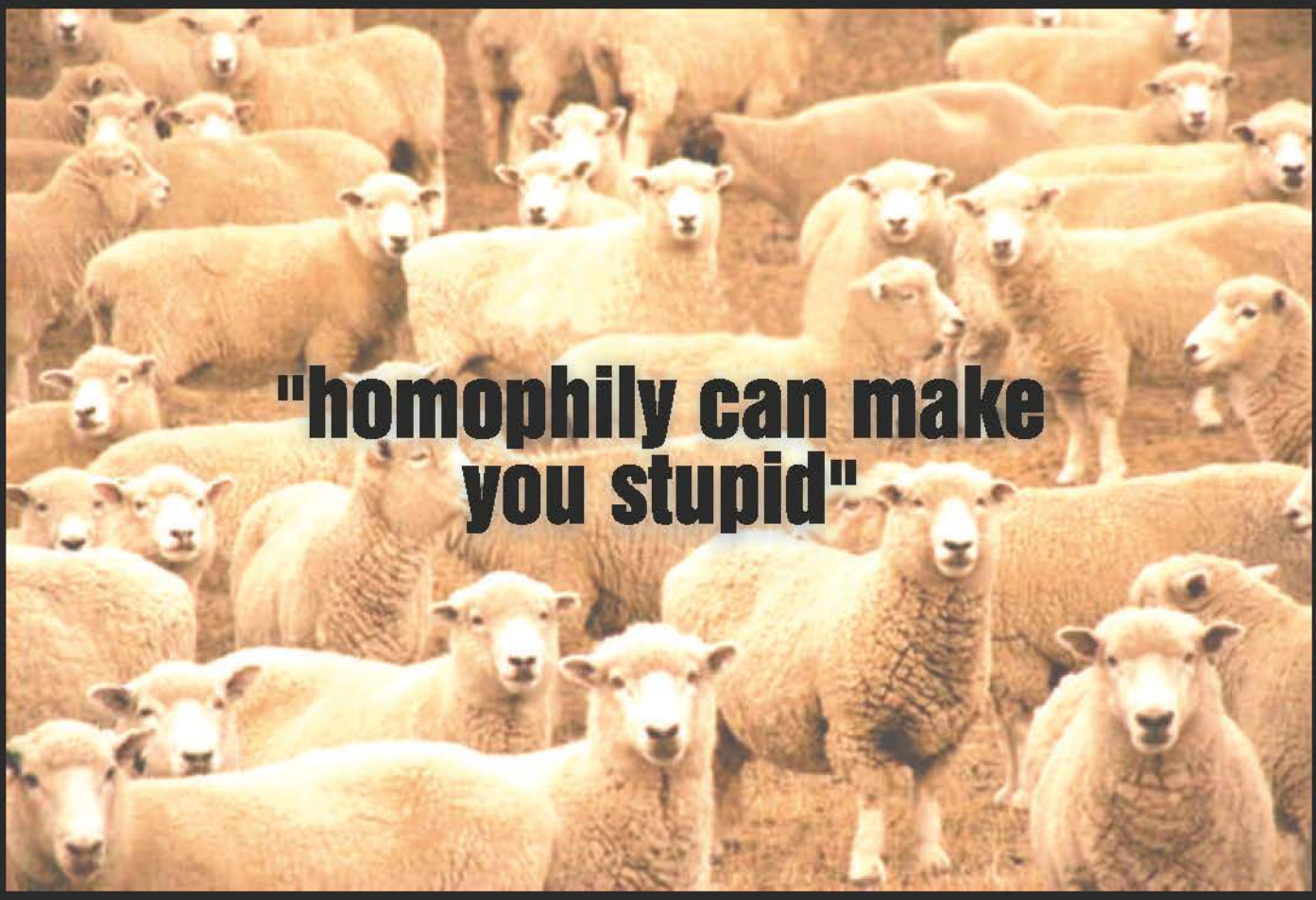

Vaccine Hesitancy:

Analysing the Microcosm!

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Vaccine Hesitancy: *Why is there an uproar?*

The View From Here:

"One of the dangers of the internet is that we're only hearing like voices, and that makes us more polarized. What's incredible about the net is we have this opportunity to hear more voices than ever. But the tools we tend to build to it have us listening to the same voices again and again."

– Ethan Zuckerman

Last month, I got a call from Mr PC Haldar, former director of Intelligence Bureau (IB) and current president of an NGO in Delhi for an informal chat in his office. I wondered what he wanted to discuss with a clinician! And that too, with one who is settled in a private sector! On meeting him, I realized that he was concerned by the happenings in the vaccine sector. Probably, he wanted to understand the nitty-gritty of this sector and the recent developments including vaccine policies, financing, decisions and lobbying, philanthropists approaches, judicial activism against certain MoHFW's decisions, and the different lobbies active in the field including those actively involved in so-called 'anti-vaxxers' movement, and perhaps,this from an 'outsider', to have an overview of the various issues assailing this sector. The meeting also changed my earlier perceptions regarding IB. Everybody thinks that this organization has only to deal with insurgency, security threats from outside and inside the nation, nabbing terrorists, etc. During the discussion, I came to know the exact scope of functioning of this agency which was far more broad-based than being confined to the security and internal strife. It was only during the early 90s' that the functioning of this establishment came to light during J&K conflicts. I was surprized to know that prior to the 90s', the agency used to perform certain tasks that were not even distantly connected to the nation's security like investigating underlying factors behind the rise in daily commodity prices, black-marketing, scarcity of daily consumable products, etc. So, the agency's role was not merely confined to safeguard the nation's security but also to ensure socio-economic well-being.

This experience was an eye-opener to me. Issues pertaining to vaccines and vaccination practices are not bothering public health professionals only, but even non-health experts and professionals are also getting increasingly concerned about them. 'Vaccine hesitancy (VH)' is one such issue that's creating lots of news in both health and non-health sectors. The WHO has recently ranked it as one of the top 10 health threats in the world for 2019. The whole western world, mainly the Europe and the US, is in the grip of this alarming threat that has the potential to neutralize all the gains made over decades by vaccination all over the globe. Confidence in vaccines is an increasingly important issue for global public health. Lack of credibility is a well-documented cause of outbreaks, delays and setbacks for global polio eradication, as well as difficulties for the achievement of other goals of immunization. So, it is understandable to see the huge attention being paid by the governments, health agencies and philanthropists on this matter.

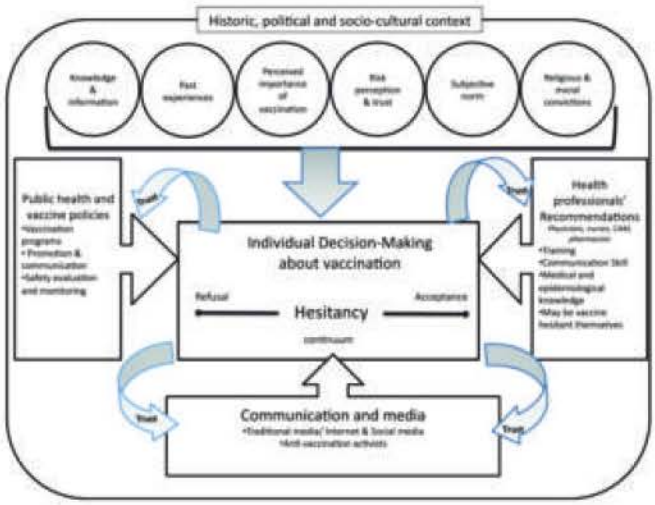

Figure 1. *The interplay of Vaccine hesitancy, communication, decision making about vaccination, and public health vaccine policies.*

Is 'hesitancy' the right term?

The growing influence of anti-vaccine lobby in the West forced international health agencies, including the WHO, to reinvigorate its efforts to take this menace head-on with the formulation of a new front under new terminology. The WHO-SAGE Working Group from 2012-2014 toiled hard to come out with a perfect term that could categorize factors that influence the behavioural decision to accept a vaccine, and in 2014 they agreed upon 'Vaccine hesitancy (VH)' as an ideal

term to describe different issues related to the implementation of vaccination drives in a community **(Figure 1).** There was some debate on whether 'hesitancy' was the most appropriate word to describe these issues. Concerns were raised that 'hesitancy' had a negative connotation. Another term that came under consideration was 'vaccine confidence', a more positive word. While 'confidence' covers a range of issues such as trust in vaccines, trust in health-care workers delivering the vaccine and in those making the decisions on approval of vaccines for a population, yet the word 'confidence' still seemed narrow in scope as if covering only one category of factors that affect vaccination acceptance decisions. Although the exact meaning of VH is the 'pause' people take before deciding to go for a particular vaccine or not, the WHO believed that it encompasses broad sentiments of the community about vaccines and vaccination, and include a variety of terms like vaccine confidence, vaccine trust, vaccine safety, misinformation about vaccines, vaccine acceptance, vaccine resistance and refusals, antivaccine movements and anti-vaxxers, vaccine demand, etc. At one end of the spectrum are those who willingly accept all the vaccines, and at another extreme are those who refuse all.

The high rate of childhood vaccination coverage in most countries indicates that vaccination remains a widely accepted public health measure. However, these national estimates may hide clusters of under-vaccinated individuals. Many recent outbreaks of vaccine-preventable diseases (VPDs) have been linked to under-vaccinated or non-vaccinated communities.

- Even though it seems impossible to quantify precisely the proportion of the population that could be categorized as vaccine-hesitant, experts worldwide acknowledge that there is an increasing trend toward vaccine hesitancy

- The repercussions of vaccine hesitance are now playing out globally — as on October 10, 2019, nearly 4,24,000 children have confirmed measles, as against a figure of 1,73,000 in the whole of 2018.

***Box 1.** Prevalence and impact of Vaccine Hesitancy*

Epidemiology of Vaccine Hesitancy

Vaccine hesitancy is not only context-specific but also varying across place and time. According to a recent publication, low- and middle-income countries (LMICs), in general, had lower rates of VH and, for example, had fewer safety concerns about vaccines compared to high-income countries (HICs). The most hesitant countries were found in eastern Europe, and then in western Europe and northern America. At 95%, people from South Asia trusted vaccines the most followed by eastern Africa at 92%. Western Europe and eastern Europe brought up the rear with just 59% and 52%, respectively.

Is it relevant to us?

No country is immune to the impact of VH on the vaccination rates against VPDs. And India is no exception. However, the face of VH is a bit different here. What we are encountering is more of misconceptions and misinformation against vaccination drives that result in resistance against vaccination and vaccine refusals. However, even in this scenario, there is a perceptible change. During the polio drives, the dissenting section of the population was the underserved, marginalized, and poorly educated people residing in two large northern states. Whereas during the recent measles-rubella (MR)-campaigns, the section of the society responsible for VH was more affluent, more educated and living in more developed southern states of the country. This was not surprizing given the heterogeneity of our population. **Boxes 2 & 3** enumerate the key attributes of Indian vaccines scenario and the existing threat of VH to the country.

How India is different from the western world?

- Huge & Heterogenous population;
- 27 million birth cohort;
- Most vaccines supplied through public sector;
- Vaccines-preventable diseases (VPDs) far outnumber the vaccines adverse reactions (VARs)
- Coverage with most antigens-still low!
- Vaccine refusals and resistance: confined to campaigns

***Box 2.** Key attributes of vaccination scenario in India*

Why India is Vulnerable to Growing Vaccine Hesitancy?

- New vaccines tailored to LMI country needs are being introduced in to the UIP
- Despite significant efforts to strengthen vaccine safety monitoring, substantial gaps exist:
- Baseline rates of many AEFIs not known
- Capacity for safety signal detection limited
- Growing access to internet, social media platforms and smart technology:
- "WhatsApp University"
- Fake news phenomenon

***Box 3.** Why India is Vulnerable to Growing Vaccine Hesitancy?*

The changing face of Vaccine Hesitancy in India

Of late, there are a flurry of activities in terms of workshops, seminars, CMEs, etc in India on vaccines safety, confidence and hesitancy and its looming threat on our vaccination scenario and vaccination rates. Is the scenario indeed equally bad here also as it is in the industrialized countries? The VH in India is characterized by rumours, religious edicts, refusals and the resistance. This trend is so far confined to the opposition of large vaccination drive undertaken by the government. The type of VH that is prevalent in the western world where the well-educated and financially well-off parents start doubting the utility and safety of vaccines and consider them as redundant, has not yet manifested overtly here.

Few recent personal experiences have pointed out that even this type of hesitancy does exist and is silently brewing even amidst top professionals. In the first instance, District Magistrate of my city refused to get the Rotavirus vaccine administered to her son despite being a medical graduate herself. Probably she was not convinced about the efficacy of the vaccine. In yet another instance, an HOD of the Microbiology department of a premier institution of the country was sceptical of the practice of giving too many vaccines at a single visit. He feared the practice may lead to overloading of the immune system if too many antigens are administered simultaneously! Another colleague of him, a renowned immunologist of the same institute, believed that the vaccines had some definitive role in the development of autoimmunity. These few instances baffled me since these apprehensions were not based on science and evidence. When your top health professionals are having reservations regarding the well-established and scientifically proven process of vaccination, what can be said about other non-medical professionals! In the west, resisting vaccines has become a vogue. Anti-vaccines sentiments are finding more and more takers there. However, the persistently high burden of many VPDs and the poor-affordability of non-UIP vaccines are the reasons why a true, west-like VH is still not seen here in India. But we need to be vigilant since the omens are not good.

Reasons for Vaccine Hesitancy

The main reason behind the genesis of VH is 'misinformation'. Social media is used in stirring fear in people by falsely blaming vaccines for unrelated diseases is the bedrock of the VH across the globe. Further, anti-vaccine conversations often centre around moral outrage and structural oppression by the government and the media, suggesting a strong logic of"conspiracy-style" beliefs and thinking. Sometimes, people give vent to their dissatisfaction with the civic administration and ruling regime through closing doors on vaccinators and refusing vaccines altogether. As mentioned above, the refusals of polio drops during the height of polio eradication drives in UP and Bihar was due to the misconception that the polio vaccine caused illness, infertility and was ineffective. Religious propaganda and inconvenience in accessing vaccines are other reasons.

Vaccines, the enemy of their own success!

At first sight, this seems quite strange and a bit 'oxymoronic'. Let me explain. Certain vaccines have been so effective that they have eliminated or significantly reduced the burden of the 'wild disease' from a large region of the globe **(Figure 2)**. There are counties where the vaccines-related adverse events have far outnumbered the actual number of VPD against which the vaccine is employed. This scenario is more prevalent in western countries. As a result, there are instances where young clinicians have not seen a particular VPD in their lifetime. I do still remember an anecdote shared by my MD guide, **Prof. Kanwal Kalra** during her ward rounds in the late 80s. During one of her visits to a reputed pediatric UK hospital, the entire pediatric unit failed to diagnose a classic case of measles - an entity not even considered worthy of a discussion during ward rounds here! The young UK pediatric residents were bewildered on seeing a case of fever with a rash that they had not encountered in their training so far. And they were equally mystified to see the ease with which she had made the spot diagnosis of the case! But now the scene has reversed. The entire US and many European countries are in the midst of huge outbreaks of measles, a disease they had so efficiently eliminated two decades back! And this was all due to this phenomenon called VH. People of these countries are now more scared of vaccines than the diseases the vaccines prevent. Hopefully, this resurgence of an old, eliminated VPD may reinstate their confidence in vaccines.

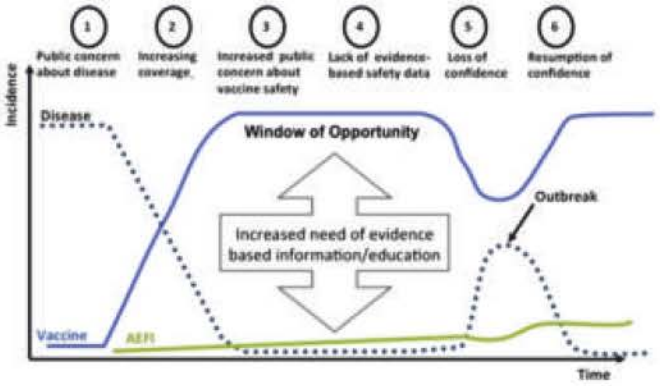

Figure 2. When the population does not see the disease, the main reason to get a vaccine disappear.
(J. Bonhoeffer et al. Biologicals 40(2012) 393-397)

The menace of internet and social media

Traditionally, the vaccination scenario is monitored with surveillance of VPDs, monitoring vaccine coverage, and surveillance of 'adverse events following immunization' (AEFI). But in 2020, the scenario has changed. It is not enough to maintain and monitor only these traditional databases. The game changed perhaps between 2010 and 2012. There was a bombardment of information transmission and exchange at digital platforms, mainly on social media. Hence, monitoring of the digital world has now become an integral component of new frontiers in vaccine safety intelligence and to safeguard against frequent disruptions of vaccination drives.

The role of digital world has reached new heightsin our lives, with more people spending more time doing more things online than ever before **(Figures 3-6, Box 4).** With the advent of social networking platforms like WhatsApp, Facebook, Twitter, Instagram, Tik-Tok, etc, the anti-vaccine movements gained momentum. While Twitter is far more popular in many European countries and the US, in India it is the WhatsApp that is at the forefront of driving most of the misinformation campaigns and fake news on vaccines. Research suggests that the anti-vaccine movements on social media 'echo-chambers' is enormous and dangerous.

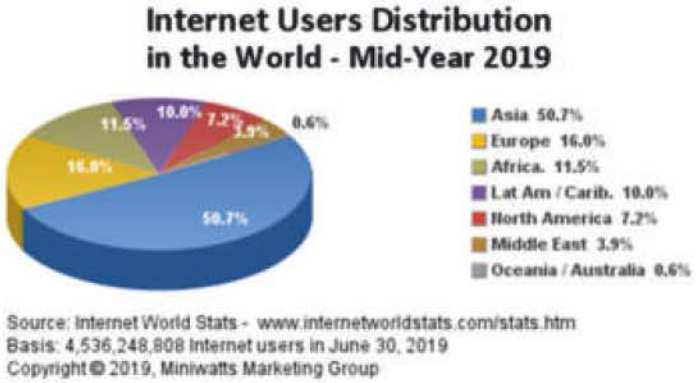

Figure 3. Internet users' distribution in the world-Mid-Year 2019.

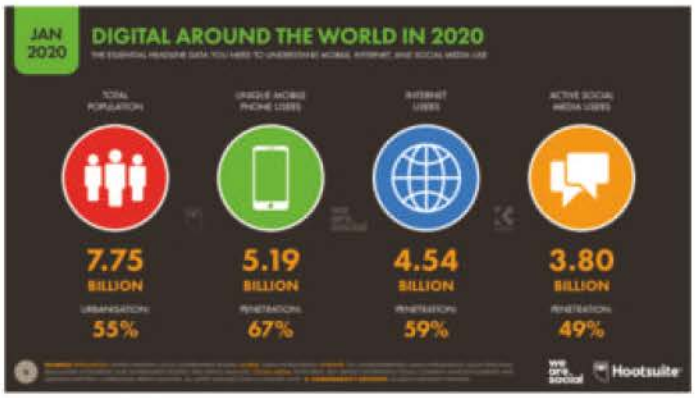

Figure 4. An overview of the 'digitalized' world in 2020

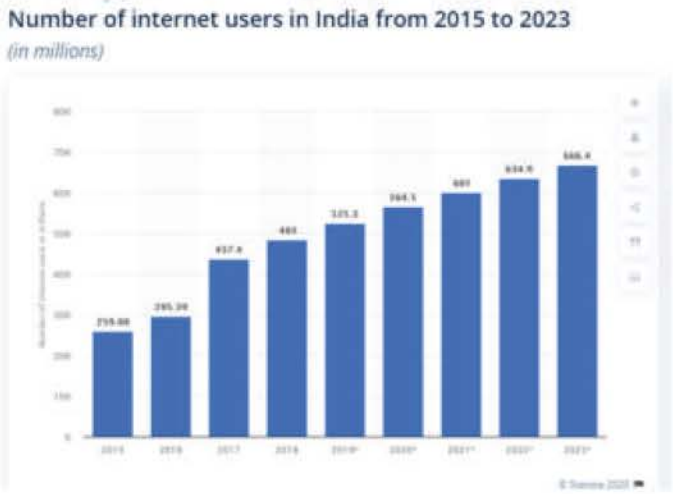

Figure 5. Number of internet users in India with projected figures till 2023 (in million)

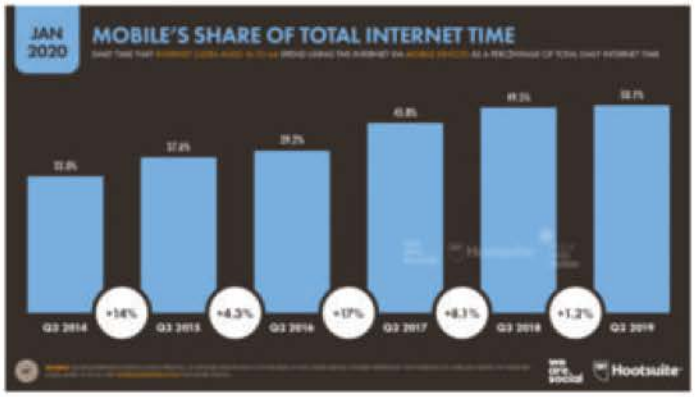

Figure 6. Mobile share of internet use per day by population aged 16-64 yrs

Vaccine refusal has also been promoted on social media. A study found that Twitter users who were more often exposed to negative opinions about the safety and utility of human papillomavirus (HPV) vaccines were more likely to tweet negative opinions than users who were more often exposed to neutral or positive information. These tweets, which included misinformation, anecdotes, and opinions that may result in vaccine hesitancy or refusal, made up most

HPV vaccine-related information exposures for nearly 30% of users that tweeted about HPV vaccines during the study period. Besides, users expressing negative opinions about HPV vaccines were more closely connected to other users expressing the same opinions.

