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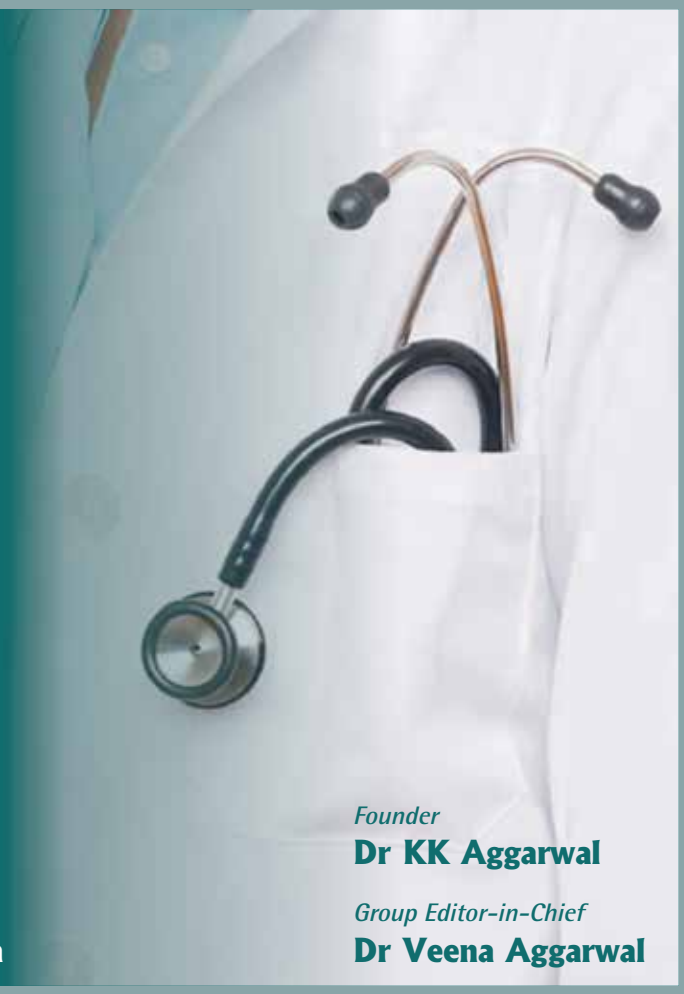

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Medicine Update

WHO UPDATES NOMENCLATURE FOR PATHOGENS TRANSMITTED THROUGH AIR

The World Health Organization (WHO) has published a technical consultation report with updated terminology for air-borne pathogens such as coronavirus disease 2019 (COVID-19), tuberculosis (TB), influenza, measles, Middle East respiratory syndrome (MERS), and severe acute respiratory syndrome (SARS). The term "*infectious respiratory particles*" or IRPs should be used to describe the pathogen containing infectious particles released during talking, breathing, sneezing, or coughing. Now there is no threshold of particle size as was prevalent earlier, when 'aerosols' (generally smaller particles), and 'droplets' (generally larger particles) were being used. Transmission through the air is now described as *airborne transmission or inhalation* (when the IRPs are exhaled into the air and inhaled by another person) and *direct deposition* (when the exhaled IRPs are directly deposited on the mouth, nose, or eyes another person in close proximity)… (*Source: WHO. Apr. 18, 2024*).

LIDOCAINE NERVE BLOCK EFFECTIVELY RELIEVE ACUTE STATUS MIGRAINOSUS IN CHILDREN

Results of a randomized controlled trial presented at the AAN 2024 Annual meeting show that children with severe, resistant migraine headaches "acute status migrainosus" are relieved by 2% lidocaine injections into the greater occipital nerve. In the lidocaine group, 69% of patients achieved a 2-point reduction in pain, compared to 34% in the saline group… (*Source: Medscape. Apr. 22, 2024*).

THE FIRST CAR T-CELL TRIAL FOR PEDIATRIC LUPUS GETS FDA APPROVAL

REACT-01 (Reversing Autoimmunity through Cell Therapy), the first clinical trial for chimeric antigen receptor (CAR) T-cell therapy in children with systemic lupus erythematosus has received the US FDA go ahead. The trial will be conducted at the Seattle Children's Hospital in Washington state… (*Source: Medscape. Apr. 10, 2024*).