Digital in 2020: the essential headline numbers

- The number of people around the world using the internet has grown to 4.54 billion, an increase of 7% (298 million new users) compared to January 2019.
- Worldwide, there are 3.80 billion social media users in January 2020, with this number increasing by more than 9% (321 million new users) since this time last year.
- Globally, more than 5.19 billion people now use mobile phones, with user numbers up by 124 million (2.4%) over the past year.
- The average internet user now spends 6 hours and 43 minutes online each day. That's 3 minutes less than this time last year, but still equates to more than 100 days of connected time per internet user, per year.
- If we allow roughly 8 hours a day for sleep, that means we currently spend more than 40% of our waking lives using the internet.
- More than 2 billion people have come online since the first mention of 'The Next Billion', but just over 40% of the world's total population – roughly 3.2 billion people – remains unconnected to the internet.
- More than 1 billion of these 'unconnected' people live in Southern Asia
- Mobile now accounts for half of internet use.

***Box 4.** Digital invasion in the lives of average citizens-Global scenario*

Another recent example is the acomment made by JaggiSadhguru through his official twitter handle. While acknowledging the contribution of vaccines in tackling many debilitating infectious diseases, he commented on the 'negative' 'side-effects' of vaccinations, particularly when 'overdone'! This will give 'anti-vaxxers' the much-needed spur to scare parents from vaccinating their children.

The above tweet by Sadhguru has a link to an article published on the Isha website on October 3, which is an excerpt of a conversation between Jaggi Vasudev and Dr Soumya Swaminathan (Chief Scientist at WHO) that was held at the UN General Assembly on June 27, 2019. (The article also has a link to the taped conversation, on YouTube.)

During the conversation with Dr Swaminathan, he is seen advocating vaccination and spelling out the gains India made by preventing children from becoming crippled through oral polio vaccination. But soon he veers off track and ends up spreading dangerous misinformation about influenza (commonly referred to as flu).

The significance of vaccination against many debilitating diseases should not be played down. But at the same time, it is important it is not overdone, without taking into consideration the many side-effects or negative impacts of vaccinations.

The Anti-Vaccination Movement - Sadhguru's Views isha.sadhguru.org

With a disclaimer that he is not a medical expert, Jaggi Vasudev says: *"...From listening to parents [in California], this is what I gathered. I thought some of the things they were giving vaccines for were just absurd. If a child catches a flu or something like this, it is all right to go through some of these illnesses when you are growing up."*

This might turn out to be an irresponsible statement to have ever been said from the hallowed platform of the UN. Unfortunately, the patently wrong message went unchallenged, giving it a ring of truth. The incorrect messaging did not stop there; it is now posted on the Isha website, increasing the chances of more people being misled. The blithe comment about flu sans any evidence is in stark contrast to the seriousness with which WHO and the CDC treat it. Its repercussions can be lethal to the society struggling hard to shrug off the challenge posed by a new, ongoing devastating pandemic of COVID19!

Analysing the Microcosm-the behaviour exploration

What causes people to doubt the utility or to refuse the intervention that's protective to their progeny and ensures long survival of them? As explained above, the lack of awareness, misconceptions, fear of adverse events, lack of affordability, poor infrastructure to deliver vaccines, lack of faith in government, political biases, etc are the reasons for low uptake of vaccines and resultantly low coverage in India **(Figure 7).** They are understandable to some extent given the overall socio-economic milieu of our population. But why the people in the affluent countries have doubts about the motive and the process of vaccination? Why suddenly the 'anti-vaccines' movements have started gaining momentum? Many public health experts those in charge of large vaccination drives, and behavioural scientists have started analysing the social nature of vaccine decision-making.

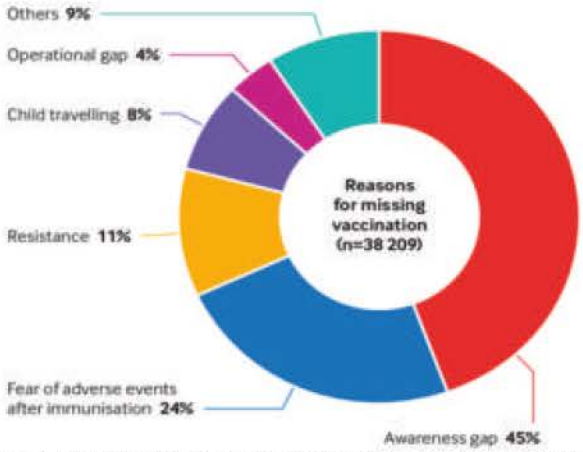

Figure 7. Reasons for missing vaccination sessions: Oct 2017 & Feb 2018 (Gurnani, et al. BMJ 2018;363:k4782)

After analysing in detail for many years, they have a good understanding of the reasons why parents reject vaccines and the aspects of vaccines that they fear the most. The most 'vaccine deniers' distrust the expert systems which design and deliver vaccines and that they regard the vaccines as an 'unwelcome' and 'unnatural intrusion' into a 'natural body' which they view as unneeded or unbeneficial.

Now we know that the vaccination behaviours of our social networks are a predictor of our behaviours, so our milieu matters to the decisions we make. And, here comes the roles of 'homophily' and 'influence' **(Figure 8).** Homophily refers to humans' tendency to associate and connect with individuals similar to them in certain aspects, people who share their interests, values, culture, who have the same demographical, racial characteristics, etc., which leads to one of the main characteristics of a social network, which is homogeneity. This principle of homophily is the foundation of the most various human relations and networks, from marriage, to friendship, work, information exchange, and others. Homophily limits people's social worlds in a way that has powerful implications for the information they receive, the attitudes they form, and the interactions they experience. The behaviour of people online seems to be following an intrinsically human principle of behaviour that guides our actions in real life.

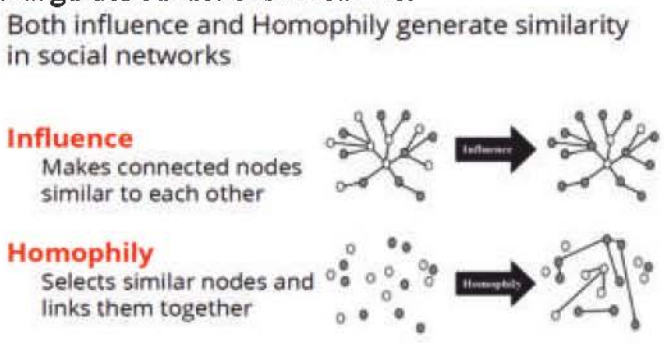

Figure 8. The interplay between influence and homophily.

'Homophily': Birds of a feather flock together:

Homophily, a concept that can be expressed by the saying: *birds of a feather flock together*, plays an essential role in shaping our individual and collective view of the world. One example is online social network platforms like Facebook. Facebook today is the most populated country on earth that too without geographical boundaries! As of the third quarter of 2019, it has 2.45 billion monthly active users. People connect with other individuals that they know in real life, and with whom they have common interests or other socio-demographical, behavioural, and intrapersonal characteristics, and then with the friends of their friends, and with potential friends that are automatically suggested to them by these applications, based on common profile characteristics.

But, as Zuckerman-an expert on behavioural science, exclaims *"Homophily can make you really, really dumb"*. This exclamation is not too far from the fact. Though we efficiently and "comfortably" communicate with like-minded individuals on the social networking sites and other digital platforms, we tend to avoid contacts that take us out of our "comfort" zone, which can be a field that we are not in control of, have few information about, or are unaware of: *"We know so little about one another, and what we do know is generally so wrong, that our first instinct is to try to shut each other off."* Fighting the homophily instinct is an effort that will lead us to the better or full use of technology.

There is another term more frequently used in context with VH, the 'Social media echo chambers'—where users only hear and see the information that echoes their own beliefs. This further energizes the anti-vaccine movement.

The homophily concept sums up nicely the formation of many anti-vaxxer groups online and on social media. It is not the digital world and the internet that is intrinsically wrong, but that people tend to use it in limitative ways: searching and selecting information and individuals mainly to reinforce their own ideas, which are sometimes not based on the scientifically proven facts. This is what is happening in the affluent society of developed countries.

What is missing is a theoretical account of how and why this is the case; how the beliefs of vaccine-hesitant or rejecting parents are socially constructed, acquired and reinforced.

Does religion have something to do with VH rates?

Religious propaganda that the vaccine may contain microbes, chemicals and animal-derived products which are forbidden by religious laws have a major impact in

certain communities. Although in certain countries particular religious groups were more vaccine-sceptical than other groups, no one religion was globally predictive of negative attitudes. This indicates that the effect of faith on vaccine attitudes is dependent on the local context and that these attitudes are not necessarily driven by religious doctrine in itself, but mediated by political, socio-cultural and other factors.

However, some religious groups like Muslims were associated with lower vaccine coverage in several sub-Saharan African countries, both for boys and girls. Hesitation and resistance to vaccination is a substantial issue in some districts of Kerala, India. In the Malappuram district of Kerala, which has a substantial Muslim population, it was found that factors such as religion have only a minor role in resistance to vaccination. On the other hand, many religious leaders openly support vaccination drives and consider that religious texts and beliefs do not oppose disease prevention.

The 'antivaccine lobby' and 'anti-vaxxers'

Figure 9. The 'antivaxxers' perception of the vaccines and vaccinations: A dreadful image!

Another issue hurting vaccines and control of VPDs is growing antivaccine lobby and anti-vaxxers. The anti-vaccination sentiment is as old as vaccination itself. And the fact is that anti-vaccination movements are unlikely to disappear soon. While a minority of parents hold strong anti-vaccination sentiment, the proportion categorized as vaccine-hesitant may be increasing; even parents who vaccinate their child can have important doubts and fears regarding immunization. With the Internet, the anti-vaccination movements are becoming more.

The 'antivaxxers' perception of the vaccines and vaccinations

powerful than ever and have the potential to reach and influence many parents. There are several anonymous anti-vaccination messages on social media that have no clear sources other than blogs and dubious publications. A lot of these websites are still referencing Andrew Wakefield's retracted and fraudulent paper published in 'The Lancet'. Compare this with the real doctors and healthcare professionals and experienced scientists who are willing to put their names and list their experience and qualifications on messages that support vaccination. Despite significant efforts, few, if any, public health strategies have effectively and long-lastingly succeeded in countering anti-vaccination movements.

How to counter Vaccine Hesitancy?

Now it is time to take VH head-on. It is time to move beyond the 'knowledge deficit model' and to develop innovative responses to address anti-vaccination sentiment. The first and important step to develop effective strategies is to have a good understanding of both the causes and the contexts leading to vaccine hesitancy and refusal. Interventions must be tailored to address the specific concerns in each context.

The methods employed to deal with vaccine misinformation and refusals until quite recently may not be effective in today's time. The world has moved forward and become a large playground without any boundaries. The walls and roofs are demolished by the onslaught of digital media. New digital platforms have unleashed innovative practices that enable novel forms of communication and greater global reach than at any point in human history. But on the other hand, disinformation and hoaxes that are popularly referred to as "fake news" are accelerating and affecting the way individuals interpret any new development. And vaccines are no exception. Fake news and sophisticated disinformation campaigns are especially problematic, and there is a growing debate on how to address these issues without undermining the benefits of digital media.

Our communication strategy to deal with disinformation and fake news should be reliable, trustworthy, timely, adapting to the context of the discussion, tailored to the needs, easy to understand, engaging, and interactive. At the same time, we must undertake some innovative projects like monitoring of social media portals using web analytics to effectively deal with 'web invasion' by anti-vaxxers and anti-vaccine lobby. There should be a provision of dealing with any vaccine safety concern with 'real-time' intervention by the nodal agency during an ongoing immunization campaign/drive. Do we provide all that?

It is heartening to see that people are giving more importance to understanding behavioural science behind vaccine acceptance and developing an 'evidence-based communication strategy' to deal with growing VH rates, especially in the western world. Many studies have shown that parental decisions to use or avoid immunization for their children are complex

and multi-dimensional, including contextual determinants, determinants related to the vaccination services and individual determinants, such as parents' knowledge, attitudes and beliefs or sociodemographic characteristics.

The growing interest in vaccine hesitancy has resulted in the development of different tools and strategies to enhance vaccination acceptance. Many experts have proposed ways to counter vaccine hesitancy at the population level, including transparency in policy-making decisions regarding vaccination programs, providing education and information to the public and health providers about the rigorous process that leads to approval of new vaccines and diversified post-marketing surveillance of vaccine-related events. Additional emphasis should be placed on listening to the concerns and understanding the perceptions of the public to inform risk communication and to incorporate public perspectives in planning vaccine policies and programmes.

How to manage social media?

As stated above, the greatest threat to vaccines and vaccination projects is from the antivaccination movements run through social media. Monitoring of social media is one option though it may have some implication on individual privacy rights. Web-analytics is another novel intervention. But can we monitor and pre-emptively disrupt any growing negative vaccine sentiment build-up that may result in outbreaks of VH (mass refusals) during a campaign by using this technology? We need to ponder over this. At the same time, there should be regular beaming of pro-vaccine information and vaccine-success stories through various social media engines.

Conclusions

Vaccination is a great success, but we need to stay vigilant. Vaccine hesitancy is a real and greatest threat to vaccination programs. It does exist in India; so far, confined to public vaccination programs, but the incidence of VH is increasing among individuals in both high and low socioeconomic strata. Social media, particularly WhatsApp is the major driver, particularly in India. We need to keep a high vigil to avoid disruption of vaccination activities and at the same time, need a new intervention strategy with a focus on social media. There is a need to understand the social behaviour of the community, and to develop a multidisciplinary approach to tackle growing anti-vaccine movement.

-Vipin M. Vashishtha

PERSPECTIVE

Our Present Crisis of Faith

Ajay Kalra

Not a day passes when we do not get news of cases of violence against doctors. We often feel we are the most common and vulnerable victims. We also wonder why this loss of faith in us. Old timers would recollect how the physicians of the past would dispense mixtures and powdered medicines without even mentioning the contents and the patients would simply accept them. Today, it is not possible. The patient would not accept any blind dispensing, nor the doctor would dare to dispense so due to fear of consequences of any adverse event. Doctors are under obligation not only to reveal the contents of the medicines, but also prescribe in legible writing. The fear has gone to the extent that it has prompted many people to opt out of medicine as a choice of profession for their children. But then, is there any profession which is free of this?

The whole society seems to be at odds with each other. Each profession is seen with suspicion and mistrust- be it the police, the doctors, the engineers, the judiciary, the lawyers, the businessmen, the social worker, the labour etc. The politicians, of course, are the favourite boxing bag. Every profession seems to be enjoying blaming the other. We are happy to criticize, but not sensitive to the feelings of others.

We are living in much better times. We are witnessing progress as never before. Our standard of living is higher. Our opportunities are much more. Our choices of education and profession are better. Our roads, cities, trains, infrastructures are getting better. We are able to travel more. We should have been celebrating this better lifestyle and ease of living. But we are busy complaining against something or the other. It is ironical that even those who have the best start saying that they feel insecure. Indeed, some celebrities are even suffering from "fear psychosis". We seem to have been gripped by a crisis of faith.

"To one who has faith, no explanation is necessary.
To one without faith, no explanation is possible."
– Thomas Aquinas

What could be the possible reasons for this crisis?

One possibility is the availability of so many options. This makes us more circumspect and sceptical while making choices. We have become more pragmatic, and do not trust anything easily.

Another possible reason could be that the pace of change is too fast,making it difficult to adhere to a choice. Yet another reason is that our interactions are too many, it is difficult to assess and believe all. Interpersonal relationships remain superficial, cool and fleeting. To trust or not to trust – that is the question.

"Faith is not belief without proof, but trust without reservation"
– D. Elton Trueblood

Moreover, we are still a developing country. There will always be some shortage. Therefore, there is a competition for whatever is available. This can give rise to a feeling of discrimination and injustice. Added to this is the age old perception that the sarkar is the provider. Also, this is an era of instant results and impatience ("instant coffee," "instant delivery", "instant delete"). We need everything instantly : Instant results, instant jobs, instant income, instant relief from illness, so on and so forth. Therefore, the frustrations are also instant.

"The principle part of faith is patience"
– George MacDonald

Any solutions?

Difficult to figure out. Perhaps, the readers may have some idea. Would be happy to learn from them? Prosperity and education is no guarantee. Look at the turmoil in some of the most affluent societies. Some of the most corrupt and fanatic are incidentally the most well-educated. Some of the renowned universities are sick themselves, afflicted by indiscipline and aggressive unrest. Education without skill is of no use getting a productive job.

I can only suggest that we need to inculcate in our children a positive attitude and bring them out of the refrain that it is a competitive world and we need to measure up to it. Instead of remaining focused only on studies, let them interact with a cross section of people in the society. Let them do case studies of people ranging from those who have been achievers in different professions to those who have been the most unfortunate (patients with terminal illnesses, unmitigated diseases and the orphans);to those who are contributing to the welfare of the communities applying the latest technology in various fields. Engage them in at least some of these activities. Teach them the dignity of labour. Let skill development be a major part of curriculum in all disciplines.Keep them busy and make them contribute something to their family at least.

But then, do not preach them to do all this. Lead them by setting examples.

"Seeds of faith are always within us; sometimes it takes a crisis to nourish and encourage their growth"
– Gregory Peck

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UPDATE

"Gluten Free Diet: Beyond Avoiding Wheat/barley/rye As Staple Diet"

Dr. Puneet Kumar

Strict, lifelong Gluten Free Diet (GFD) is the only treatment available for management of Celiac Disease (CD) currently. Since the damage to the intestinal villi is mediated immunologically, ingestion of even minute amount of gluten precipitates the villi-devastating cascade. Thus, unlike food intolerance (even non-celiac gluten sensitivity), just avoiding wheat, barley and rye in staple diet is not enough in management of Celiac Disease. It is ***essential*** to avoid even the minute amounts of ubiquitous gluten. To achieve this, one needs to adopt not only gluten-free staple cereals, but also gluten-free ingredients, gluten free-storage of food items and gluten-free cooking.

This article aims to provide deeper insight and practical tips about gluten-free diet, which is often out of the scope of standard pediatric textbooks, and is essential to maintain gluten free status of your patients of Celiac Disease. Since the incidence of Celiac Disease is increasing (increasing incidence and increased detection) exponentially globally, it is imperative for pediatricians to be aware of the nuances.

The principle sources of gluten are wheat, rye and barley. It must be clarified that rye is a cereal that looks like wheat (figure-1) and is principally used as a forage food (animal fodder) or for brewing. It is also used to make flour and breads: it is popular in Eastern Europe and is hardly used in India. This clarification is essential for patients since Indians often confuse it with black mustard seeds, since it is called "*Rai*" (same pronunciation as rye) (figure-2) in Hindi and Gujarati. Black mustard seed ("*Rai*") is popular in India and is gluten free.

Figure 1. *Grains of Rye*

Figure 2. *Grains of Rye*

Another common confusion among parents is regarding use of oats as they get divergent opinions on the internet. The confusion is understandable, as the gluten-free status of oats has historically flip-flopped even in academic circles (1) and continues to be debated (2). As such, oats are generally considered gluten-free, but contain *avenins* that share antigenic epitopes with gluten. This was the reason why oats were initially clubbed with wheat, rye and barley on the allergen list. However, the ability of avenins to trigger the villi-damage is controversial, as many CD patients can tolerate oats without any problem. However, it has increasingly been recognized that it is the contamination of oats with wheat that is the problem. Oat is a winter (*rabi*) crop just like wheat and is often grown in the same field as wheat and same harvesting and storage equipment is used for it. Further, it is processed on the same equipment line where wheat is also processed. Hence oats are almost always contaminated with minute amounts of wheat. Hernando et al (3) tested 134 samples of various grains and commercial products of oats available in North America, Canada and Europe for gluten. If was found that only 25 of these were devoid of gluten. In 109 samples, the gluten was found at an average of 200 ppm that is 10 times the level that is considered as safe. It has been suggested that even the clinical studies that tried to study tolerance of oats in CD patients might have used the oats that were contaminated (at harvesting/ transportation/ processing stage), thus confounding the results (4). The 2009 European Commission Regulations and 2013 US laws specifically mention that products containing oats can be sold as gluten-free food only if any contamination with gluten is below 20ppm (1). However, the legal status in Australia and New Zealand is different. The authorities there

maintain that the tests for gluten do not test for avenin. Hence even the foods with undetectable level of gluten can only be marketed as "wheat-free" and not gluten-free. The position statement of Coeliac Australia on this issue also mentions that some patients with Celiac Disease can adversely react with even uncontaminated oats. They recommend duodenal biopsy before and 3 months after regular consumption of oats to be sure that oats are safe for the Celiac patients who wish to consume oats as a part of Gluten Free diet (5). In view of above and the sad fact that the regulations and degree of law enforcement are poorer in India, I personally don't advise oats at all as a part of Gluten Free diet. Simply put, patients need to avoid wheat, barley, oats (and rye).

Gluten free diet ideally should be "gluten free": that is, should not have any detectable gluten. The sensitivity of currently available tests for gluten in food is 5ppm and any level below this is reported as "undetectable". This (5ppm) is the cut-off that authorities in Australia/ New Zealand require to be for the food to be labelled as gluten-free. However, the guidelines by the Codex Alimentarius Commission, established by Food and Agricultural Organization (FAO) and World Health Organization (WHO) recommend a cut off of 20ppm. This is followed by most countries globally. The same is notified recently by Government of India in Food Safety and Standards (Food Product Safety and Food Additives) Second Amendment Regulations, 2016. To understand this figure of 20ppm realistic terms, let us take an example of bread. A slice of regular bread roughly weighs 25 grams and it has about 5grams (5000mg) of gluten. Hence, ***1/250th (20/5000) of a slice of bread in 1kg of food is damaging for a patient of CD*** (figure-3)! Thus, even when wheat/ barley/ oats/ rye is not used directly as an ingredient in a food item, it is crucial to know and avoid any ingredient with "hidden gluten", avoid cross-contamination of gluten while cooking/ storing of food and know and avoid other possible sources of gluten other than food per se. Only then the patients of CD can maintain their gluten-free status.

Figure-3. *Can you see a grain of regular bread on this plate? If gluten-free bread is served on this plate to a celiac patient, this much gluten is enough to trigger villi-damaging cascade!*

Table-1 lists the possible sources of hidden gluten in food ingredients and non-food products. Even some medicines have gluten as a part of excipients. To protect celiac disease patients, many countries have banned gluten across all medicines, while others have made it mandatory to disclose information on gluten on all medicines. Sadly, India has no such policy whatsoever! Unlike FSSAI which has made some steps towards safety of food for celiac disease patients, the Drug Controller is far behind in this direction. In the absence of any information on presence of gluten in medicines, I have not mentioned anything on the subject in table-1. But treating clinicians need to be aware of this source of hidden gluten also (how??)

Table 1. *Some examples (not an exhaustive list) of sources of hidden gluten in food ingredients and other products and how to avoid these (adapted from Ref no. 6 and ingredient lists of commercially available packaged food items)*

Source	Avoidance / Alternatives
Asafetida (heeng) (It is a strong and expensive spice. Usually available commercial packs has wheat flour (45-50% concentration) for the purpose of diluting, and this may or may not be mentioned clearly)	Either buy pure asafetida rock and powder it carefully or buy gluten-free labeled packs (gluten free packs use corn flour or sorghum instead of wheat flour for dilution). If any food is consumed outside, patient/ must avoid anything with asafetida.
Other Spices (Spices are often ground in machines that also grind wheat, hence are often contaminated with gluten…and this is not expected to be mentioned in "ingredients")	Either buy solid spices (e.g., solid turmeric, dry chilies etc.) and grind at home carefully or buy labelled gluten-free spices.
Vinegar Malt vinegar is obtained from barley and is unsafe	Use distilled vinegar, Apple cider / cider vinegar / grape vinegar these are gluten-free
Sauces Vinegar is used, which adds gluten in it. Spices used may also be contaminated with gluten. Moreover, some brands may also use wheat starch as thickening agent	Using gluten-free labelled brand or use home-made dips (*Chutneys*)
Gravies, marinades Starch may be used as thickening agent; spices used may be contaminated	Avoid consuming such food items from outside
Seasonings May use ingredients that are contaminated with gluten	Avoid consuming / using these

Packaged soups Starch may be used as thickening agent; spices used may be contaminated	Avoid consuming these
Baking powder Baking powder has wheat flour as one of the ingredients	Use labelled gluten-free brand (they use corn flour instead of wheat flour)
Salad dressing, non-dairy creamer May use wheat starch as thickening agent	Avoid consuming/ using these
Brewer's yeast Most brewer's yeast is a byproduct of the beer brewing process and contains gluten from the barley used to make beer.	Some brands of brewer's yeast created using sugar beets and are gluten-free. Baker's yeast and active dry yeast are gluten free
Frozen products Many products have bread crumbs and/ or starch (this might be wheat starch or even corn starch that is contaminated with gluten). In addition, the oil used might be contaminated by gluten because of other gluten-containing products being processed in the same oil	Avoid consuming these
Toffees, candies, chocolates and even cough lozenges Often wheat starch is used as thickening agent; many flavoring agents/ choco-chips have gluten	Gluten-free brands of toffee / chocolates are available
Food colours (especially caramel colour), some food additives and flavouring agents They often contain gluten	Only certified gluten free products should be used
Commercially available sweets They often use wheat starch as thickner/ binder. Even traditional peanut strip (*mungfalikipatti*) that contains only jaggery and peanut can't be consumed, since during making these, wheat flour/ refined flour (*maida)* is sprinkled on the workstation so that the strips do not stick.	Only home-made sweets with gluten free ingredients in gluten free environment or certified gluten-free sweets can be used.
Commercially available ice creams Often use wheat starch as thickening agent	Only home-made ice creams with no such ingredient or certified gluten free product is to be used.
Some lip balms, lipsticks, certain cosmetics Some of these can also have gluten in them. Just to give an example, lip balm of Himalaya® brand has wheat germ oil as one of the ingredients	Alternative products with no such ingredient need to be used
Play doh (clay) and some other art supplies These also can have gluten, as they use wheat flour as the main ingredient; but are harmful only if ingested	Due caution is advised while using these things; there are online sources that teach making clay for playing using ingredients like rice flour, coconut oil and baking soda at home.

Other than these hidden sources of gluten, the gluten-free diet can easily get compromised due to cross-contamination with gluten during storage, cooking or serving the food. Table-2 lists some of such common scenarios and the ways to avoid these.

Table 2. *Some practical examples of scenarios whereby cross contamination of gluten-free food occurs with gluten-containing food.*

Scenario	Tips for Prevention
Getting gluten-free grains / spices milled at same grinder that mills wheat also	The grinder / *chakki* used for gluten free grains / spices needs to be dedicated for these only.
Storing gluten free flour and other ingredients in the containers that are contaminated with gluten	Using new / scrupulously cleaned containers for storing gluten-free ingredients
Contamination in refrigerator: gluten-containing food can drop in the bowl storing gluten free food	Having a separate refrigerator or dedicating upper-most rack of the refrigerator for gluten free food and lower ones for others. The refrigerator must be cleaned scrupulously before starting to store gluten free food
Wheat dough or other gluten-containing material sticking to ones hands/ cooking slab while cooking gluten free food	Preparing gluten-free food before cooking other items; thorough washing of hands and scrupulous cleaning of cooking area
Cooking pan / *tawa / chakla / belan (*rolling pin) that is contaminated with gluten	Preferably separate equipment should be there for gluten-free food; otherwise, scrupulous cleaning (extremely difficult!) and cooking gluten-free food prior to the other food
Frying in same oil in which some gluten-containing food was fried	Fresh oil to be used for gluten-free diet; if oil needs to be re-used, first fry gluten-free food
Air-borne gluten where gluten-free food is being cooked can also be harmful. Whenever wheat *roti* is cooked, the dry wheat flour is suspended in air…it can enter the gluten-free food and compromise it.	Gluten-free food is to be cooked first. The dry flour used for cooking can be of gluten-free flour even for making wheat *rotis*.
Getting gluten-free grains / spices milled at same grinder that mills wheat also	The grinder / *chakki* used for gluten free grains / spices needs to be dedicated for these only.

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Air-borne gluten where gluten-free food is being cooked can also be harmful. Whenever wheat *roti* is cooked, the dry wheat flour is suspended in air…it can enter the gluten-free food and compromise it.	Gluten-free food is to be cooked first. The dry flour used for cooking can be of gluten-free flour even for making wheat *rotis*.
Microwave / toaster etc. can be contaminated with gluten	It is preferable to have a separate / dedicated toaster; Gluten-free food is to be cooked first; scrupulous cleaning
Butter / jam / ghee contaminated with gluten: If butter / jam is applied on wheat / white bread and then from the same container, the jam / butter is used to apply on gluten-free bread, it won't remain gluten-free	Jam / butter should be dedicated for the celiac disease patient.
Use of salt / spices from "open containers" while cooking food: The open containers of salt / spices can be contaminated due to air-borne gluten or with hands while cooking gluten-containing food	"Sprinklers" should be used as far as possible to avoid cross-contamination
Uncovered gluten-free food lying in the cooking space where other food is being cooked can easily get contaminated	Due caution is essential to prevent such cross contamination
Contaminated utensils (knife, spoon, chopping board, serving spoon etc.) used while cooking / serving food. For example, if the knife used on a regular bread is used to cut gluten-free bread, latter won't remain gluten-free!	Thorough washing before and after use is essential; even soap and sponge used to wash utensils need to be separate for the utensils of celiac patient.

Thus, it is clear that maintaining a gluten-free status requires much more than just avoiding wheat and barley as staple food. It requires significant effort on the part of the patient and the family to adopt the changes in procuring, cooking and consuming food: the basic necessity of life. At the same time, it requires tremendous efforts on the part of the treating clinician to convince, counsel and support on a continuing basis to achieve the desired results. Trouble-shooting when the patient is not doing well clinically despite being apparently motivated and compliant is equally troublesome for the clinician!!! However, surmounting big challenges is what gives unparalleled satisfaction, isn't it?

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THINK IT OVER

"A Peep into The Irrational & Unethical Pharma Practices"

Yash Paul

Petrol available all over the country is of uniform quality. One may buy from Hindustan Petroleum, Bharat Petroleum or Indian Oil outlet. Petroleum authorities take care of it, so that no damage occurs to the engines of vehicles. In the year 2012 I had stated: "A doctor prescribes or administers drugs to a patient and is expected to follow 'cause no harm' principle. Safety and Welfare of a patient is a main concern of the medical profession, which includes medical and paramedical personnel and even drug industry. While pharmaceutical companies make legitimate profits from the sale of drugs, but at the same time they should take necessary steps to ensure the wellbeing of the people" (1).

It is being said that Pharmaceutical industry has commercialized. We have to remember that drug manufacturers are commercial houses and not charitable NGOs. What should be the margin of profit is for the government and other agencies to deliberate upon? The drugs should be safe and rational products. Unfortunately, these issues are not being taken up by the concerned authorities (2). In the year 2013 I had stated: "The most important point is that drug formulations should be appropriate, safe and uniform (3).

In our country we the doctors face following problems regarding medicines:

1. Spurious drugs: Where ingredients mentioned do not exist or in very low quantity, thus provide no benefit to the patients.

2. Substandard medicines: Where quantity of ingredients is less than 90% of required quantity. Such medicines may not provide full benefit, on the other hand in case of antibiotics may result in resistant microbes.

3. Problematic formulations: Varying concentrations of different constituents in combination formulations can pose problems for doctors and risks for patients (4). Anticold formulations having Chlorphenaramine Maleate and Phenylephrine Hydrochloride as the main ingredients have sometimes other molecules like Cetirizine or Levocotirizine and Paracetamol also. Cetirizine and Levocetirizine are to be administered once in 24 hrs while other ingredients are to be administered 3 to 4 times in a day. Different pharmaceutical houses make products with different quantities of different ingredients. There are 32 formulations in tablet forms, 16 in syrup forms and 6 in drop forms (5).

4. Irrational formulations: Clavulanic Acid is approved in combination with Amoxicillin and Sulbactum for combination with Cefoperezone. Presently many antibiotics in combination with Clavulanic Acid or Sulbactum are available in the market. These formulations add tremendously to the cost of therapy without providing any additional benefit to the patients. I checked a Therapeutic Index and noted the number of brands apart from the approved combinations as following :

A. Clavulanic Acid : Cefpodoxime 48, Cefexime 38, Cefuroxime 18, and Cefadroxyl 2.

B. Sulbactum: Ceftriaxone 47, Meropenen 7, Cefexime 6, Cefotaxime 4, Cefuroxime 4, Cefpodoxime 1, Cefepime 1, Ceftriaxone 1, Cefpirome 1, Ampicillin 1, and Amoxicillin 1.

5. Combinations of antagonistic ingredients : Iron and Zinc have many similar absorption and transport mechanisms, and may therefore compete for absorption (6, 7). Iron may interfere with absorption of Zinc when ingested together. Many drug manufacturers market formulations havine Iron and Zinc.

6. Funny combinations :

A. Paracetamol syrups. Paracetamol syrups containing 120 mg, 125 mg, 156.25 mg and 250 mg paracetamol per 5 ml are available. Manufacturer marketing the brand having 156.25 mg per 5 ml must be using very advanced technology to make drugs of such accurate quantity. Doctors would need calculators to calculate the accurate dose for a child.

B. Some time back a reputed manufacturer introduced a Multivitamin, Multimineral, and Axtioxidant with addition of Amino Acids, which no other similar product contained. Print on the packing provides information regarding the percentage of RDA (Recommended Daily Allowance) of Amino Acids which are : L-Valine 0.16%, and rest between 0.19 and 0.59% of RDA, i.e. none of Amino Acid ingredient is even 0.6% of required RDA. Prescribing such product amounts to be fooling oneself and cheating the parents.

C. Addition of Probiotics to Antibiotics. The rationale for the use of Probiotics is based on the assumption that the use of Antibiotics leads to a disturbance in the normal intestinal microflora leading to Antibiotic Associated Diarrhea. Can probiotic in combination with antibiotic survive while similar microflora in gut is destroyed by antibiotics. Probiotic provides benefit in the gut when the antibiotic has been absorbed.

7. Misinformations by Pharma Houses : Chlorpheniramine Maleate is not recommended for children below 1 year of age and Phenylephrine HCl is not recommended for children below two years of age. Anticold drug Flucold AF drops marketed by Wallace contains phenylephrine HCl 5 mg and Chlorpheniramine Maleate 2 mg per 1 ml. On the packing printed is dosage schedule which is 0.1 ml for children 1 – 6 months, 0.1 – 0.2 ml for 7 – 12 month, age group, 0.2 – 0.4 ml for 1 – 3 year age group and 0.3 – 1.0 ml for children 3 – 6 years. Hatric 3 Drops marketed by Aristo Pharma contains Phenylephrine HCl 2.5 mg and Chlorpheniramine Molecte 1 mg per 1 ml. Recommended dose is 0.5 ml three times daily for children below 6 months and 0.5 ml three to four times for children aged 7 months to 2 years. It is important to note that this drug contains Paracetamol 125 mg per ml. This means that dose of Paracetamol remains same for 1 month old baby and 2 years old child. Two months old babies weigh between 4 and 6 kg. 0.5 ml of Hatric 3 contains 62.5 mg of paracetamol which would be appropriate dose for a baby weighing 4 kg, would be under dose for babies above 3 months and grossly under dose for children above 1 year of age. Now a days one can check the facts on internet. Parents may know from the internet that Chlorpheniramine Maleate is not recommended for children below 1 year of age and Phenylephrine HCl is not recommended for children below 2 years of age. Parents will have very poor opinion about the doctor who prescribes such drugs for children below 2 years of age.

In 1961 when I qualified as a doctor there were about a dozen or so pharmaceutical companies both Indian and foreign. Presently their number is in three digits and so there is tough competition. Business philosophy dictates that competitors must strive not only to maintain the quality of the product, but, to provide better product at competitive price or even at lower price to attract more clients. It appears that the pharmaceutical industry has turned upside down all the principles of business.

Price of petrol available at different petrol pumps in an area is same. But, prices of products having same drug formulations produced by different manufacturers are some times different. I would like to mention lowest and highest MRP of some products. Cefpodoxime 200 mg tablets. Podomox (Torrent) Rs. 10.20 and Bactiloc (Intralife) Rs. 22; Cefexime 200 mg tablets – Milixim (Glenmark) Rs. 7.24, Crinux (Pax Healthcare) Rs. 21.00, Amoxicillin 500 mg + Clavulanic Acid 125 mg tablets – Aculav (Macleods) Rs. 14.80, Adentin (Aden Healthcare) Rs. 25.00, Azithromycin 100 mg / 5 ml in 15 ml bottle – Zathrin (FDC Ltd.) Rs. 26.10, Azibact (IPCA) Rs. 35.87.

What could be the reason for such difference in prices of same drugs by different manufacturers? It could be due to some special overhead expenditures incurred by different pharma houses. A study by Support for Advocacy and Training to Health Initiative (SATHI) reported by The Times of India dated November 29, 2019 captioned 'Bribes to Doctors by Pharmaceutical Industry' states: "Medical Representatives have revealed wide spread use of bribes including foreign trips, microwave ovens, expensive smart phones, jewellery and even women, by pharmaceutical companies. According to medical representatives, hardly 10 – 20% doctors follow the MCI code of ethics, while the rest accept or even demand 'incentives' to prescribe products of a company. The most common inducement is the sponsoring of doctors for conferences". Naturally the burden is passed on to the consumers.

This study is based on interviews of 50 Medical Representatives from six cities. It states that 'hardly 10 – 20% of doctors follow the MCI code of ethics, while rest accept or even demand' incentives' to prescribe products of a company. It means 80 – 90% of doctors prescribe unnecessary, irrational and more expensive drugs for their own benefits. I would not like to comment on the purpose and outcome of this study by SATHI. But, it has rendered great service to the pharmaceutical industry as it has projected doctors as villains and drug manufacturers as hapless victims.

One would take this study with a pinch of salt. Perhaps the truth about this phenomenon is other way around. Some pharmaceutical houses produce irrational, substandard and even potentially harmful drugs and then they look for some greedy and gullible doctors with carrots of incentives (bribes) to prescribe their products.

It seems that in race for one-upmanship the pharma industry has turned blind eye to the science of pharmacy and safety of people. Issue of concern is that irrational drugs are manufactured after obtaining licenses from appropriate authorities and prices which are different

for same drug by different manufacturers must have been fixed after approval of pricing authorities.

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Adeh Appeal:

Make Code on Pharma Firms Mandatory!

The Alliance of Doctors for Ethical Healthcare (ADEH) has demanded that the Uniform Code of Pharmaceutical Marketing Practices (UCPMP) be made mandatory. It is unfortunate that even after 5 years the code remains voluntary. This is despite the fact that several medical organizations have demanded this repeatedly from the government. The global experience also shows that voluntary code does not work.

The Prime Minister, as published in a section of the media has warned pharmaceutical companies not to indulge in unethical practices and stop giving freebies to the doctors with a purpose to procure business. However, that any such deliberations occurred in the meeting with the Prime Minister has been denied by the pharmaceutical companies. It may be pointed out here that the companies spend crores of rupees through associations by sponsoring the medical conferences. They spend huge amount on travel, accommodation and other expenditures on the doctors for lavish arrangements of the conferences.

As per the clause 7.2 of the UCPMP "companies or their associations/representatives shall not extend any hospitality like hotel accommodation to healthcare practitioners and their family members under any pretext". The implied meaning of this is that even extending benefits to the doctors through associations is unethical. But this is being flouted with impunity.

Unfortunately, the Medical Council of India (MCI) had amended THE INDIAN MEDICAL COUNCIL (PROFESSIONAL CONDUCT, ETIQUETTE & ETHICS) REGULATIONS, 2002 in its meeting on 18 February 2014 and exempted the "Professional Associations of Doctors" from the purview of Medical Ethics. There is urgent need to take steps to reverse this amendment of the MCI and make the UCPMP mandatory.

Since the corporate hospitals are not covered under this ethics, they take advantage and openly flout the ethics. They should also be brought under the MCI regulations on ethics. It is also equally important that the any freebies from the Pharmaceutical companies be madetaxable. These were taxable earlier but the decision was reversed later by the Pune Bench of the Income Tax Appellate Tribunal.

Without these steps the Prime Minister's statement will remain only a rhetoric, particularly when the PMO has not clarified its position over the denial by the pharmaceutical companies about prime minister's warning.

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Next Generation Supplement for Next Generation Care

ANTIBIOTIC

- OFAX-100DT — Ofloxacin 100 DT Suspension
- Aldecef — Cefpodoxime Proxetil 50 mg / 5 ml Dry Syrup
- MICFOX-100DT — Cefepime Tab. / Dry Syp
- ZYLOCEF 250/ 500/ 1000 — Ceftriaxone Injection
- ZYLOCEF-T 250/500/1000 — Ceftriaxone + Tazobactam Injection
- ZYLOCEF-S 375 — Ceftriaxone + Sulbactam Injection
- AMIKANIT 100/500 — Amikacin Injection
- PIZOBAC — Piperacillin + Tazobactam 1.125/4.5gm
- MEDINEM 125/250 — Meropenem Injection
- MXY — Moxifloxacin 0.5 % w/v Eye/ Ear Drop
- DEMOXIN-CV — Amoxicillin 250 mg + Clavulanate Potassium 125 mg Tablet / Amoxicillin 200 mg + Clavulanate Potassium 28.5 mg Dry Syrup

ANTI-COUGH & COLD RANGE

- TUSP® — Dextromethorphan HBr 10 mg + Guaiphenesin 100 mg + CPM 2 mg + Phenylephrine 5 mg / 5 ml Syrup
- TUSP-BR® — Terbutaline Sulphate 1.5 mg + Bromhexine HCl 4mg + Guaiphenesin 100 mg / 5 ml Expectorant
- WINDRYL — Ambroxol 15 mg + CPM 2 mg + Guaiphenesin 50mg + Phenylephrine 5 mg + Menthol 1 mg / 5 ml Syrup
- ENTIMIN — Phenylephrine + Chlorpheniramine Maleate Syrup/ Drops / Tablet
- ENTIMIN-P — Phenylephrine + Chlorpheniramine Maleate + Paracetamol Syrup

ANALGESIC

- DECAMB — Ibuprofen + Paracetamol Suspension
- PFC — Paracetamol 125 mg Syp / Drops
- PFC-DS — Paracetamol 250 mg Syp

NUTRITIONAL SUPPORT

- aldevit® — Protein + Multivitamins + Multiminerals Syrup
- aldevit® — Multivitamin Drops
- aldevit® — Protein + Bovine Colostrum + DHA + Multivitamins + Multiminerals (DA3487 30gm / 250gm)
- Aldezyme® — Fungal Diastase + Pepsin Syrup (Sugar Free)
- Florill — Saccharomyces Boulardii 282.5mg eq. to 250 mg yeast
- DECYP-P — Cyproheptadine + Tricholine Citrate Drops / Syp

ANTIDIARRHOEAL

- ALZIN — Zinc Acetate eq. to Elemental Zinc 20 mg Syrup
- COLGIT — Colistin Sulphate 12.5 mg / 5 ml Syrup
- COLGIT-DS — Colistin Sulphate 25 mg / 5 ml
- NOGIT-M — Norfloxacin + Metronidazole Suspension
- OFAX-OZ — Ofloxacin + Ornidazole Suspension

CALCIUM PREPARATION

- AVICAL-P — Calcium phosphate eq. to Elemental calcium 300 mg Elemental phosphorous 150 mg Magnesium + Zinc + Vit. D3
- AVICAL — Calcium Citrate + Calcitriol Suspension
- AL-D3 — Cholecalciferol 60,000 I.U Sachet / Cholecalciferol 400 I.U Drops

ANTHELMINTIC

- ALDEZOLE — Albendazole Suspension / Tablet

HAEMATINIC

- ALFER — Ferrous bis Glycinate + Zinc bis Glycinate Tab. / Syrup / Drops

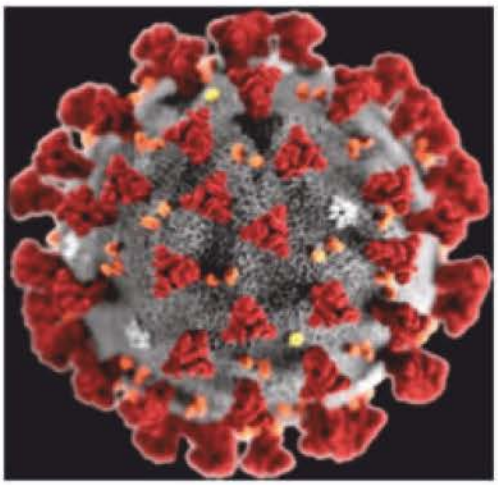
Novel Coronavirus (COVID 19; 2019-nCoV)

Unmesh Upadhyay

Coronaviruses (CoV) are a large family of viruses. This virus causes usually common cold to more severe diseases such as MERS-CoV (Middle east respiratory syndrome) and SARS-CoV (Severe acute respiratory syndrome). A novel coronavirus (n COV) is a new human strain. As a result, we don't have immunity against novel coronavirus.