AGA BEST PRACTICE ADVICE FOR A HIGH-QUALITY UPPER ENDOSCOPY EXAM

The pre- and post-endoscopy deliberations with the patient must be meticulously documented. This and other best practice statements, which include ensuring that esophagogastoduodenoscopy (EGD) is being performed for the right indication, address intra- and post-procedure recommendations to optimize the procedure have been published in *Clinical Gastroenterology and Hepatology*… (*Source: Medscape. Apr. 19, 2024*).

NIGERIA BECOMES THE FIRST COUNTRY TO EMPLOY A 5-IN-1 VACCINE AGAINST MENINGITIS

Nigeria has made history by being the first nation to implement Men5CV, a new WHO recommended vaccine against five major strains of the meningococcus bacteria (A, C, W, Y, and X) in a single dose. Situated in the African Meningitis Belt, Nigeria is one of the 26 nations in Africa where meningitis is hyperendemic… (*Source: WHO. Apr. 12, 2024*).

Preventive PCI Prevents Cardiac Events in Patients with High-Risk Coronary Plaques

In the PREVENT trial, patients with high-risk coronary plaques at risk of rupturing and who underwent preventive percutaneous coronary intervention (PCI) reduced their risk of experience the composite primary end point of cardiac death, heart attack in the target vessel, revascularization due to ischemia in the target vessel or hospitalization for unstable or progressive chest pain compared to those who received only medications… (*Source: ACC News. Apr. 9, 2024*).

ALECTINIB APPROVED AS ADJUVANT TREATMENT FOR ALK-POSITIVE NON-SMALL CELL LUNG CANCER

After tumor resection, patients with anaplastic lymphoma kinase (ALK)-positive non-small cell lung cancer (NSCLC) may receive adjuvant treatment with alectinib, recently approved by the US Food and Drug Administration (FDA). Hepatotoxicity, constipation, myalgia, COVID-19, fatigue, rash, and cough were the most frequent side effects among patients taking alectinib. It should be taken orally twice daily with food in doses of 600 mg for 2 years, or until the disease recurs or the toxicity becomes intolerable … (*Source: US FDA. Apr. 18, 2024*).

WHO PREQUALIFIES A NOVEL ORAL CHOLERA VACCINE

The WHO has prequalified Euvichol-S, a novel inactivated oral cholera vaccine. With a simpler formulation and comparable efficacy to current vaccines, it presents prospects for a quick increase in production capacity. Dr Rogerio Gaspar, Director of the WHO Department for Regulation and Prequalification said, "The new vaccine is the third product of the same family of vaccines we have for cholera in our WHO prequalification list"… (*Source: WHO. Apr. 18, 2024*).

PRACTICING GRATITUDE AND FORGIVENESS GOOD FOR HEART HEALTH

Receiving daily WhatsApp messages or videos focusing on fostering spirituality by "encouraging optimism, gratitude and forgiveness" led to reduction in systolic blood pressure by 7 mmHg in hypertensive individuals. Flow mediated dilation also increased by 4.5% in the intervention group… (*Source: ACC News. Apr. 7, 2024*).

THREE INDICATIONS FOR A NEW ANTIBIOTIC

Injectable ceftobiprole medocaril, available as Zevtera, has been accorded FDA approval for the treatment of adults with *Staphylococcus aureus* bacteremia and acute bacterial skin and skin structure infections. It is also approved for patients, aged 3 months to <18 years, with community-acquired bacterial pneumonia.

The Agency has cautioned about increased mortality in cases of ventilator-associated bacterial pneumonia… (*Source: US FDA. Apr. 3, 2024*).

ONE IN FOUR RHEUMATOID ARTHRITIS PATIENTS WITH STAPH BACTEREMIA DEVELOP OSTEOARTICULAR INFECTIONS

Patients with rheumatoid arthritis (RA) face twice the risk of osteoarticular infections (23.1%) such as septic arthritis, spondylitis, osteomyelitis, psoas muscle abscess, or prosthetic joint infection after *S. aureus* bacteremia, compared to those who do not have RA (12.5%).

However, all-cause mortality was comparable between the two groups (35.4% vs. 33.9%, respectively... (*Source: Rheumatology. March 9, 2024*).

STUDY LINKS *HELICOBACTER PYLORI* TO COLORECTAL CANCER

Helicobacter pylori-positive patients may have an 18% higher risk for colorectal cancer (CRC) (adjusted hazard ratio [aHR] 1.18) and 12% (aHR 1.12) higher risk of fatal disease compared to those who were *H. pylori* negative. Untreated infection was associated with 23% higher incidence of CRC (aHR 1.23) and 40% higher risk of related mortality (aHR 1.40)… (*Source: J Clin Oncol. March 1, 2024*).