In COVID 19, 'CO' stands for corona, 'VI' for virus, 'D' for disease. Coronaviruses are named as such because they look like little crowns under a microscope. In 2003 it was SARS. In 2012 it was MERS. Now in 2020 novel coronavirus initially reported on December 2019 in the city of Wuhan in the Chinese province of Hubei. Coronaviruses are zoonotic. It is circulated in camels, cats and bats. The novel coronavirus transmitted from animal to human. Preliminary evidence suggests that the virus that causes COVID-19 may have originated in horseshoe bats in china.

SARS-COV was transmitted from civet cats to humans. Now transmission from snakes to rodents is possible.



Common Human Coronaviruses

Common human coronaviruses including types 229E, NL63, OC43 and HKU-1 usually cause common cold like illness for a short amount of time.

Current outbreak of nCoV in China

As the coronavirus outbreak continues to spread across China, a flurry of early research is drawing a clearer picture of how the pathogen behaves and the key factors that will determine whether it can be contained.

Table 6 Clinical presentation in different cohorts of patients with COVID-19 pneumonia (frequency of reported symptoms)

	Chen Lancet 2020 (n=99*)	Song Radiol 2020 (n=51)	Chang JAMA 2020 (n=13)	Guan NEJM 2020 (n=1099**)	Wang JAMA 2020 (n=138)
fever	83%	96%	92.3%	88.7%	98.6%
cough	82%	47%	46.3%	67.8%	59.4%
shortness of breath (dyspnoea)	31%			18.7%	31.2%
muscle ache (myalgia)	11%	31%	23.1%	14.9%	34.8%
fatigue				38.1%	69.6%
confusion	9%				
headache	8%	16%	23.1%	13.6%	
sore throat	5%			13.9%	
rhinorrhoea	4%				
chest pain	2%				
diarrhoea	2%	10%		3.8%	10.1%
nausea and vomiting	1%			5%	10.1%
acute respiratory distress syndrome	17%			3.4%	

As per research published in the New England Journal of Medicine based on calculations the novel coronavirus has a Ro of 2.2 meaning each case patient could infect more than 2 other people. The study was based on first 425 cases of 2019 nCoV China. It also determined a mean incubation period of 5.2 days (2 – 14 days).

While the virus is a serious public health concern, the risk to most people outside China remains very low, and seasonal flu is a more immediate threat. To avoid any viral illness, experts advise washing your hands frequently and avoiding your office or school when you're sick. Most healthy people don't need masks and hoarding them may contribute to shortages for health workers who do need them, experts say.

If each person infected with the new coronavirus infects two to three others, that may be enough to sustain and accelerate an outbreak, if nothing is done to reduce it. The scale of an outbreak depends on how quickly and easily a virus is transmitted from person to person. While research has just begun, scientists have estimated that each person with the new coronavirus could infect somewhere between 1.5 and 3.5 people without effective containment measures.

That would make the virus roughly as contagious as SARS, another coronavirus that circulated in China in 2003 and was contained after it sickened 8,098 people and killed 774. Respiratory viruses like these can travel through the air, enveloped in tiny droplets that are produced when a sick person breathes, talks, coughs or sneezes.These droplets are larger than 5 microns in diameter and form a direct spray propelled upto 2 meters away from the infected person.Aerosol are droplets too but much smaller and may remain afloat for longer distances.

But the transmission numbers of any disease aren't set in stone. They can be reduced by effective public health measures, such as isolating sick people and tracking individuals they've had contact with. When global health authorities methodically tracked and isolated people infected with SARS in 2003, they were able to bring the average number each sick person infected down to 0.4, enough to stop the outbreak. Health authorities around the world are expending enormous effort trying to repeat that.

How deadly is the virus?

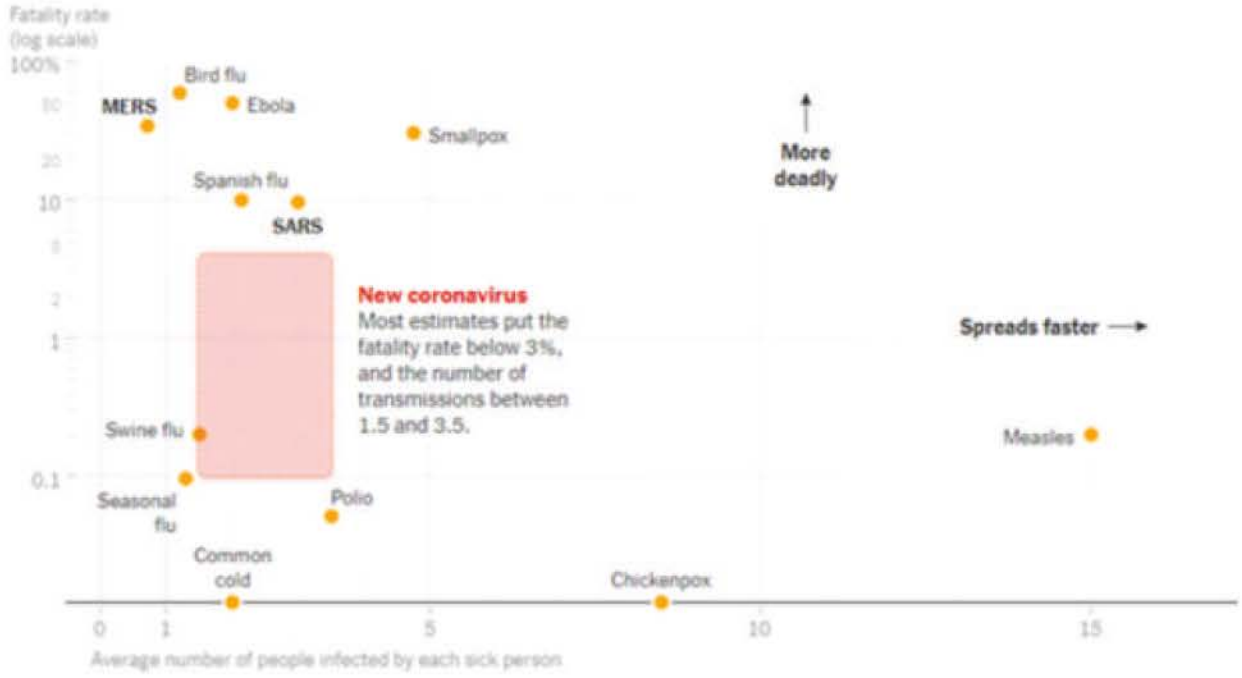
It's hard to know yet. But the fatality rate is probably less than 3 percent, much less than SARS.

This is one of the most important factors in how damaging the outbreak will be, and one of the least understood.

It's tough to assess the lethality of a new virus. The worst cases are usually detected first, which can skew our understanding of how likely patients are to die. About a third of the first 41 patients reported in Wuhan had to be treated in an I.C.U., many with symptoms of fever, severe cough, shortness of breath and pneumonia. But people with mild cases may never visit a doctor. So there may be more cases than we know, and the death rate may be lower than we initially thought.

At the same time, deaths from the virus may be underreported. The Chinese cities at the center of the outbreak face a shortage of testing kits and hospital beds, and many sick people have not been able to see a doctor.

Here's how the new coronavirus compares with other infectious diseases:



Note: Average case-fatality rates and transmission numbers are shown. Estimates of case-fatality rates can vary, and numbers for the new coronavirus are preliminary estimates.

Early indications suggest the fatality rate for this virus is considerably less than another coronavirus, MERS, which kills about one in three people who become infected, and SARS, which kills about one in 10. All of the diseases appear to latch on to proteins on the surface of lung cells, but MERS and SARS seem to be more destructive to lung tissue. As of Jan. 31, fewer than one in 40 of the people with confirmed infections had died. Many of those who died were older men with underlying health problems.

Cold Vs. Flu Vs. Coronavirus

If you have a sore throat, it's more likely a cold than flu or coronavirus, in general.

	Cold	Flu	Coronavirus
Time between catching the virus and beginning to show symptoms	1-3 days	1-4 days	2-14 days
Symptom onset	Gradual	Abrupt	Gradual
How long do symptoms last	7-12 days	3-7 days	Mild cases=2 weeks. Severe or critical disease: 3-6 weeks
Major symptoms			
Fever	Sometimes	Common	Common
Runny nose	Common	Sometimes	Less Common
Sore throat	Common	Sometimes	Less Common
Cough	Common	Sometimes	Common
Body Ache	Rare; if occurs, mild	Common	Less Common
Difficulty Breathing	Rare	Rare	Common

'Quick fact checks on nCoV"

SYMPTOMS

1. Fever (83%) (Thermal scanners are effective in detecting people who have developed fever because of COVID- 19 infection) 2. Cough (82%) 3. Difficulty in breathing (31%) 4. Mild gastrointestinal symptoms 5. Sore throat 6. Rhinorrhea

Complications

1. Pneumonia is commonest (Bilateral pneumonia on imaging- 75%)
2. Acute respiratory distress syndrome (29 %)
3. Renal failure
4. Acute cardiac injury (12%)
5. Death

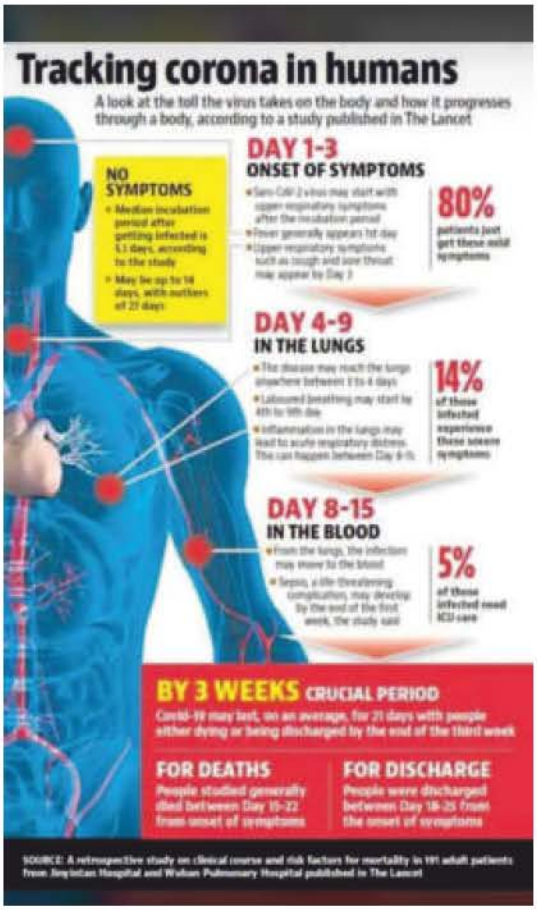
Complications are more common in people with cardio-pulmonary disease,Diabetes,weakened immune systems, infants and older adults (age >6o year).

Death rates are lower in age less than 30 year.

DIAGNOSIS

1. Case Definition -

Suspect- Severe acute respiratory infection (SARI) in a Person with history of fever and cough ,shortness of breath (at least one sign/ symptoms of respiratory disease)requiring admission to hospital, with no other etiology that fully explains the clinical presentation AND any one of the following- 1, A history of travel to or residence in country/ area or territory reporting local transmission (see NCDC website for an update list) of COVID 19 disease , 14 days prior to symptom onset OR The person develops an unusual or unexpected clinical course especially sudden deterioration despite appropriate treatment,without regard to place of residence or history of travel.



Probable

A person with acute respiratory illness of any degree of severity who within 14 days before onset of illness, had any of the following exposure-

a. Close physical contact with a confirmed case of nCOV infection, while patient was symptomatic OR
b. A healthcare facility in a country where hospital associated nCOV infections have been reported OR
c. Direct contact with animals in countries where

nCOV is known to be circulate in animal populations or where human infections have occurred as a result of presumed zoonotic transmission.

Laboratory-The only diagnostic test to identify nCoV is RT-PCR.(Viral genome sequence) Two consecutive negative PCR tests at least 24 hours remain gold standard.

C T Chest is a choice for pneumonia.

Difference between COVID-19 & Influenza.

1. COVID-19 does not transmit as efficiently as influenza.The speed of propagation is different.The serial interval (the time between successive cases) for COVID-19 virus is estimated to be 5-6 days, while influenza virus serial interval is 3 days.This means that influenza can spread faster than COVID-19.
2. Patients transmit the virus at different times.Influenza virus transmission mainly occurs within 3-5 days after a person begins to develop symptoms and may spread before symptoms appear.
3. The contagious power is different.as per study COVID-19 pneumonia is more infectious than influenza and one patient can infect about 2 to 2.5 people.However, assessment of the infectivity of the two viruses is related to specific circumstance and time.
4. COVID-19 causes more severe disease (Mortality rate-3-4%) than seasonal influenza mortality (below 0.1%).
5. Children are important drivers of influenza virus transmission in the community.For COVID-19 virus, initial data indicates that children are less affected than adults and that clinical attack rate in 0-19 age group are low.As per data from china childrens are usually affected from adults.
6. Those most risk for severe influenza infection are children,pregnant women,elderly with underlying chronic medical conditions and those who are immunocompromised.For COVID-19 as per current data older age and underlying conditions increase risk of infection.
7. For COVID-19 data suggest 80% of infections are mild or asymptomatic.15% severe infections requiring oxygen and 5% are critical infections , requiring ventilation.These fractions of severe and critical infection would be higher than what is observed for influenza infection.
8. Vaccines and therapeutic drugs available for seasonal flu but no specific drugs and vaccine currently licensed for COVID-19.

TREATMENT

symptomatic treatment.No vaccine at present.

Chloroquine,Tocilizumab,Interferon alfa 2b, Remdesivir,Favipiravir,sarilumab drugs efficacy study done for COVID-19.

PREVENTION

1. Clean hands with soap and water for at least 20 seconds or alcohol based hand rub.
2. Cover nose and mouth with tissue or inside elbow when coughing or sneezing.
3. Avoid close contact with anyone with cold or flu like symptoms
4. Throughly cook meat and eggs.
5. Avoid unprotected contact with live wild or farm animals.
6. Cover your cough or sneeze with tissue then throw tissue in trash.
7. N95 mask or Surgical mask for symptomatic cases.
8. schools are advised to avoid any large gathering of students during the course of the day in school.
9. Social distancing - It is a public health practice that aims to prevent sick people from coming in close contact with healthy people in order to reduce opportunities for disease transmission.CDC define social distancing as it applies for covid 19 as " remaining out of congregate setting , avoid mass gatherings maintaining distance (approximately 6 feet or 2 meters) from other when possible.
10. Any student/staff with travel history to any COVID-19 affected country OR in contact with such person in the last 28 days should be monitored and home quarantined for 14 days.

ADVICE for travellers returning from china and other countries affected by COVID-19.

If you have recently travelled to china (within 14 days) or had possible contact with an nCOV infected person, it is advisable to,

1. Stay in home isolation for 14 days after your return.
2. Cover nose and mouth when coughing and sneezing.
3. Avoid close contact with anyone with cold or flu like symptoms.

(references - 1.www.cdc.gov 2.www.who.in 3.CIDRAP)

EQUIPMENT REVIEW

'NEO THERM'-an indigenous, servo-controlled, whole-body cooling system

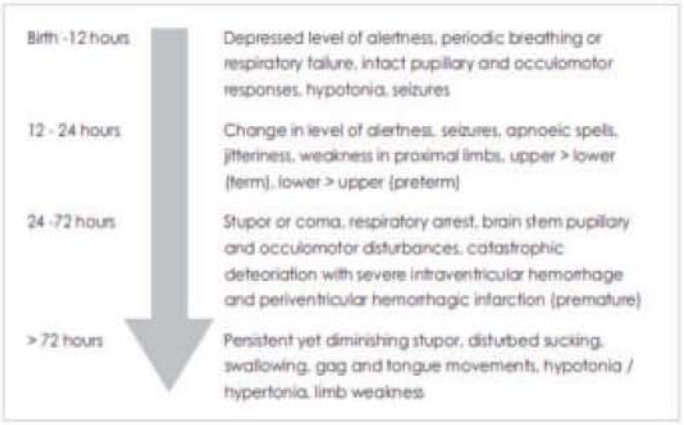
"There is now unequivocal and high-quality evidence from multiple large RCTs that neonates with moderate to severe hypoxic-ischemic encephalopathy (HIE) following a perinatal event benefit from hypothermia under tightly controlled conditions"

An estimated 4 million babies die every year in the neonatal period. Ninety nine percentage of these deaths are in low to middle income countries. It is a sad fact that most of the neonatal deaths due to asphyxia (99%)occur in developing countries. India contributes to one-fifth of global live births and more than a quarter of neonatal deaths. HIE occurs in 1.5 per1000 full term births. While 15 - 20% of neonates with HIE die early, 25% will survive with disabilities. Moreover HIE is a major problem at all levels - individual, family and society, contributing to 15-28% of children with cerebralpalsy and 25% of all children with developmental delay. Despitesignificant advances in perinatal care, cerebral palsy among terminfants continues to occur.

A recent systematic analysis has shown that low technology device in tertiary level settings has improved survival and neurological outcome in HIE babies with moderate to severe encephalopathy.

***Figure 1.** NEO THERM by VNG*

***Box 1.** HIE - Clinical Features*



Therapeutic Hypothermia (TH) has been proven to be effective inreducing morbidity associated with HIE and has become the standard of care for HIE in developed countries. However, in under developed and transitional countries where the problem is more common, therapeutic cooling is still in the nascent phase.

As of today, the only modality for treatment and a means to decrease long term morbidity in babies with perinatal asphyxia is the initiation of therapeutic hypothermia within the first 6 hours of life.

Cooling appears to reduce DNA damage induced by oxidative stress and improve neuro developmental outcome.

Early application of TH preferably within 6 hours i.e. before the onset of the secondary phase of energy failure is likely to be effective and improve neurodevelopmental outcome. **Usually it is continued for a period of 72 hours** for better neuro protection. There is also evidence that therapeutic hypothermia limits myocardial and renal injury interm infants with HIE.

***BOX 2.** Summary: Mechanism of actions of Therapeutic Hypothermia*

- Reduction of cerebralmetabolism and prevention of edema
- Decrease in energy utilization
- Reduction of cytotoxic amino acid accumulation and nitric oxide
- Inhibition of platelet-activating factor and inflammatory cascade
- Suppression of free radicalactivity
- Attenuation of secondary energy failure
- Inhibition of apoptosis (cell death)
- Reduction of the extent of brain injury

WHICH NEONATES TO COOL?

Neonates can be considered for cooling if the following criteria are met (NICHD criteria):

1. Gestational age ⩾ 36 weeks
2. Less than 6 hours old
3. A pH of 7.0 or less or a base deficit of 16 mmol per liter or more in a sample of umbilical cord blood or any blood during the first hour after birth.

If the pH is between 7.01 and 7.15, a base deficit is between 10 and 15.9 mmol per liter,

If a blood gas is not available, additional criteria are required. These include an acute perinatal event (e.g., late or variable decelerations, cord prolapse, cord rupture, uterine rupture, maternal trauma, hemorrhage, or cardiorespiratory arrest) and either a 10-minute Apgar score of 5 or less or assisted ventilation initiated at birth and continued for at least 10 minutes.

4. Moderate to severe encephalopathy on clinical examination.

PREREQUISITES TO PRACTICE THERAPEUTIC HYPOTHERMIA

The minimum prerequisites to start the practice of therapeutic hypothermia have been depicted in Table.1:

Place	Personnel	Paraphernalia	Protocols
Well established level-3 NICU care.	Trained doctors & Staff nurse	Radiant warmer, Cooling device, ABG machine, Multi-parametric parameters, Ventilators	Evidence based standard protocol. Neuro-development follow up.

***Table 1:** Minimum requirements to practice therapeutic hypothermia*

DIFFERENT PHASES OF COOLING THERAPY

The different phases of therapeutic hypothermia are depicted in the Table 2.

Hypothermia phases	Strategies
INDUCTION	Rapid cooling to 33-34°C. Duration: 45 minutes-1 hour. Monitor temperature and vitals. Treatment of shock and seizures. Avoid shivering and overcooling. Rectal probe inserted 5 cm into the rectum and skin probe over the abdomen are connected to the monitor for continuous monitoring. The radiant warmer is switched off.
MAINTENANCE	The target temperature is monitored every 15 minutes for the first four hours and later hourly for 72 hours. Vital parameters like heart rate, capillary filling time and blood pressure are recorded hourly. Close monitoring of temperature and vitals. Maintain temperature: 33-34°C. Total Duration: 72 hours. Monitor urine output and adjust total fluid intake. Monitor for multi-organ damage. Adjust drug dosages. Look for bed sores and skin damage.
REWARMING PHASE	Slow rewarming initiated. Duration: 6-10 hours. Temperature raise: 0.5°C/hour. Look for seizures. Avoid fluid shifts. Careful vitals monitoring. After rewarming feeding is started gradually.

***Table 2:** Phases of therapeutic hypothermia*

MONITORING OF NEONATESDURING THERAPEUTICHYPOTHERMIA

As cooling is used more widely and has been newly introduced in neonatal units, continued surveillance of its use in clinical practice is mandatory. The initial management of infants with HIE following admission to the neonatal unit consists of standard neonatal intensive care measures, continuous core temperature monitoring using a rectal probe and initiation of therapeutic hypothermia. Monitoring of such infants is critical to the neurological outcome.

COOLING DEVICES

Various low technologies methods like passive cooling, ice gel pack, cooling fan, etc.; havebeen tried to achieve therapeutic hypothermia because of the high cost and unavailabilityof servo-controlled equipment. There have been concerns of overcooling, fluctuations intemperature, cold injury like subcutaneous fat necrosis, increased shivering and need ofmore nursing input.

While most western centers currently prefer systemic hypothermia delivered using servo-controlledmattresses, these devices are expensive. **Passive cooling**[by fans, ice/gel packs and phase-changingmaterials (PCMs)] is a very practical and inexpensive option, especially for transportingoutborn infants who may not arrive in an NICU within the 6-hour window for initiatinghypothermia. But some infants do not cool enough with passive cooling, while others mayovershoot the target temperature.

One of the limiting factors to provide therapeutic hypothermia in India is availability of cooling device.

Fully automated servo controlled Cooling devices are ideal for providing therapeutic hypothermia to newborn with asphyxia.

Affordability is the main issue. Low technology cooling devices like frozen gel packs and Phase change materials are effective, safe and an affordable alternative in intensive care settings.

The use of phase changing material (PCM)(MiraCradle™ by M/s VNGMedical Innovation System) **(Figure 2)**for cooling is increasingly popular in India because ofthe availability of a relatively inexpensive device. This has been studied as an alternative toservo-controlled cooling and appears to perform reasonably well, with one study reportingthat the target temperature was maintained during 96.2% of the cooling phase.

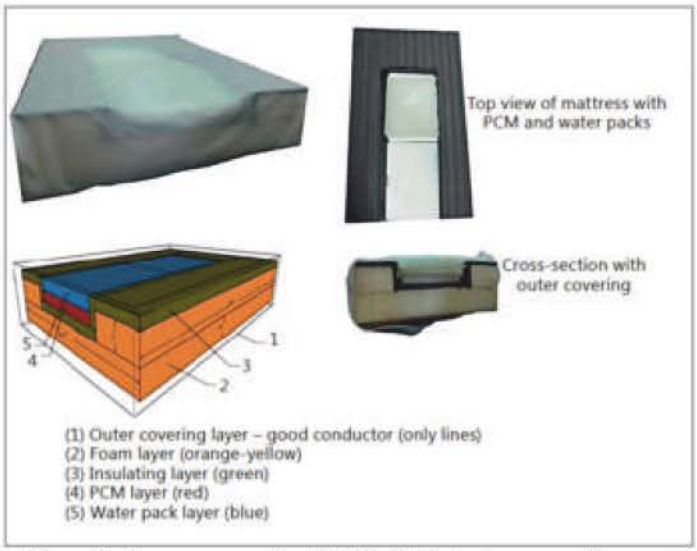


Figure 2. *Construction of the PCM bed. The bed consists of an outer covering made of nylon (1), a hollowed-out foam layer (2) lined with an insulating material like extruded polystyrene (3), PCM blocks kept in the hollowed-out area (4) and a water mattress above the PCM blocks and below the outer covering (5).*

NEO THERM™ An indigenous, servo-controlled, whole-body cooling system for birth asphyxia

Recently, a new low-cost, servo-controlledmattress - based device, **NEO THERM™** by the M/S VNG Medical Innovation System is introduced in the market**(Figures 1 &3).** It is an upgrade model of their earlier **MiraCradle™** unit with servo-controlled cooling and rewarming facility.Thisconsists of a mattress that is placed below the baby or can also be wrapped around baby'strunk. The device is fully automated andrequires no further input after initiation. The baby'stemperature is cooled to 33.5°C within 30 minutes. Thistemperature is maintained for 72 hours and a fullyautomated rewarming process starts. The rewarmingoccurs to 37°C at 0.5°C/hour (requiring around 12hours for rewarming). The monitor displays rectal andskin temperature. Default temperature settingson the machine can be altered according toindividual needs.

Figure 3 A & B.3(A) *The touch screen to feed desired value for cooling and re-warming. 3(B) The servo-controlled mattress to be placed underneath the neonate.*

DURATION OF COOLING

The duration of hypothermia in most trials was **72 hours.** One trial cooled infants for 48 hours and another for 48 to 72 hours depending on the neurological status of the infant. **Cooling at 33.5°C for 72 hours in term infants with moderate to severe HIE is now considered safe and beneficial,** and current evidence therefore suggests that cooling for a duration longer than 72hours is not beneficial.

DEPTH OF COOLING

Deeper cooling did notappear to be beneficial.There is currently no evidence to cool below the commonly used **target temperature of 33.5°C** (range of 33°C-34°C).

REWARMING

There is concern about decrease in systemic blood pressure during rewarming. Rebound seizures can occur during rewarming. Rewarming has also been reported toaffect the EEG background. However, it is not clear if another regime for rewarming will bebetter than the ones used in the RCTs. With current evidence, **it appears prudent to rewarm slowly, at a rate of no more than 0.5°C per hour for over 12 hours.**

COOLING PRETERM INFANTS

Most RCTs have been done in term and late preterm infants,with a gestational age of 35 weeks or higher. Most enrolled infants in thesetrials were born at term.Initial reports of cooling preterm infants indicate that caution is warranted. Trials are undergoing to assess safety and utility of cooling preterm infants of 33-35 weeks gestation. Until moreevidence is generated by this and other trials,

hypothermia should not be offered to infants below 35 weeks of gestation.

BOX 3. *The Characteristics of An Ideal Cooling Device*

It should induce cooling rapidly to the desired core temperature
It should maintain the core temperature tightly within the target range
It should allow re-warming in a slow and controlled manner
It should be easy to use
It should require minimal nursing input
It should not interfere with access to the baby
Environmental temperature should not affect cooling efficacy
Safety systems in case of accidental probe displacement

	Frozen gel pack	Phase changing material	Servo controlled device
Time taken to reach target temperature, minutes: median (IQR)	45 (10, 100)	90 (25, 150)	90 minutes (NICHD) 30 minutes (TOBY)
Temperature fluctuation during cooling phase, °C: mean (SD)	0.4	0.28	0.4 (TOBY) 0.5 (NICHD) (semi-automated)
Temperature readings outside the target range	9.8 %	3.8 %	
Subcutaneous Fat Necrosis	13 %	2.2 %	2.8 %
Laborious nursing input	More	Less	Least

Table 3: Comparison of Different Cooling Devices

MONITORING OF NEONATES DURING THERAPEUTIC HYPOTHERMIA

As cooling is used more widely and has been newly introduced in neonatal units, continued surveillance of its use in clinical practice is mandatory. The initial management of infants with HIE following admission to the neonatal unit consists of standard neonatal intensive care measures, continuous core temperature monitoring using a rectal probe and initiation of therapeutic hypothermia. Monitoring of such infants is critical to the neurological outcome.

Temperature monitoring

Both the core temperature and skin temperature are monitoredcontinuously. The core temperature is usually monitored by rectal oroesophageal probe. The rectal probe should be inserted 3-6 cm and secured to the thigh. The temperature is recorded every 15 minutes till a core temperature of 33.5°C is achieved and thereafter every hour till rewarming is completed. The core temperature should be maintained between 33.5°C to 34°C. The fluctuation of temperature during the maintenance phase should be very minimal as it can adversely affect the neurological outcome.

Cardiorespiratory care

Hypothermia is consistently associated with sinus bradycardia as itslows the atrialpacemaker and intracardiac conduction.The heart rate can be even lower than 100. Heart rate dropsby nearly 14 beats per one degree drop in temperature. HR up to 70 can be tolerated aslong as it is normal sinus rhythm and normal SpO2 and BP are observed**(Box 4).**Sinus bradycardia usually does not need intervention. Close monitoring of BP is very essential to identify shock since CRT will be not a reliable indicator ofhypo perfusion in babies receiving cooling therapy. All infants should be monitored closelywith invasive blood pressure monitoring (if possible) and treated with inotropes accordingly.

Mechanical ventilation

Ventilation may not be needed for all neonates during cooling, however, it is important to maintain normal pCO2 , pO2 , pH and respiratory effort. Decreasing body temperature lowers metabolic rate by about 5-8% per °C. Furthermore, partial pressure of blood gases and pH are also affected because of altered gas solubility during hypothermia. With each degree Celsius decrease in core temperature, pH increases by 0.015, pCO2 and pO2 decrease by 4% and 7% respectively**(Box 4).**Excessively low pCO during therapeutic hypothermia may result in altered cerebral blood flow auto regulation, and reduced cerebral perfusion, and may lower the seizure threshold.

CARDIO-RESPIRATORY MANAGEMENT

- Correct respiratory acidosis by manipulating ventilator support
- Start mechanical ventilation if repeated desaturations associated with seizures or incipient respiratory failure with rising oxygen requirements and increasing respiratory acidosis are observed.
- Avoid hypocapnia. Aim for pCO2 around 45 - 50 mm during cooling
- Maintain SaO2>92%to lessen risk of pulmonary hypertension
- Obtain arterial access to monitor blood pressure if mechanical ventilation is required
- Monitor regional perfusion using capillary refill scores and core-peripheral temperature gap as guides to peripheral blood distribution
- Aim for mean blood pressure (BP) > 40 mm Hg. A low BP requires assessment. Perform echocardiographic assessment (if available) of cardiac contractility and stroke volume to guide fluid/inotrope administration

BOX 4. Cardio-respiratory Monitoring Skin monitoring

Poor skin perfusion occurs during cooling. The skin has to be inspected periodically and the back to be inspected at least 12 hourly. The position has to be changed 6 to 12 hourly from flat to slightly tilted in the supine position. Cyanosis of the hands and feet is common and usually transient.

Fluid balance

Disturbances in electrolytes and glucose homeostasis are common in infants with HIE,including those receiving therapeutic hypothermia. Fluid balance is essential in coolingneonates as the metabolic rate is low, and they may not need large volume of fluids**(Box 5).**

Fluid boluses should be avoidedas it can lead to exacerbation of oedema which is due to capillary leak. The cooled babiesmay need more volume during rewarming phase due to redistribution of fluid into the tissuesand increased diuresis.It is recommended that serum electrolytes and plasma glucose should be kept within thenormal range during hypothermia treatment. Hypocalcemia, hypomagnesemia, andhypoglycemia are common in asphyxiated newborn infants.

FLUID BALANCE

- Hypoglycemia can be a serious complicating factor in HIE. Monitor plasma glucose closely (4 hourly) and adjust glucose intake accordingly.
- Oliguria/anuria is common following HIE. Monitor urinary output and aim for urine output 1ml/kg/hour. Observe for bladder retention. Urinary catheterization may be useful.
- Daily weight monitoring should be carried out.
- Initial intravenous fluid requirements are approximately 40 ml/kg/day 10% Dextrose solution. Monitor blood electrolyte levels 8 hourly for first 24–48 hours.
- Grade up fluid depending on the weight gain and presence of oedema, as these babies tend to retain lot of fluid.
- Consider electrolyte additives or parenteral nutrition after 24 - 48 hours when electrolytes/ renal function stable.
- Give maintenance potassium supplementation if renal function is adequate (2 mmol/ kg/day). Avoid potassium supplementation during cooling, as hyperkalemia may occur on rewarming.

BOX 5. Fluid Balance Monitoring

COMPLICATIONS OF THERAPEUTIC HYPOTHERMIA

Though therapeutic hypothermia is generally safe, it is important to cool neonates using strict protocols and often at centers with considerable experience with cooling.

Excessive cooling can cause cardiovascular instability and re-emergenceof seizures. Some of the problems associated with coldinjury syndrome include increased mortality; development ofsclerema, skin erythema, and acrocyanosis; pulmonary hemorrhage;renal failure; increased blood viscosity and DIC; hypoglycemia; acid base and electrolyte disturbances; increased risk ofinfections (secondary to decreasedleukocytemobility and phagocytosis); significant cardiovasculardisturbances including sudden cardiac arrest and ventriculartachyarrhythmia.

Sinus bradycardia and thrombocytopenia havebeen reported to be the only significant adverse effects ofhypothermia **(Box6).**

- Bradycardia (25%) and other cardiac arrhythmia (1%)
- Thrombocytopenia (13% -25%)
- Hypoglycemia (10%)
- Hypocalcemia (6%)
- Shock (8%)
- Sclerema and Subcutaneous fat necrosis (6%)
- Acid-base and electrolyte disturbances
- DIC (5%)
- Pulmonary hemorrhage
- Increased blood viscosity- hemoconcentration

BOX 6 . Complications of Therapeutic Hypothermia

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(Source: Manual on Therapeutic Hypothermia For Perinatal Asphyxia; National Neonatology Forum, An NNf Publication)

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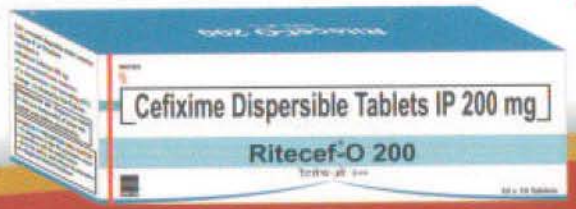

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* Kundu R et al., Indian Pediatr. 2006; 43 (10):884-7

IN FOCUS

'C-Reactive Protein in Late-Onset Neonatal Sepsis'

Assessment of C-Reactive Protein Diagnostic Test Accuracy for Late-Onset Infection in Newborn Infants: A Systematic Review and Meta-analysis

Key Points

Question Is serum C-reactive protein level sufficiently accurate to aid the diagnosis of late-onset infection in newborn infants?

Findings In this systematic review and meta-analysis of 22 cohort studies (2255 infants) comparing the diagnostic test accuracy of serum C-reactive protein with microbiological culture, median specificity was 0.74 and pooled sensitivity was 0.62. Assuming a orwould miss 152 cases of infection and wrongly diagnose 156 cases.

Meaning The findings suggest that serum C-reactive protein level is not sufficiently accurate to aid diagnosis or to inform treatment decisions in infants with suspected late-onset infection.

Abstract

Importance Rapid and accurate diagnosis of late-onset infection in newborn infants could inform treatment decisions and avoid unnecessary administration of antibiotics.

Objective To compare the accuracy of serum C-reactive protein (CRP) with that of microbiological blood culture for diagnosing late-onset infection in newborns.

Study Selection Cohort and cross-sectional studies were included that compared the accuracy of serum CRP levels with microbiological culture results to diagnose late-onset (>72 hours after birth) infection in newborns (any gestational age) hospitalized after birth. Two reviewers assessed study eligibility. Among 10□394 records, 148 studies were assessed as full texts.

Main Outcomes and Measures The primary meta-analysis outcome was diagnostic test accuracy of serum CRP level taken at initial investigation of an infant with suspected late-onset infection. The median specificity (proportion of true-negative results) and calculated pooled sensitivity (proportion of true-positive results) were determined by generating hierarchical summary receiver characteristic operating curves.

Results In total, 22 studies with 2255 infants were included (sample size range, 11-590 infants). Participants in most studies were preterm (<37 weeks) or very low-birth weight (<1500 g) infants. Two studies additionally enrolled infants born at term. Most studies (14 of 16) used a prespecified CRP level cutoff for a "positive" index test (5-10 mg/L) and the culture of a pathogenic microorganism from blood as the reference standard. Risk of bias was low with independent assessment of index and reference tests. At median specificity (0.74), pooled sensitivity was 0.62 (95% CI, 0.50-0.72). Adding serum CRP level to the assessment of an infant with a 40% pretest probability of late-onset infection (the median for the included studies) generated posttest probabilities of 26% for a negative test result and 61% for a positive test result.

Conclusions and Relevance The findings suggest that determination of serum CRP level at initial evaluation of an infant with suspected late-onset infection is unlikely to aid early diagnosis or to select infants to undergo further investigation or treatment with antimicrobial therapy or other interventions.

(Jennifer Valeska Elli Brown, et al. JAMA Pediatr. Published online February 3, 2020. doi:10.1001/jamapediatrics. 2019.5669)

C-Reactive Protein Testing in Late-Onset Neonatal Sepsis: Hazardous Waste!

Imagine for a moment you are counseling a patient with a suspicious mass and symptoms that are concerning but nonspecific. Although there are several possible diagnoses, one hangs unspoken between you and the patient—a diagnosis that carries significant morbidity and mortality. You propose an immediate biopsy. After all, a tissue diagnosis is the criterion standard, and this matter is urgent. The patient agrees, and as the patient begins to stand, you raise a hand and mention another test you would like to order. The patient is curious. "What are the benefits of this test?" You explain that the test involves sending a portion of the biopsied tissue to a separate part of the laboratory, where the pathology department will look for other markers of disease. Of course, the patient nods; that makes sense. "If this extra test result is negative, I will be okay, right?" "No," you answer, "a negative test result does not mean the biopsy result will be negative."

The patient frowns. "Well, is it a bad sign if the test result is positive?" "Not necessarily," you explain. "Many things can make the other test results abnormal, so we'll still have to wait on the biopsy results. The biopsy is the key." The patient sits down again, looking confused. "If the biopsy is so important, why are we wasting tissue on this other test?" "Well," you glance helplessly toward the window then look back to your frowning patient. "It's just what we've always done in these cases."

This exchange is hypothetical, but in the case of C-reactive protein (CRP) for neonatal sepsis, it is all too real. The nonspecific signs of late-onset infection in infants, particularly those born preterm, combined with the high risk of morbidity and mortality have underscored the need for accurate diagnosis of neonatal sepsis.1 Culture of blood and other sterile sites is the criterion standard for neonatal sepsis. However, myriad ancillary laboratory tests have been suggested as potential biomarkers for neonatal sepsis; these include CRP, complete blood counts with differential, procalcitonin, a variety of interleukins, and presepsin.2 The value of those tests in the clinical management of suspected sepsis is questionable. In this issue of *JAMA Pediatrics*, Brown et al3 report their systematic review and meta-analysis of the sensitivity, specificity, and test accuracy of CRP for late-onset neonatal sepsis. They analyzed 22 studies including 2255 infants, the majority being 32 weeks or less gestational age or 1500 g or less birth weight. The median specificity of CRP was 0.74 and median sensitivity was 0.62. Assuming a cohort of 1000 preterm infants with a 20% prevalence rate of late-onset sepsis, this means that 76 cases of infection would be missed, and 208 infants would be incorrectly diagnosed as having sepsis—more than the number of infants with sepsis (200).

The poor sensitivity and specificity of CRP as a biomarker renders the test essentially useless. The poor sensitivity means that CRP levels cannot be used to prevent antimicrobial treatment; infants with suspected late-onset sepsis require empirical antibiotics while their cultures are incubating. The sensitivity of the CRP test may be lowest among infants with lower gestational age and birth weight, meaning that CRP performs the worst among infants with the highest risk for sepsis.4 In addition, the poor specificity means that CRP should not be used to make decisions regarding antibiotic duration when cultures are sterile because most abnormal CRP results are false-positives. The positive predictive value of CRP becomes truly abysmal as the prevalence rate of late-onset sepsis declines. For example, the prevalence rate of sepsis decreases to less than 5% by 30 weeks' gestation, decreasing the positive predictive value to below 10%.5 For infants with birth weight higher than 1500 g, the positive predictive value is negligible. Unfortunately, treatment of "culture-negative" sepsis is both common and often driven by falsely positive ancillary laboratory testing, such as CRP.6

Proponents of CRP for the diagnosis of neonatal sepsis point to its excellent negative predictive value as a redeeming feature. However, the negative predictive value is driven more by the relatively low prevalence of late-onset sepsis than by the test characteristics of CRP. For example, by applying CRP level results to the diagnosis of late-onset sepsis in a large cohort of preterm infants 23 to 33 weeks' gestation admitted to the Neonatal Research Network neonatal intensive care units,5 we calculated a negative predictive value of 95.5% (Table). However, when a fair coin pulled from a desk drawer is used on the same cohort, "tails"—arbitrarily chosen as a negative screening test—performs almost as well (91.5%). In any case, the poor sensitivity of CRP means that physicians are forced to treat the infant empirically regardless of the test result so as not to miss the meaningful number of septic infants with falsely negative CRPs. The negative predictive value of CRP is not clinically useful.

Table.

Table. Sensitivity, Specificity, and Positive and Negative Predictive Value of C-Reactive Protein and a Fair Coin for the Diagnosis of Late-Onset Sepsis in 11 367 Preterm Infants (23-33 Weeks' Gestation)[a]

Test	Late-Onset Sepsis	No Sepsis	PPV or NPV, %
CRP	Sensitivity, 62%	Specificity, 74%	
Positive	596	2705	PPV, 18.1
Negative	366	7700	NPV, 95.5
Coin	Sensitivity, 50%	Specificity, 50%	
Heads	481	5202.5	PPV, 10.3
Tails	481	5202.5	NPV, 91.5

Abbreviations: CRP, C-reactive protein; NPV, negative predictive value; PPV, positive predictive value.

The unacceptable number of false-positive and false-negative results means that trusting CRP results is dangerous. The systematic use of CRP in the diagnosis of late-onset sepsis is not only hazardous, it is wasteful. A better use for the blood required to conduct the test would be to inoculate it into culture media. The criterion standard for late-onset sepsis is blood culture, and the accuracy of blood culture is driven directly by the volume of blood obtained for culture.7,8 The challenges of obtaining sufficient volume for culture in preterm infants have been well described.9 Why are we devoting between 0.2 and 0.5 mL of precious blood volume to CRP and its poor test characteristics, instead of optimizing our criterion standard? The potential harm from the systematic use of CRP—delay in empirical therapy, overtreatment of uninfected infants, and decreased sensitivity of blood culture because of the redirected blood volume—greatly outweighs the negligible benefit to clinical management. This applies not only to CRP but to complete blood counts with differential, procalcitonin, and other biomarkers.10-12

Neonatal sepsis remains a question in search of better answers, and we applaud the clinical investigators working toward a rapid, accurate assay that precludes the need for antibiotic exposure in low-risk infants. Such an assay would significantly advance our ability to avoid unnecessary antimicrobial therapy while still ensuring that no infant with sepsis is missed. However, as Brown et al3 so eloquently illustrate in their systematic review, CRP testing is far from being such an assay. Instead, CRP is an insensitive, nonspecific test that steals blood volume from the criterion standard culture. The continued use of CRP in the diagnosis of late-onset neonatal sepsis should be considered hazardous waste.

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(Joseph B. Cantey, Charlene R. Bultmann, In JAMA Pediatr. Published online February 3, 2020. doi:10.1001/jamapediatrics.2019.5684)

SNIPPETS

"Clinic Practice Guidelines: Pediatric GERD"

Dr Piyush Gupta

Diagnosis

- Avoid barium contrast studies, esophago-gastro-duodenoscopy, scintigraphy, and manometry to diagnose GERD in both infants and children
- The diagnosis is mainly by a careful history, physical examination, ruling out other conditions in presence of 'red flag' signs; pH-metry and pH impedance studies may be required in few cases to correlate symptoms with episodes of acid reflux events.
- A 4- to 8-week trial of PPIs may be considered as a diagnostic test for typical GERD symptoms in children, but not in infants or in children with extra-gastrointestinal symptoms

Treatment

Infants

- Modify feeding volumes and frequency to avoid overfeeding and use thickened feeds for treating visible regurgitation/vomiting.
- Continue breastfeeding; consider elimination of animal milk protein in mothers in case of non-improvement
- A 2- to 4-week trial of a formula with extensively hydrolyzed protein (or amino-based formula) in formula-fed infants suspected of having GERD after optimal nonpharmacological treatment described above has failed.
- Avoid positional therapy (ie, head elevation, lateral and prone positioning) in sleeping infants.
- Consider 4-8 week trial of acid suppression with H2 antagonists or PPI, then wean if symptoms improved

Children

- Avoid H2RA or PPIs in children with extra-esophageal symptoms (eg, respiratory) except in presence of typical GERD symptoms
- Consider head elevation or left lateral position to treat GERD symptoms.
- Consider 4-8 week trial of acid suppression with H2 antagonists or PPI, then wean if symptoms improved

(Source: 2018 Pediatric Gastroesophageal Reflux Clinical Practice Guidelines: Joint Recommendations of the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition (NASPGHAN) and the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN). JAMA Pediatr. 2019;173(5):485-486. doi:10.1001/jamapediatrics.2019.0170)

Guidelines for Maintenance IV Fluids

1. Maintenance intravenous fluids are needed (if sufficient enteral fluids cannot be provided due to illness/other reasons) to preserve the extracellular volume, prevent depletion of intravascular volume, and minimize the risk of hypo/hypernatremia,

2. The osmolarity of plasma is 308 mOsm/L. Osmolarity calculations for IV fluids usually exclude the dextrose in the solution because dextrose is rapidly metabolized in solution.

3. Hypotonic fluids for maintenance therapy result in a high incidence of hyponatremia. Hypotonic fluids include N/5 (0.2%) NaCl with 5% dextrose (Osmolarity 78 mOsm/L), and N/2 (0.45%) NaCl with 5% dextrose (Osmolarity 154 mOsm/L).

4. Patients between 28 days to 18 years of life should receive isotonic fluid for maintenance fluid therapy with appropriate potassium chloride and dextrose, to reduce the risk of developing hyponatremia. NaCl 0.9 % with 5% dextrose (308 mOsm/L) is an isotonic IV fluid. Ringer lactate with 5% dextrose (273 mOsm/L) is near isotonic.

5. These guidelines applies to children in surgical (postoperative) and medical acute care settings, including critical care and the general inpatient ward. Patients with neurosurgical disorders, congenital or acquired cardiac disease, hepatic disease, cancer, renal dysfunction, diabetes insipidus, voluminous watery diarrhea, or severe burns; neonates who are younger than 28 days old or in the NICU; and adolescents older than 18 years old are excluded.

(Reference: Clinical Practice Guideline: Maintenance Intravenous Fluids in Children. American Academy of Pediatrics. Pediatrics 2018;142:e20183083. To read full text, click: http://pediatrics.aappublications.org/content/pediatrics/early/2018/11/21/peds.2018-3083.full.pdf)

Broad-Spectrum or Narrow Spectrum Antibiotics for Pediatric Acute Bacterial Respiratory Tract Infections

Antibiotics are the most frequently prescribed medications in children, most commonly for otitis media, sinusitis, or pharyngitis. Broad-spectrum

antibiotics such as amoxicillin/clavulanate, cephalosporins, and macrolides are increasingly used based on theoretical benefits against emerging resistant pathogens.

Findings

An investigation in USA examined 1 retrospective (n□=□30□159) and 1 prospective (n□=□2472) cohort, having patients with otitis media, sinusitis, or pharyngitis (aged 6 months to 12 years).

In the retrospective cohort, 14% were prescribed broad-spectrum antibiotics. Analysis found no difference in the primary outcome of treatment failure at 14 days for broad- vs narrow-spectrum antibiotics (3.4% vs 3.1%; risk difference, 0.3%; 95% CI, −0.4% to 0.9%).

The prospective cohort found that patient-centered outcomes were not improved for those receiving broad-spectrum antibiotics (no difference in missed school or daycare; slightly worse quality of life) and that adverse events were higher, whether reported by clinicians (3.7% broad- vs 2.7% narrow-spectrum) or patients (35.6% broad- vs 25.1% narrow-spectrum).

Implications

1. Narrow-spectrum antibiotics (eg, penicillin, amoxicillin) should be the mainstays for antibiotic treatment of acute otitis media, acute sinusitis, and group A streptococcal pharyngitis.

2. Broad-spectrum antibiotics do not confer additional treatment benefit and may be associated with more adverse events.

*Source:*https://jamanetwork.com/journals/jamapediatrics/fullarticle/2725043?guestAccessKey=01243e62-1ff2-4e99-bcb1-7df6d82e714c&utm_source=silverchair&utm_medium=email&utm_campaign=article_alert-jamapediatrics&utm_term=mostread&utm_content=olf-widget_02252019

Kawasaki Disease: 10 Key Points

(American Heart Association)

1. KD affects predominantly, but not exclusively, young children (age <5 years).

2. Classic or Complete KD is diagnosed in the presence of fever for at least 5 d together with at least 4 of the 5 of following: (i) erythema and cracking of lips, strawberry tongue, and/or erythema of oral and pharyngeal mucosa; (ii) bilateral bulbar conjunctival injection without exudate; (iii) maculopapular, diffuse erythroderma, or erythema multiforme-like rash; (iv) erythema and edema of the hands and feet and/or periungual desquamation; (v) cervical lymphadenopathy (=1.5 cm diameter), usually unilateral.

3. The diagnosis of incomplete (or atypical) KD should be considered in prolonged unexplained fever, <4 of the above criteria, and compatible laboratory or echocardiographic findings.

4. Echocardiography should be performed when the diagnosis of KD is considered, but unavailability or technical limitations should not delay treatment

5. Patients with complete KD criteria and those who meet the algorithm criteria for incomplete KD should be treated with high-dose IVIG (2 g/kg given as a single intravenous infusion) within 10 days of illness onset but as soon as possible after diagnosis

6. Administration of moderate- (30–50 mg/kg/d) to high-dose (80–100 mg/kg/d) Aspirin is reasonable until the patient is afebrile, although there is no evidence that it reduces coronary artery aneurysms

7. Administration of a longer course of corticosteroids (eg, tapering over 2–3 weeks), together with IVIG 2 g/kg and ASA, may be considered for treatment of high-risk patients with acute KD, when such high risk can be identified in patients before initiation of treatment

8. Administer IVIG to children presenting after the 10th day of illness (ie, in whom the diagnosis was missed earlier) if they have either persistent fever without other explanation or coronary artery abnormalities together with ongoing systemic inflammation, as manifested by elevation of ESR or CRP (CRP>3.0 mg/dL)

9. Single-dose pulse methylprednisolone should not be administered with IVIG as routine primary therapy for patients with KD

10. For uncomplicated patients, echocardiography should be repeated both within 1 to 2 weeks and 4 to 6 weeks after treatment; more frequent (twice a week) evaluation is required for those with initial coronary artery abnormalities. To read full Guidelines: https://www.ahajournals.org/doi/full/10.1161/cir.0000000000000484

*(**Compiled by:** Dr Piyush Gupta,MD, FAMS, Professor of Pediatrics and In-charge, Medical Education Unit, University College of Medical Sciences, Delhi.)*


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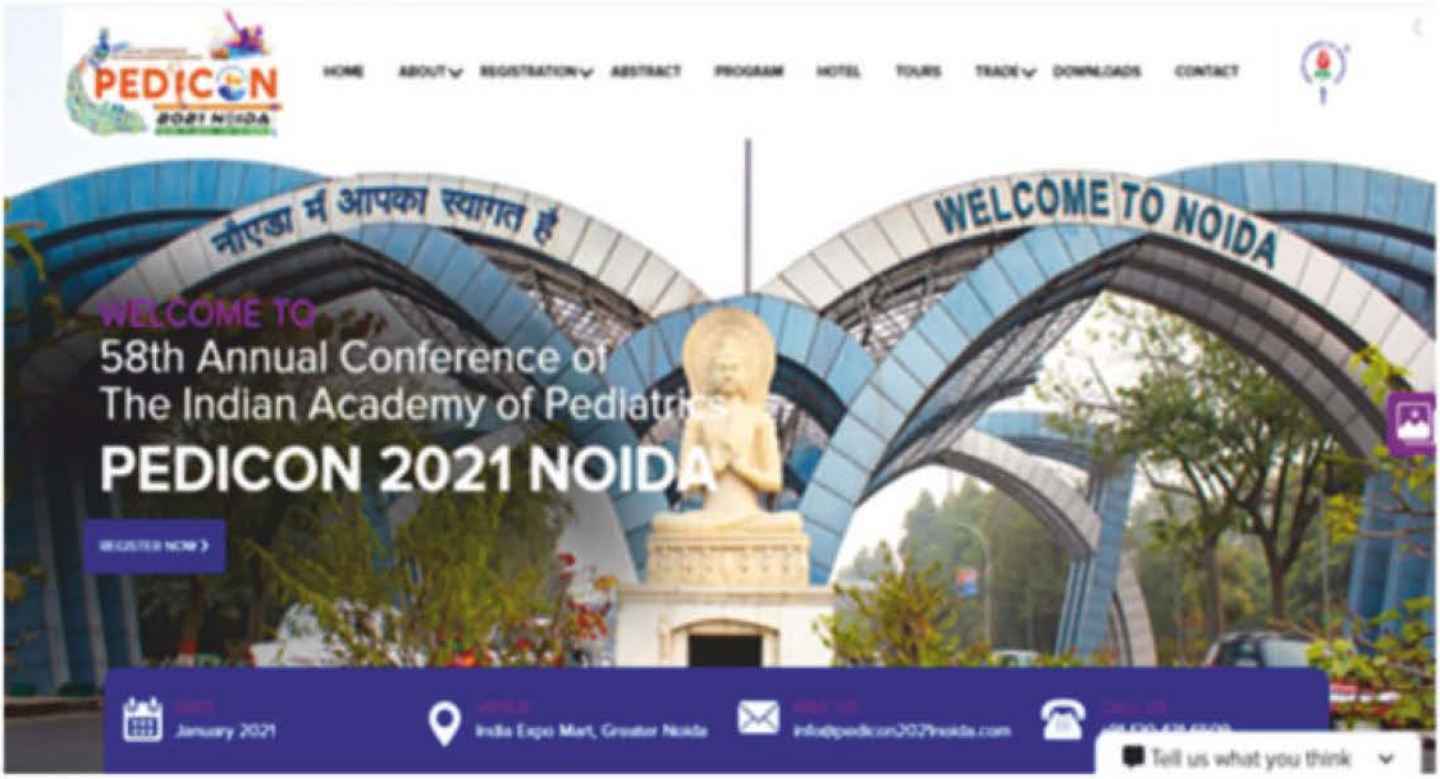
All the best, NOIDA!

January 2021 is just a year away. The countdown for the National Pediconat Noida has begun. Remain assured that the chilly winds of North India at that time will be reciprocated in equal measure with the warmth of the hosts in Noida.

Incidentally, this is the fourth Pedicon to be held in the state of Uttar Pradesh. The first was in 1972 in Agra, the second in 1974 in Kanpur and the third in 1989 in Agra again. So, it is nearly after three decades that UP is getting an opportunity to welcome Pediatricians from all over the country.

The first two Pedicons held in Uttar Pradesh i.e. 1972 (Agra) and 1974 (Kanpur) were held in the medical college campuses. Even the delegates stayed in hostels and wards of the College/ Hospitals, but the 1989 conference in Agra was held in a five star hotel. Only one hotel was sufficient to accommodate the delegates and also hold all the scientific sessions.

There were no computers in that era. Even the typewriters were manual. The organizers had to



maintain large bulky registers for registration, accommodation etc. The correspondence was mostly by postal mail.The lunches and dinners were laid down in the grounds/ lawns of the colleges/ hotel. Banquet was different from the dinners. It was more formal with seating arrangements and toasts were raised in the customary manner. There was no loud music or dances in the dinners. One or two evenings had a cultural program which was mostly by local or regional artists. The pharmas organized only exhibition stalls and there were no amusement parks and playgrounds. Few stalls were arranged for shopping of the local products especially momentos, artisan products and sweets etc.

Things have changed now. The Pedicons are longer and much more elaborate. The sessions need to be spread out in different locations. Therefore, herculean task awaits the organizing team. But, we are sure that they will be able to deliver their best. Noida is a new, modern city with all the infrastructure needed for a successful scientific meet. Delhi, Vrindavan, Agra are additional tourist attractions.

Wishing all good luck to the organizers and the UP State Branch of IAP.

Visit http://www.pedicon2021noida.com/index.php *for more details.*

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"Long-Term Risk for Chronic Kidney Disease After Premature Birth"

Prematurity and extreme prematurity were associated with doubled and tripled risks, respectively, for CKD from childhood into mid-adulthood.

Because much of nephrogenesis occurs late in gestation, what is the impact of premature birth upon renal function later in life?

To address this question, researchers used Swedish birth and health registries to examine the risk for chronic kidney disease (CKD) in childhood through mid-adulthood among 4.2 million residents by birth term status: extremely preterm (22–27 weeks, very preterm (28–33 weeks), late preterm (34–36 weeks), early term (37–38 weeks), term (39–41 weeks), and post-term (≥42 weeks). Results were as follows:

CKD developed in 4305 individuals (0.1%) during 87 million person-years of follow-up. Incidence rates of CKD were 9.2 per 100,000 person-years for all preterm births combined, 5.9 for early term, and 4.5 for term births. Individuals born extremely preterm had a threefold greater risk for developing CKD compared with those born at term. Among individuals with neonatal acute kidney injury, 24% developed CKD.

Preterm birth was associated with a fivefold greater risk for developing CKD before age 10 years compared with term birth. The presence of congenital anomalies was associated with a 20-fold greater incidence of CKD. Other risk factors were male sex, maternal obesity, and maternal preeclampsia.

Among siblings, the association between prematurity and risk for CKD was maintained, suggesting that the association was not genetically or environmentally determined.

Comment

Premature birth carries a significant risk for later kidney disease. When we care for children who were born premature, we should monitor the urinalysis, measure blood pressure, and periodically check the serum creatinine. Proteinuria and hypertension are especially important early signs of kidney injury.

(F. Bruder Stapleton, MD reviewing Crump C et al. BMJ 2019 May 1)

"Minimum Duration of Antibiotic Treatment Based on Blood Culture in Rule Out Neonatal Sepsis"

Neonatologists usually wait 48 hours for blood culture results before deciding to discontinue antibiotics. The objective of the study was to analyze time to positive blood culture in rule out sepsis and estimate the minimum duration of antibiotics.

Methods: Retrospective analysis of blood culture at the Neonatal Intensive Care Unit, McMaster Children's Hospital (January 2004 to December 2013) using BacT/Alert® 3D microbial system was conducted. We calculated average time taken for blood culture samples to emit a positive signal and compared it between Gram-positive and Gram-negative organisms. Kaplan-Meier curves for time to detect positive culture were generated. A Cox proportional hazard regression model with the outcome variable "time to detect positive blood culture" and predictor variables "early-onset sepsis (EOS) versus late-onset sepsis (LOS)", "Gram-positive versus Gram-negative" and "definite versus possible pathogen versus contaminant" was generated.

Results: Of 7,480 blood cultures performed in 9,254 neonates, 885 samples grew microorganisms. 845 culture reports from 627 neonates were analyzed. Definite or opportunistic pathogens caused 815 (96%) infections (54 EOS and 791 LOS) and the rest were contaminants. Gram-negative organisms grew significantly faster than Gram-positive ($P < 0.001$). Cultures from EOS were positive significantly earlier than LOS ($P = 0.032$). Gram-negative status was an independent predictor of early detection of a positive culture (hazard ratio 3.5 [95% CI, 2.7–4.5] $P < 0.001$).

Conclusion: The probability of positive blood culture beyond 24 hours for a Gram-negative organism is small. Empiric antimicrobial treatment can be reduced after 24 hours to target only Gram-positive organisms in LOS and can be stopped in EOS unless clinical or laboratory parameters strongly suggest sepsis.

(Durrani UR, et al In The Pediatr Infect Dis J 2019; 38: 528-532)

"Platelet Transfusion for PDA Closure in Preterm Infants: A Randomized Controlled Trial"

Thrombocytopenia is associated with late closure of patent ductus arteriosus (PDA). There are few studies evaluating platelet transfusions to treat PDA. We compared liberal platelet-transfusion criteria (to maintain a platelet count >100□000 per μL) versus standard criteria achieve earlier PDA closure among thrombocytopenic preterm neonates (<35 weeks' gestation) with hemodynamically significant PDA (hs-PDA) presenting within the first 2 weeks of life.

Methods: Thrombocytopenic (<100□000 per μL) preterm neonates with hs-PDA were enrolled and randomly allocated to the liberal and standard transfusion groups: 22 in each arm. They underwent echocardiography daily until closure of PDA, completion of 120 hours follow-up, or death. All subjects received standard cotreatment with nonsteroidal antiinflammatory drugs. Primary outcome of time to PDA closure was compared by survival analysis. Multivariate Cox proportional hazard regression was performed with randomization group, baseline platelet count, gestational age, and age at enrollment as predictor variables.

Results: Median time to PDA closure was 72 (95% confidence interval [CI] 55.9–88.1) versus 72 (95% CI 45.5–98.4) hours in the liberal versus restrictive transfusion groups, respectively (unadjusted hazard ratio 0.88 [95% CI 0.4–1.9]; P = .697). Despite adjusting for potential confounders, there was no significant difference in time to PDA closure. In the liberal transfusion group, 41% of infants had any grade of intraventricular hemorrhage compared with 4.5% in the restrictive group (P = .009).

Conclusions: Attempting to maintain a platelet count >100□000 per μL by liberally transfusing platelets in preterm thrombocytopenic neonates with hs-PDA does not hasten PDA closure.

(Kumar J, et al. Pediatrics 2019, 143 (5) e20182565; DOI: https://doi.org/10.1542/peds.2018-2565)

"Preterm, full-term infants have similar immunity to viruses"

Bruce Thiel

Preterm infants exhibited similar repertoires of maternal immunoglobulin G as full-term infants, which can protect against viruses such as respiratory syncytial virus, according to a study published in *Nature Medicine*.

"We need to reconsider our ideas that preterm children are more susceptible to infectious diseases due to a lack of maternal antibodies," PetterBrodin, MD, PhD, associate professor in the Science for Life Laboratory and the department of women's and children's health at the Karolinska Institutet, told *Infectious Diseases in Children*.

Brodin and colleagues wrote that newborn infants cannot produce immunoglobulin G (IgG) antibodies until 15 weeks after birth, and during that time, the infants rely on passive immunity from maternal IgG.

"The concentration of IgG increases during the third trimester of gestation, and children delivered extremely preterm are believed to lack this passive immunity," the researchers wrote.

They studied 78 mother and child pairs, which included 32 babies who were very premature (born before week 30) and 46 full-term babies. They measured antibodies against 93,904 epitopes from 206 viruses in the mother-child dyads.

They wrote that the extremely preterm children received "comparable repertoires of IgG" as term children, but the absolute concentrations were lower, which related to a shorter half-life. Neutralization of RSV also was comparable until 3 months of age.

"I hope this makes us question some preconceived ideas about the neonate immune system and infection sensitivity, so that we can take even better care of newborns," Brodin said in a press release. "Premature babies can be especially sensitive to infection, but that is not because they lack maternal antibodies. We should concentrate more on other possible causes, maybe like their having underdeveloped lung function or weaker skin barriers."

Brodin told *Infectious Diseases in Children* that the findings show what epitopes are targeted by maternal antibodies, "which will have important implications for vaccine development."

– by Bruce Thiel(Pou C, et al.NatMed.2019;doi:10.1038/s41591-019-0392-8.)

WEB-WATCH

"How Long Should We Treat the Initial Episode of Childhood Nephrotic Syndrome?"

Prednisolone therapy regimens lasting 8 weeks or 16 weeks showed no significant differences in time to relapse, number of relapses, or development of steroid unresponsiveness.

Although 90% of children with idiopathic nephrotic syndrome respond to prednisolone, the length of treatment for the initial episode has remained a matter of debate. These researchers conducted a controlled, double-blind, randomized, multicenter trial in the U.K. to compare the clinical response and stability of remission after either 8 or 16 weeks of prednisolone in 223 children with an initial episode of nephrotic syndrome (age range, 1–14 years; mean age, 4.9 years).

Both treatment regimens started with 60 mg/m2 daily for 4 weeks (to verify steroid sensitivity). Then, the shorter regimen provided 40 mg/m2 on alternate days for 4 weeks, followed by placebo, whereas the extended treatment involved 60 mg/m2 on alternate days with doses tapering by 10 mg/m2 every 2 weeks. Of the study participants, 80% had a relapse during 24 months of follow-up. The two treatment protocols showed no significant difference in the time to relapse (medians: 16-week protocol, 139 days; 8-week protocol, 87 days). The regimens also showed no statistical differences in adverse events, the number of relapses, or the number of children who developed frequently relapsing or prednisolone-resistant nephrotic syndrome. Overall, the 16-week plan was slightly more cost-effective and provided a small improvement in quality of life.

Comment

This study shows that extending prednisolone therapy to provide a tapering period does not improve outcomes in the initial episode of nephrotic syndrome. I had previously changed from an 8-week protocol to a 16-week one. Now I will return to the 8-week regimen.

Citation(s): *Webb NJA et al. Long term tapering versus standard prednisolone treatment for first episode of childhood nephrotic syndrome: Phase III randomised controlled trial and economic evaluation. BMJ 2019 May 23; 365:l1800. (https://doi.org/10.1136/bmj.l1800)*

"In Pediatric Status Epilepticus, Levetiracetam is not Superior to Phenytoin as a Second-Line Therapy"

While either agent is acceptable, side effects and ease of administration may influence treatment choice.

Most seizures stop without intervention and do not progress to status epilepticus, and most cases of status epilepticus resolve with one or two adequate doses of benzodiazepines. Although many medication options exist, there is little evidence to guide the choice of a second-line agent when benzodiazepines fail. Two open-label multicenter randomized trials compared the efficacy and safety of phenytoin (20 mg/kg infused over 20 minutes) versus levetiracetam (40 mg/kg infused over 5 minutes) for the treatment of pediatric status epilepticus refractory to two doses of benzodiazepines.

The ConSEPT trial enrolled 233 children aged 3 months to 16 years in Australia and New Zealand who were not taking either study medication at baseline. Convulsions stopped within 5 minutes of completion of treatment in 60% of children treated with phenytoin and 50% treated with levetiracetam (not statistically significant). Two hours after the start of infusion roughly half the children in both groups remained seizure-free without additional medications.

The EcLiPSE trial enrolled 286 children aged 6 months to 18 years in the United Kingdom regardless of the medications they were taking at home. Levetiracetam and phenytoin terminated convulsions in 70% and 64% of children, respectively (not statistically significant).

In both trials, the median time to seizure cessation was 17 to 33 minutes after the start of drug infusion and did not differ significantly between treatment groups. Drug safety profiles were also similar.

Comment

Aggressive benzodiazepine dosing is essential to treating status epilepticus, and it is unclear if dosing in either study meets current U.S. guidelines (Proposed Algorithm for Convulsive Status Epilepticus; Neurocrit

Care 2012; 17:3). However, these results demonstrate that levetiracetam is not superior to phenytoin as a second-line treatment. Levetiracetam does not share phenytoin's cardiovascular risks if infused very rapidly, which may influence the choice between the two. Because I don't commonly use phenytoin, my decision awaits results from future trials.

(Jason T. McMullan, MD, MS, FAEMS reviewing Dalziel SR et al. Lancet 2019 Apr 17 Lyttle MD et al. Lancet 2019 Apr 17 Silbergleit R and Elm JJ. Lancet 2019 Apr 17).

"Seizure Rescue Medication Use among Pediatric Epilepsy Providers"

Objective

To assess how pediatric neurologists prescribe home seizure rescue medications to treat acute prolonged seizures and clusters of seizures in children.

Study design

A brief, email survey was sent to the members of the Pediatric Epilepsy Research Consortium assessing seizure rescue medication prescribing practices for patients of different age groups, cognitive abilities, and seizure type. Survey responses were anonymous.

Table I. "Standard" pediatric doses of rescue medications

Medications	Dose
Diazepam rectal	0.5 mg/kg for 2-5 years of age, 0.3 mg/kg for 6-11 years of age, 0.2 mg/kg for ≥12 years of age, max 20 mg
Diazepam buccal	0.5 mg/kg, nearest 2.5 mg increment, max 10 mg
Clonazepam ODT	0.01-0.03 mg/kg, max 2 mg
Midazolam IN	0.2 mg/kg, max 10 mg
Midazolam buccal	2.5 mg for 6 mo-1 year of age, 5 mg for 1-5 years of age, 7.5 mg for 5-10 years of age, 10 mg for ≥10 years of age
Lorazepam buccal	0.1 mg/kg, max 4 mg

Results

Thirty-six respondents (of 76 surveyed; 47% response rate) completed the survey. Rectal diazepam was the most commonly chosen rescue medication for a prolonged convulsive seizure in a severely developmentally delayed 16-year-old (44%) and typical and delayed 7-year-old (44% and 61%, respectively), 3-year-old (78% and 86%, respectively), and 9-month-old (83%) patients. Most responders (69%) indicated that developmentally typical 16-year-olds would be prescribed intranasal midazolam. For clusters of seizures, clonazepam orally disintegrating tablets were the most frequent first-line option in all age groups, except developmentally delayed 3-yearold and 9-month-old children, for whom rectal diazepam was chosen more commonly. Medication dosing generally followed standard dosing guidelines with very few exceptions.

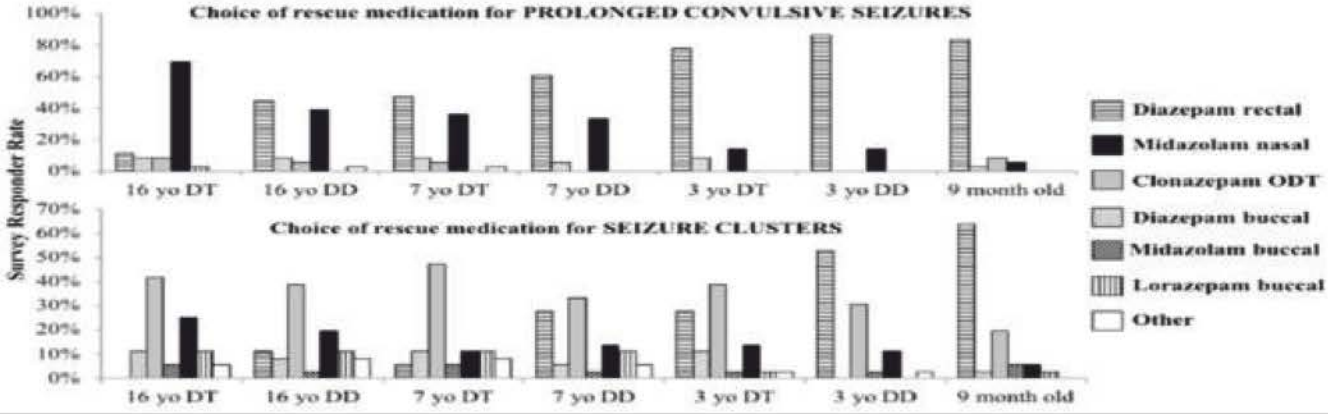

Figure 2. The response of choice of rescue medications for different ages/developmental level for patients with either prolonged or clusters of seizures. *DD*, developmentally delayed; *DT*, developmentally typical; *yo*, years of age.

Conclusions

Rectal diazepam remains the most frequently used rescue medication for prolonged seizures fornearly all age groups, except in developmentally typical teenagers, for whom intranasal midazolam is used more often. Clonazepam orally disintegrating tablets are the most frequently used medication for treatment of clusters of seizures, except in younger patients. Further work is necessary to establish best practices for type and administration route of seizure rescue medications.

(Wallace A, et al. J Pediatr 2019;212:111-6).

"Prednisolone Versus Dexamethasone for Croup"

Objectives: The use of either prednisolone or low-dose dexamethasone in the treatment of childhood croup lacks a rigorous evidence base despite widespread use. In this study, we compare dexamethasone at 0.6 mg/kg with both low-dose dexamethasone at 0.15 mg/kg and prednisolone at 1 mg/kg.

Methods: Prospective, double-blind, noninferiority randomized controlled trial based in 1 tertiary pediatric emergency department and 1 urban district emergency department in Perth, Western Australia. Inclusions were age >6 months, maximum weight 20 kg, contactable by telephone, and English-speaking caregivers. Exclusion criteria were known prednisolone or dexamethasone allergy, immunosuppressive disease or treatment, steroid therapy or enrollment in the study within the previous 14 days, and a high clinical suspicion of an alternative diagnosis. A total of 1252 participants were enrolled and randomly assigned to receive dexamethasone (0.6 mg/kg; n = 410), low-dose dexamethasone (0.15 mg/kg; n = 410), or prednisolone (1 mg/kg; n = 411). Primary outcome measures included Westley Croup Score 1-hour after treatment and unscheduled medical re-attendance during the 7 days after treatment.

Results: Mean Westley Croup Score at baseline was 1.4 for dexamethasone, 1.5 for low-dose dexamethasone, and 1.5 for prednisolone. Adjusted difference in scores at 1 hour, compared with dexamethasone, was 0.03 (95% confidence interval −0.09 to 0.15) for low-dose dexamethasone and 0.05 (95% confidence interval −0.07 to 0.17) for prednisolone. Re-attendance rates were 17.8% for dexamethasone, 19.5% for low-dose dexamethasone, and 21.7% for prednisolone (not significant [P = .59 and .19]).

Conclusions: Noninferiority was demonstrated for both low-dose dexamethasone and prednisolone. The type of oral steroid seems to have no clinically significant impact on efficacy, both acutely and during the week after treatment.

(Parker CM, Cooper MN. Prednisolone Versus Dexamethasone for Croup: a Randomized Controlled Trial. Pediatrics. 2019;144(3):e20183772. doi:10.1542/peds.2018-3772)

"Asthma Attacks Not Stopped by Boosting Inhaled Steroids"

Thomas Egwan

More than 15% of breast milk samples from mothers with asymptomatic malaria contain malaria antigens, according to a study published in *JAMA Pediatrics*, which showed that blood levels of malaria antigens may determine their levels in breast milk.

Thomas Egwan

"We think the presence of malaria antigens in breast milk may lead to two possible consequences — either stimulating specific immune responses or reducing specific immune responses due to induction of immune tolerance," **Thomas Egwang, BVM, PhD,** founding director and CEO of Med Biotech Laboratories, told Healio. "If the antigen in question is a target of protective immunity, then this could translate into a reduced or increased risk of malaria. We need to do a prospective follow-up of children breastfed on milk containing antigen in order to test this hypothesis."

Egwang and colleagues collected breast milk samples from lactating mothers who visited a single malaria clinic in northeastern Uganda during the high or low malaria transmission seasons. They collected samples from 123 and 201 mothers during the low and high transmission seasons, respectively, and tested the samples for the presence of malaria antigens pHRP-2 and pLDH.

None of the mothers had clinical malaria, whereas 14 of the low-transmission season mothers and 74 of the high-transmission season mothers had asymptomatic malaria (P < .001). Among the breast milk samples from mothers with asymptomatic malaria, seven had detectable levels of pHRP-2 and 10 had detectable pLDH. In total, 14 (15.9%) of the samples were positive for either pHRP-2 and pLDH and three were positive for both antigens.

Egwang noted that the analysis is the first study to detect malaria antigens in human breast milk, and that future research could benefit from follow-ups among children of mothers with malaria.

"We took breast milk at only one time point and from moms at different stages of lactation," Egwang said. "We also did not follow up the children to see if breastfeeding on milk containing antigen affected malaria outcomes. In future studies, we will recruit moms at the same stage of lactation and follow them up over time to see how long they shed antigens."

Egwang also emphasized that until further testing is performed, breastfeeding should still be encouraged. "We still have a lot of follow-up work to do," Egwang said. "Breast milk is safe and offers the best nutrition for infants, and breastfeeding within an hour of birth and for at least 6 months should be promoted."

(Source: Van den Elsen LWJ, et al. JAMA Pediatr. 2020;doi:10.1001/jamapediatrics.2019.5209.)

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VACCINOLOGY UPDATE

"Are we on the verge of developing an effective vaccine against atherosclerosis?"

Cardiovascular diseases (CVD) constitute a heterogeneousgroup of heart and blood vessel disorders that together are theleading cause of death worldwide.Atherosclerosis, a disease of large- and medium-sized arteriescharacterised by lipid-rich atherosclerotic plaques, is the mostcommon pathology of CVD. When plaques rupture or erode, MajorAdverse Cardiovascular Events (MACE) ensue, including stroke andmyocardial infarction (MI). The etiology of atherosclerosis is complex,with contributions from genetic, dietary, lifestyle, metabolicand immune components. However, the primary events involveaccumulation of modified lipoproteins, especially low densitylipoprotein (LDL) in the vessel walls, which then triggers a cascadeof pro-inflammatory events. During atherogenesis, LDL accumulatesin the artery wall, where it becomes oxidized, resultingin reactive aldehyde groups such as malonaldehyde (MDA). Scavengerreceptor mediated uptake of oxLDL by macrophages resultin foam cell formation. It is controversial whether foam cells arepro-inflammatory. Current therapies available for atherosclerosis,such as statins and Proprotein Convertase Subtilisin/Kexin type 9(PCSK9) inhibitors, decrease LDL cholesterol levels in the blood.Although these interventions are among the most successfulprevention strategies known in medicine, significant residual riskpersists due to ongoing inflammation.

Recently, immunomodulatory therapeutic approaches to combatatherosclerosis have beenexplored. Anti-inflammatory drugsand monoclonal antibodies (mAbs) that target the ongoingimmune reaction have been tested in both pre-clinical and clinicalstudies. For example, in a large cohort of patients with coronaryheart disease, the Canakinumab Anti-inflammatory thrombosisoutcomes study (CANTOS) trial tested the effects of the anti-IL-1bmAb canakinumab that successfully reduced MACE. However,systemic suppression of IL-1b negatively impacted host defence,leaving subjects more susceptible to lethal and non-lethalinfections.

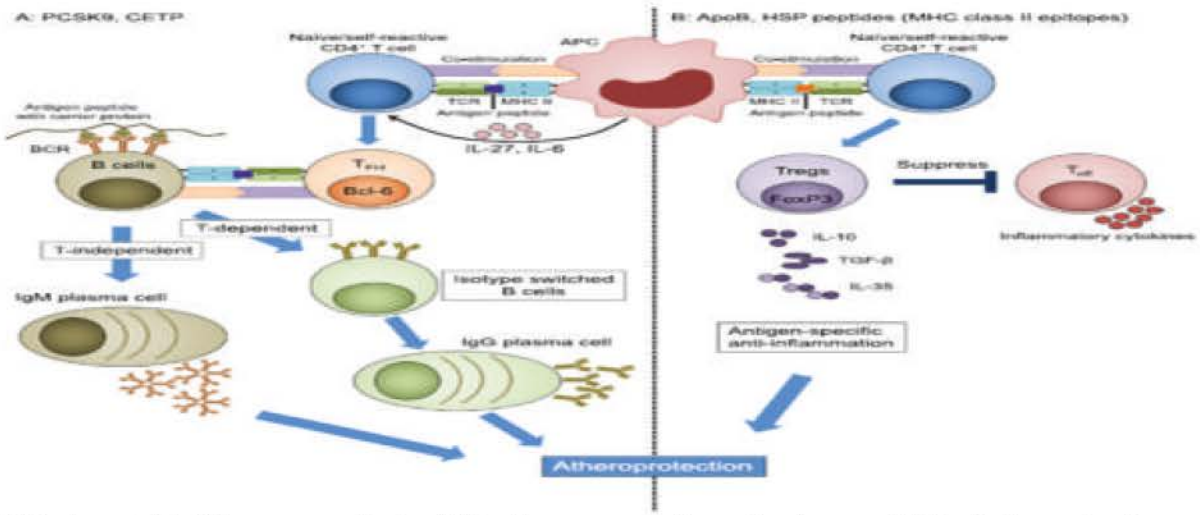
Substantial evidence from experimental models and clinical studies has established the role of inflammation and immune effector mechanisms in the pathogenesis of atherosclerosis. Several stages of the disease are affected by host-mediated antigen-specific adaptiveimmune responses that play either protective or proatherogenic roles. Therefore, strategies to boost ananti-atherogenic humoral and T regulatory cell response are emerging as preventative or therapeuticstrategies to lowering inflammatory residual risks. Vaccination holds promise as an efficient, durableand relatively inexpensive approach to induce protective adaptive immunity in atherosclerotic patients.

There are several issues that need further elucidation before an effective vaccine against it can be developed. For example, there is a need to identify the immunetargetsin pre-clinical and clinical investigations, proper evaluation of immunization strategies inanimal models, clinical trials to examine the safety and efficacy of human atherosclerosisvaccines and strategies to improve and optimize vaccination in humans (antigen selection,formulation, dose and delivery).

Vaccination as a promising strategy to combat atherosclerosis

Vaccination involves an active immunization process that can induce a durable and highly specific anti-atherogenic adaptive immune response in the recipient. However, unlike vaccines for infectious diseases and cancer that aim to boost pro-inflammatory and lytic T cell response, atherosclerosis vaccine formulations need to induce immunological tolerance and/or functional neutralization to alleviate the inflammatory response. Fundamentally, there are two strategies: inducing B cell-dependent production of neutralizing antibodies that can either block protein function (eg: anti-PCSK9) to improve lipid profiles or may facilitate increased oxLDL uptake by phagocytosis and subsequent clearance from circulation(eg: anti-oxLDL); inducing a durable Treg or Tr1 response. Ideally,vaccination promises specific and long-term protection, is inexpensiveand thus accessible to millions of people around the globe.

Fig. 1. Approaches to atherosclerosis vaccines. A: Antibody-based vaccines may target PCSK9, CETP or other proteins. The antigenic protein is engineered, possibly using acarrier protein (tan). MHC-II-restricted T cell epitopes induce a CD4 T cell response that, in the



presence of IL-6 and IL-27, can result in follicular helper TFH cells,characterized by the transcription factor Bcl6 (orange). In germinal centres, TFH cells provide help to B cells, induce antibody isotype switch from IgM to IgG and support thematuration of B cells to long-lived IgG-secreting plasma cells (green). Without T cell help, B cells can mature into IgM-producing plasma cells (tan). B: Self-reactive Tregs canbe targeted when self- peptides are administered through an appropriate route and formulated in a suitable adjuvant. After vaccination, antigen-specific peptides arepresented to naïve self-reactive T cells through MHC class II on APCs. This results in activation of antigen-specific Tregs. Activated Tregs suppress effector T cells by cellcontact-dependent mechanisms and by secreting anti-inflammatory cytokines, such as IL-10, IL-35, and TGFb. ApoB: apolipoprotein B, APC: antigen-presenting cell, TFH: Tfollicular cell, Treg: regulatory T cell, Teff: T effector cell, MHC: major histocompatibility complex, TCR: T cell receptor. (For interpretation of the references to colour in thisfigure legend, the reader is referred to the web version of this article.)

Conclusions

A pivotal role of the adaptive immune system has now beenfirmly established in animal models of atherosclerosis, with strongcorrelative evidence emerging from clinical studies as well. Thesestudies have provided ample motivation for the development ofnovel therapeutic interventions that target inflammation. Globalimmunosuppressive or anti-cytokine strategies can increase therisk of infections. Monoclonal antibodies to PCSK9 are approved,successful, but inconvenient for the patient and expensive for thehealth care system. siRNA to PCSK9 promises longer-livedresponses of up to 9 months. Pre-clinical data suggests thatimmunization-induced humoral and cell-based adaptive immuneresponses can curb the progression of atherosclerosis. However,the antigen selection, vaccine design and the immunization regimeneed to be optimized before a human atherosclerosis vaccine maybe developed. To achieve these goals, it is critical to have abetter understanding of the human-specific molecular mechanismsunderlying disease progression. Likely, the design and developmentof a preventative vaccine will differ substantially from thatof a therapeutic vaccine.

Original citation: Payel Roy P, et al. Opportunities for an atherosclerosis vaccine: From mice to humans. Vaccines 2020; DOI: https://doi.org/10.1016/j.vaccine.2019.12.039

"Reduced efficacy from repeat flu vaccination depends on vaccine type, strain"

McLean HQ, et al.JPediatrInfect Dis Soc. 2019;doi:10.1092/jpids/piz001/5316806. Infectious Diseases in Children, April 2019

Huong Q. McLean

Repeat immunization with inactivated influenza vaccine appears to reduce children's antibody responses to influenza strains A(H1N1)pdm09 and B, according to findings published in the *Journal of the Pediatric Infectious Diseases Society*. The effect of previous-season vaccination on the efficacy of live-attenuated influenza vaccine was less clear, researchers said.

Previous research has shown waning protection from influenza vaccine in patients who had been vaccinated during the previous season, but findings recently published in *Annals of Family Medicine* showed that repeat immunization with IIV appeared to

increase long-term protection against some respiratory illness episodes in children with pre-existing medical conditions.

SEE ALSO

Repeated inactivated influenza vaccine may increase… Flu vaccine 47% effective in US, early estimates show One-third of parents are declining flu vaccination for…

"The few studies that have examined the effect of repeated annual vaccination on influenza vaccine effectiveness (VE) in children found that VE was modified by their previous-season vaccination status and that the effect of previous-season vaccination history varied according to the vaccine type received," Huong Q. McLean, PhD, MPH, a research scientist at the Marshfield Clinic Research Institute's Center for Clinical Epidemiology and Public Health, and colleagues wrote.

McLean and colleagues examined the association between previous vaccination history and hemagglutination-inhibition antibody titers in children (n = 267) vaccinated during three influenza seasons: 2013-2014, 2014–2015 and 2015-2016.

Results showed that the geometric mean fold rise (GMFR) — a measure of the increase in geometric mean titers (GMTs) after vaccination — was significantly lower in previous-season IIV recipients (1.5 to 2.3) than in children who were unvaccinated or received LAIV in the previous season (4.3 to 12.9) for influenza strains A(H1N1)pdm09 and influenza B. The same findings were less pronounced for influenza A(H3N2) — a strain that had caused a severe influenza season in the United States last year.

According to the researchers, most children had a post-IIV vaccination titer of 40 or more for vaccine strains in all seasons, regardless of previous-season vaccination history. Little or no increase in antibody levels was observed after children had been vaccinated with LAIV.

"The difference in response following vaccination was not consistent across vaccine strains and seasons," McLean told *Infectious Diseases in Children*.

McLean said "additional studies are needed to better understand the variation in response and any age cohort effects."

– by Katherine Bortz

Disclosures: The authors report no relevant financial disclosures.

"Varicella zoster vaccine reduced risk for subsequent herpes zoster by 72%"

Herpes zoster (HZ) is a result of reactivation of varicella zoster virus (VZV) sometime after chicken pox, the primary infection caused by the virus. Although the incidence of HZ is lower in children than in adults, it is well described, and children with primary VZV before age 1 year are at greatest risk. Children can also develop HZ after vaccination, but the risk for reactivation following vaccination has been challenging to study, requiring many children infected with vaccine-type virus (vaccinated) and wild-type virus (unvaccinated).

In this study, researchers assessed physician-documented HZ incidence and VZV vaccination status during 2003 to 2014 among 6.4 million children enrolled in six healthcare organizations. Results include the following:

Overall, 50% of children were vaccinated for VZV during the study period; this rate increased over time, reaching 91% in 2014.

Incidence of HZ was 74 per 100,000 (61 per 100,000 for laboratory-confirmed HZ) and declined by 72% over time.

HZ incidence was 78% lower in vaccinated children (38 per 100,000) than in unvaccinated children (170 per 100,000).

Among 1-year-olds, vaccinated children had a higher HZ rate than unvaccinated children, but among children aged 5–17 years, vaccinated children had a significantly lower risk for HZ than unvaccinated children.

Children vaccinated with two VZV vaccine doses, as is recommended, had 50% lower risk for HZ compared with those who had received just one dose.

Comment

This vaccine does double duty: in addition to protecting children from varicella zoster infection, and all the complications that can result, the vaccine significantly reduces the incidence of herpes zoster. Although further evidence supporting the benefits of vaccinating children should not be necessary, these findings provide just that.

(Weinmann S et al. Pediatrics. 2019 Jul;144(1). pii: e20182917. Epub 2019 Jun 10)

For the first time in 27 years, influenza B viruses have predominated in the United States

'Mixed bag' flu season has been particularly tough on children. "Flu is going to be a much bigger killer in the United States than this coronavirus and people aren't doing everything that they possibly can to diminish the spread!"

Aaron E. Glatt

For the first time in 27 years, influenza B viruses have predominated in the United States, accounting for more than 56% of samples tested in public health laboratories as of Jan. 18, according to CDC data. Influenza B viruses are more common in children than adults, which potentially explains some incongruities in U.S surveillance data, according to Lynnette Brammer, MPH, who leads the CDC's domestic influenza surveillance team. CDC data showed that the percentage of outpatient

visits for influenza-like illness increased from 4.7% to 5% for the week ending Jan. 18, after declining sharply for 2 weeks in a row. CDC estimates showed a cumulative rate of influenza-related hospitalization of 24.1 per 100,000 people, not out of line with previous seasons. The rate of deaths attributed to pneumonia or influenza declined slightly in the week ending Jan. 18, from 7.1% to 6.7%, remaining below the epidemic threshold. Brammer called the season a "mixed bag." "Influenza B — particularly the B Victoria [viruses] that are out there — don't tend to impact the elderly very much. **Aaron E. Glatt**

But they do impact kids, particularly school-age kids," Brammer told Healio. "Our influenza-like illness graph looks like it was a bad season — it's pretty high at the peak. But if you look at the hospitalizations and the pneumonia and influenza mortality, that's not very remarkable, and that's because the people that tend to get hospitalized and die from influenza in the largest numbers are the elderly." Brammer suggested the uncommon predominance of influenza B viruses may be explained by the lack of circulating B viruses in previous seasons, particularly of the B/Victoria lineage, which have accounted for almost all influenza B specimens tested this season. "The Victorias have been changing, and I think it got to the point to where there wasn't a lot of population immunity to them," Brammer said.

Bernhard L. "Bud" Wiedermann

The CDC reported an additional 15 pediatric influenza deaths for the week ending Jan. 18, raising the seasonal total to 54. There were 143 influenza-related pediatric deaths in the U.S. last season. Bernhard L. "Bud" Wiedermann, MD, MA, attending physician in infectious diseases at Children's National Hospital in Washington, D.C., and professor of pediatrics at The George Washington University School of Medicine & Health Sciences, said his hospital was "clearly still in the midst of a very busy flu **Bernhard L. "Bud" Wiedermann**

season." He wondered if there would be a second peak attributed to influenza A. "We will need to continue to be prepared as best we can, knowing that any season can contain surprises," he told Healio. Overall, the CDC estimated that 15 million to 21 million influenza-related illnesses and 7 million to 10 million influenza-related medical visits occurred as of Jan. 18. In addition, it estimated there were 140,000 to 250,000 influenza-related hospitalizations and 8,200 to 20,000 influenza-related deaths. "The critical message has to still be vaccinate, vaccinate, vaccinate," Infectious Diseases Society of America spokesperson Aaron E. Glatt, MD, professor of medicine at Mount Sinai's Icahn School of Medicine and chair of medicine at Mount Sinai South Nassau in Oceanside, New York, told Healio. "When you get vaccinated, you're not only helping yourself, you're also preventing everybody else around you from getting sick — and it's not too late to get vaccinated." Brammer said the CDC would have preliminary estimates of the effectiveness of the 2019-2020 influenza vaccine in the coming weeks. "Flu is going to be a much bigger killer in the United States than this coronavirus and people aren't doing everything that they possibly can to diminish the spread," Glatt said.

(https://www.healio.com/pediatrics/influenza/news/on

line/%7Bc549dba8-356e-4e8e-a870-2d43a85d2303%7D/mixed-bag-flu-season-has-been-particularly-tough-on-children?utm_source=selligent&utm_medium=email&utm_campaign=pediatrics%20news&m_bt=858086025592)

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CDC. 2019-2020 U.S. Flu Season: Preliminary Burden Estimates. https://www.cdc.gov/flu/ about/burden/preliminary-in-season-estimates.htm. Accessed January 27, 2020.

"Does Herpes 6 Infection Have a Role in Bell's Palsy Among Children and Adolescents?"

Bell's palsy is a peripheral paralysis of the seventh cranial nerve, whose etiology is unknown. Using polymerase chain reaction technology, it is possible to sample accessible body fluids and identify possible viral factors. The purpose of this research is to investigate its connection to the herpes virus family by testing for the presence of the virus in the saliva and tear fluid of Bell's palsy patients.

Methods: Saliva and tears were collected from 42 children and adolescents suffering from idiopathic facial nerve paralysis. Polymerase chain reaction was used to test for the presence of the viruses Epstein-Barr virus, cytomegalovirus, herpes simplex virus 1 and 2, varicella zoster virus and human herpes virus 6 (HHV-6). Samples were also taken from a control group without paralysis. A second specimen was taken from patients who tested positive for HHV-6 several months after their recovery.

Results: Of the 42 patients in the study group, 71% (30 patients) tested positive for HHV-6, compared with only 37% of the control group (P = 0.001). The prevalence of the other 5 viruses tested was low—herpes simplex virus 1: 9.5%, Epstein-Barr virus: 9.5%, cytomegalovirus: 4.8%, varicella zoster virus: 2.3% and herpes simplex virus 2: 0%. Twenty-four of the 30 patients who were HHV-6-positive during their illness were reexamined following recovery. Only 13 patients (54.2%) excreted the virus after recovery from the paralysis.

Conclusions: Herpes 6 virus appears to play some role in the etiology of facial nerve paralysis. The virus was detected in the saliva of children during acute illness and decreased with resolution. Our research opens new insights linking HHV-6 to the etiology of Bell's palsy in children.

(Genizi, J, et al. The Pediatr Infect Dis J2019;38: 481-83. DOI: 10.1097/INF.0000000000002278)

"Placebo vs Amoxicillin for Non-severe Fast-Breathing Pneumonia in Children Aged 2 to 59 Months"

A Double-blind, Randomized Clinical Noninferiority Trial

Question: Are antibiotics necessary for the treatment of non-severe fast-breathing pneumonia in children?

Findings: In this double-blind, randomized clinical noninferiority trial that included 1126 HIV-uninfected children aged 2 to 59 months in a malaria-endemic region of Malawi, Africa, placebo treatment of non-severe fast-breathing pneumonia was significantly inferior to 3 days of amoxicillin treatment with respect to treatment failure at day 4. Fast-breathing pneumonia resolved by day 4 in 93% of children without the use of the antibiotic.

Meaning: Without amoxicillin treatment, 7% of Malawian children with non-severe fast-breathing pneumonia failed treatment by day 4, and treating 33 children with amoxicillin was necessary for 1 child to benefit.

Comment: *These results should motivate the World Health Organization to update their recommendation for the use of amoxicillin for all cases of non-severe fast-breathing pneumonia in resource-constrained settings (Compiled by Dr Piyush Gupta, To read free full text, go to* https://jamanetwork.com/journals/jamapediatrics /fullarticle/2714280*)*

REGIMENS FOR NEONATAL SEPSIS

"Non-Carbapenems May Provide Limited Empirical Neonatal Sepsis Coverage in Many Asian Countries"

Evaluation of the Coverage of 3 Antibiotic Regimens for Neonatal Sepsis in the Hospital Setting Across Asian Countries

High levels of antimicrobial resistance in neonatal bloodstream isolates are beingreported globally, including in Asia. Local hospital antibiogram data may include too few isolates tomeaningfully examine the expected coverage of antibiotic regimens.

Objective: To assess the coverage offered by 3 antibiotic regimens for empirical treatment ofneonatal sepsis in Asian countries.

Design, Setting, And Participants : A decision analytical modelwas used to estimate coverageof 3 prespecified antibiotic regimens according to a weighted-incidence syndromic combination antibiogram. Relevant data to parameterize the models were identified from a systematic search ofOvid MEDLINE and Embase. Data from Asian countries published from 2014 onwardwere of interest.

Only data on blood culture isolates from neonates with sepsis, bloodstream infection, or bacteremiareported from the relevant setting were included. Data analysis was performed from April 2019 toJuly 2019.

Exposures : The prespecified regimens of interest were aminopenicillin-gentamicin, thirdgenerationcephalosporins (cefotaxime or ceftriaxone), and meropenem. The relative incidence ofdifferent bacteria and their antimicrobial susceptibility to antibiotics relevant for determiningexpected concordance with these regimens were extracted.

Main Outcomes And Measures : Coverage was calculated on the basis of a decision-tree modelincorporating relative bacterial incidence and antimicrobial susceptibility of relevant isolates. Dataon 7 bacteria most commonly reported in the included studies were used for estimating coverage,which was reported at the country level.

Table 1. Relative Incidence Data

Pathogen	Isolates, No. (%)[a]										
	Cambodia (n = 185)	China (n = 2043)	India (n = 6284)	Indonesia (n = 225)	Laos (n = 75)	Malaysia (n = 29)	Nepal (n = 640)	Pakistan (n = 1875)	Taiwan (n = 36)	Vietnam (n = 75)	Total (N = 11 467)
Contributing to WISCA											
Escherichia coli	25 (16)	300 (33)	671 (14)	0	8 (13)	6 (33)	50 (10)	976 (57)	11 (92)	2 (4)	2049 (24)
Klebsiella species	60 (39)	264 (29)	1065 (22)	49 (40)	9 (14)	1 (6)	45 (9)	159 (9)	1 (8)	18 (35)	1671 (20)
Enterobacter species	18 (11)	58 (6)	167 (3)	20 (17)	4 (6)	0	30 (6)	0	0	6 (12)	303 (4)
Acinetobacter species	16 (10)	27 (3)	992 (21)	21 (17)	2 (3)	0	63 (13)	0	0	17 (33)	1138 (14)
Pseudomonas species	6 (4)	53 (6)	430 (9)	31 (26)	1 (2)	1 (6)	25 (5)	199 (12)	0	4 (8)	750 (9)
Staphylococcus aureus	33 (21)	112 (12)	1235 (26)	0	37 (58)	10 (55)	261 (53)	388 (23)	0	4 (8)	2080 (25)
Enterococcus species	0	91 (10)	275 (6)	0	3 (5)	0	15 (3)	1 (<1)	0	0	385 (5)
Total reported during observation period											
Total contributing to WISCA	158 (85)	905 (44)	4835 (77)	121 (54)	64 (85)	18 (62)	489 (76)	1723 (92)	12 (33)	51 (68)	8376 (73)
Other (not contributing to WISCA)	27 (15)	1138 (56)	1449 (23)	104 (46)	11 (15)	11 (38)	151 (24)	152 (8)	24 (67)	24 (32)	3091 (27)
Coagulase-negative staphylococci (not contributing to WISCA)	0	741 (36)	980 (16)	63 (28)	0	0	137 (21)	28 (1)	0	23 (31)	1972 (17)

Abbreviation: WISCA, weighted-incidence syndromic combination antibiogram.

[a] Percentages may not add to 100% because of rounding.

Results : Data from 48 studies reporting on 10 countries and 8376 isolates were used. Individualcountries reported 51 (Vietnam) to 6284 (India) isolates. Coverage varied considerably betweencountries. Meropenem was generally estimated to provide the highest coverage, ranging from64.0%(95%credible interval [CrI], 62.6%-65.4%) in India to 90.6%(95%CrI, 86.2%-94.4%) inCambodia, followed by aminopenicillin-gentamicin (from 35.9%[95%CrI, 27.7%-44.0%] inIndonesia to 81.0%[95%CrI, 71.1%-89.7%] in Laos) and cefotaxime or ceftriaxone (from 17.9%[95%CrI, 11.7%-24.7%] in Indonesia to 75.0%[95%CrI, 64.8%-84.1%] in Laos). Aminopenicillin-gentamicincoverage was lower than that of meropenem in all countries except Laos (81.0%; 95%CrI, 71.1%-89.7%) and Nepal (74.3%; 95%CrI, 70.3%-78.2%), where 95%CrIs for aminopenicillingentamicinand meropenem were overlapping. Third-generation cephalosporin coverage was lowestof the 3 regimens in all countries. The coverage difference between aminopenicillin-gentamicin andmeropenem for countries with nonoverlapping 95%CrIs ranged from −15.9% in China to −52.9%in Indonesia.

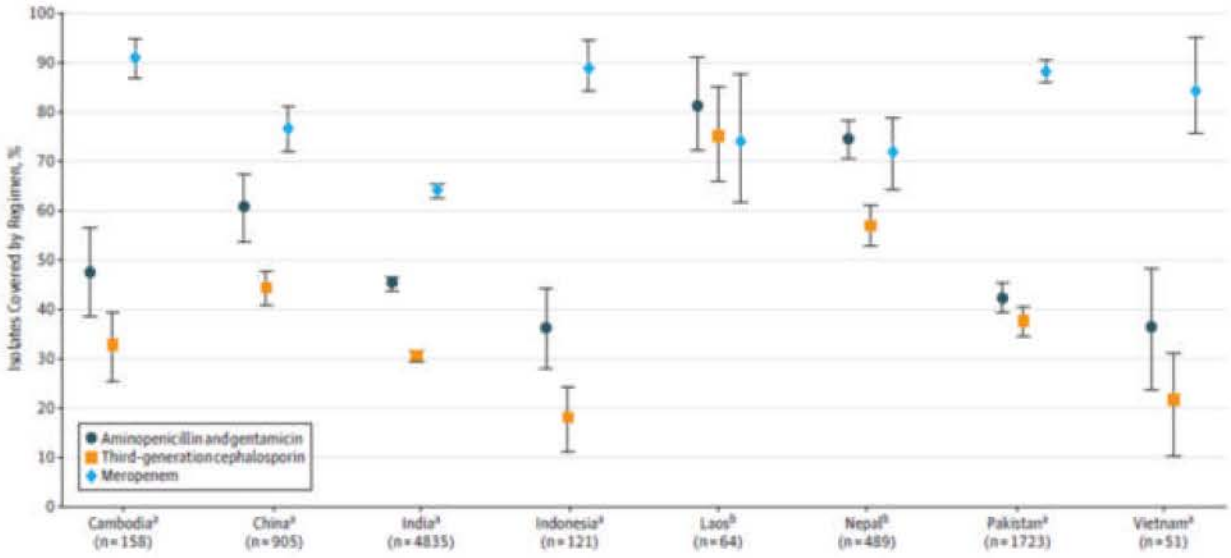
Conclusions And Relevance : This study's findings suggest that non-carbapenem antibioticregimens may provide limited coverage for empirical treatment of neonatal sepsis in many Asiancountries. Alternative regimens must be studied to limit carbapenem consumption.

Key Points

Question: What is the antibioticcoverageoffered by empirical neonatalsepsis treatment with aminopenicillin-gentamicin,third-generationcephalosporins (cefotaxime orceftriaxone), and meropenem in Asiancountries?

Findings: In this decision analvticalmodel based on a decision tree, 8376isolates from 10 countries were used toestimate coverage. Meropenemgenerally had the highest coverage(from 64.0%in India to 90.6%inCambodia) followed by aminopenicillin-gentamicin(from 35.9%in Indonesia to81.0% in Laos) and cefotaxime orceftriaxone (from 17.9%in Indonesia to75.0%in Laos); in all countries exceptLaos and Nepal, meropenem coveragewas higher than that of the other 2regimens.

Figure. Coverage Estimates for 8 Asian Countries



Point estimates are shown with 95% credible intervals, as denoted by error bars. Nonoverlapping 95% credible intervals indicate likely within-country differences in regimen coverage. Countries are shown together with the overall number of isolates used for estimating coverage.

[a] The highest coverage offered by meropenem was in Cambodia (90.6%), China (76.5%), India (64.0%), Indonesia (88.8%), Pakistan (88.1%), and Vietnam (84.1%).

[b] The highest coverage offered by aminopenicillin-gentamicin combination was in Laos (81.0%) and Nepal (74.3%).

Meaning The findings suggest thatnon-carbapenems may provide limitedempirical neonatal sepsis coverage inmany Asian countries.

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OPINION

It's Time to Re-evaluate the Apgar Score

When Virginia Apgar, MD, proposed her now-universal scoring system for newborns in 1953, her primary purpose was to get attention paid to the newborn because, as she wrote, "Nine months observation of the mother surely warrants one-minute observation of the baby." 1. After the national Collaborative Perinatal Study showed that low Apgar scores occurred more frequently in those who died in the neonatal period or had higher rates of neurological morbidity at 1 year of life, the Apgar score spread to where it is now assigned to newborns in almost every country in the world. A PubMed search for Apgar score yields almost 12□000 publications.

However, almost 40 years ago, questions arose about the (mis)use of the Apgar score, mainly based on studies that found limitations when using the score to predict short-term or long-term morbidity and mortality. 2. In these studies, scores were often parsed into low (0-3), medium (4-6), and high (7-10) groups, but to our knowledge, these divisions have never been validated. Warnings about equating low scores with asphyxia or telling parents what was likely to happen in the future to their newborn based on the Apgar scores have been sounded for decades, including by the American Academy of Pediatrics, which in 1986 stated, "the scores alone should not be considered either of or consequent to substantial asphyxia." 3. Nevertheless, recent publications still use the score to predict outcome in groups of newborns.

While problems with poor prognostic ability are well documented and referenced, other very important concerns about the clinical use of the Apgar score have become apparent over the last 20 years. First, there are a number of studies that have demonstrated high levels of interobserver variability. There are even geographic or cultural differences in assigning the Apgar score. For example, while 8.8% of newborns born in Latvia get a 5-minute score of 10, that's the score assigned to 92.7% of newborns born in France. 4. Second, there is the issue of prematurity. The original Apgar score did not specify how to assess parameters such as reflex irritability and tone in premature newborns. As a result, there is no consensus on how to score a newborn born at 24 weeks' gestation, even if tone and reflex irritability are completely normal for this stage of development.

Third, once people began to pay attention to the newborn, they began to respond when the newborn had bradycardia or apnea, but there is no consensus on how to account for interventions when assigning the Apgar score. Apgar did not specify how to score newborns receiving an intervention, even though 7% of the newborns in her first article were ventilated, 1 resulting in large variation in how these newborns are scored. Acceptable oxygen saturation levels defined in the latest edition of the Neonatal Resuscitation Program (NRP)5 could result in a newborn getting marked off for color but still have a normal oxygen level. Finally, and most significantly, with the advent of the NRP and its requirement that "at least 1 qualified individual…whose only responsibility is the management of the newly born baby" 5. be at every delivery, Apgar's initial goal for her score, to focus attention on the newborn, has been achieved. The Apgar score is not used in the NRP.

If a medical procedure or test had similar problems with accuracy, reproducibility, universality, and even utility, there would be calls for its retirement, and there have been several such calls over the years. Yet as recently as 2015, the American Academy of Pediatrics and the American College of Obstetrics and Gynecology endorsed the continued use of the Apgar score. 6. They also recommended to report resuscitative interventions along with the traditional scoring, what they termed the Expanded Apgar score. It consists of 7 possible treatments and subtracts points for resuscitation interventions performed at each point. Another modification is the Specified Apgar score, in which the definitions of the 5 parameters of the original score are specified to ignore the need for any interventions and just assess the newborn and are renormalized to gestational age for the neurological responses rather than comparing them to what a term newborn would look like. The Combined Apgar score incorporates the Specified and the Expanded Apgar scores. 7. These alternatives, and others, have only been assessed in relatively small prospective studies in selected populations, to our knowledge.

Given the multiple concerns and limitations, we believe that the time has come to relook at the Apgar score to determine if it is still useful, if it needs to be revised or replaced by a different system, or if we should do away with scoring newborns after delivery altogether. However, to do so, we must first define the purpose of a scoring system. There are 3 potential goals

for any quantitative assessment of a newborn after delivery: (1) it can be an easy way to describe the condition (and interventions needed to achieve that condition) in a reproducible (and numerical) way and help in clinical communication; (2) it can measure the immediate clinical results of delivery and resuscitation; and (3) it can quantify the individual condition (and intervention) of a newborn at different points and will thus make groups of newborns comparable, becoming a tool for classifying risk of short-term and long-term complications, research, and quality improvement.

Based on these scoring goals, useful end points for a large prospective clinical trial can be defined. Thus, we suggest to borrow from the experience of researchers investigating plasma transfusion practices in the pediatric intensive care unit, who needed to define clinically significant bleeding before embarking on any large prospective trials. A panel of international experts developed a set of clinical definitions or scenarios, and these were assessed by more than 500 practitioners using a web-based survey platform. The expert panel then formulated bleeding definitions that reflected a high level of agreement among the survey respondents. A second expert panel used a Delphi process until there was agreement on all the elements.

To begin this process, a library of potential outcomes important to measure in a clinical trial is needed. We invite readers to send their suggestions for the purpose(s) of why a scoring system for all newborns should be performed and/or what outcomes should be measured in a clinical trial to determine the best scoring system, if any.

(Mario Rüdiger, Henry J. Rozycki, JAMA Pediatr. Published online February 24, 2020. doi:10.1001/jamapediatrics.2019.6016)

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