PLOZASIRAN: A NEW PROMISING TREATMENT FOR SEVERE HYPERTRIGLYCERIDEMIA

Use of the investigational drug plozasiran, an APOC3 (apolipoprotein C3) inhibitor, as add-on treatment in patients with severe hypertriglyceridemia resulted in 74% reduction (average) in triglyceride levels, according to the phase 2 SHASTA-2 trial. No safety issues were observed… (*Source: ACC News. Apr. 7, 2024*).

BENZODIAZEPINE USE DURING PREGNANCY INCREASES CHANCES OF MISCARRIAGE

Women who used benzodiazepines during the early stages of pregnancy were 70% more likely to experience miscarriage compared to those who did not use these medications. The odds ratios for miscarriage risk associated with each benzodiazepine type ranged from 1.39 for alprazolam to 2.52 for fludiazepam… (*Source: JAMA Psychiatry. Dec. 27, 2023*).

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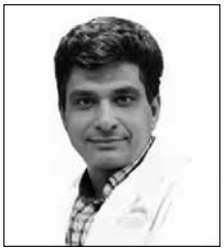

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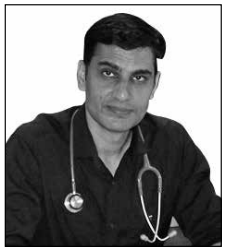

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Health and Harmony: Teamwork is the Key

Om! May He protect us both together; may He nourish us both together;

May we work conjointly with great energy,

May our study be vigorous and effective;

May we not hate any.

Om! Let there be Peace in me!

Let there be Peace in my environment!

Let there be Peace in the forces that act on me!

—Taittiriya Upanishad

THE PARADOX OF HEALTH

Good health is a paradox. As we bask in justified pride about our increasing life expectancy and longevity, we cannot ignore the rapid increase in human suffering, quantified as disability-adjusted life years (DALYs)[1]. Neither can we trivialize the low levels of public satisfaction with health care professionals, despite tremendous advances in diagnostics and therapeutics.

The changing burden of disease, characterized by an epidemic of noncommunicable illness, calls for a relook at our approach to the optimization of health. This is especially true in persons living with chronic, metabolic or psychological diseases, where the focus is on 'healthy living with the disease'. In fact, recent commentators have highlighted the need to include 'sustainable' and 'optimized' well-being as part of the definition of health[2].

THE COMPLEXITY OF HEALTH CARE

One added complexity in today's world is the existence of multiple comorbidities and the usage of multiple concomitant medications. While the words 'multimorbidity' is used frequently, a case can be built for the concept of 'grand-multimorbidity'. Taking guidance from the definition of grand multipara in obstetrics, grand-multimorbidity can be used to refer to a clinical state where 5, or more than 5, disease states are present. Similarly, a grand-comedication prescription may be an apt descriptor for a treatment, which includes ≥5 drugs. Our method of management must take these inescapable challenges of today's medical praxis, into account.

Yet another layer of complexity is added by the patronage of alternative schools of medicine. While the word 'alternative' suggests a binary, 'this or that' attitude, using the complementary adjective offers a more inclusive view of current health care[3]. Many persons living with chronic disease use both modern and traditional medications in varying proportions, at different times in their lifespan. This fluidity of choice needs to be respected as well.

THE NEED FOR TEAMWORK

The multifactorial nature of disease, and multifaceted options for treatment, calls for a multidimensional style of management. No single health care system, service or professional can claim to manage all aspects

of an individual's or society's health. It is necessary therefore, to work as a team, in order to ensure optimal therapeutic outcomes[4,5].

Teamwork has its own challenges. An able leader or manager, who can lead a motivated group of professionals, united in their aim to achieve better health for all, is required. Even more importantly, the person living with chronic disease should view himself or herself as an integral part of the team. This means not only understanding one's rights, but shouldering one's responsibilities as well[6].

As health care professionals, we must understand our primary objective that of ensuring health and work as part of an efficient, effective team, to accomplish this goal. Apart from professional expertise, therefore, we should learn team dynamics and kinetics. We should respect and be responsive to the requirements, strengths and limitations of other team members.

Identification of an appropriate team leader or manager is also important. In obesity or diabetes, for example, the team leader may be an endocrinologist. In a person with obesity or diabetes and multimorbidity, such as seizure disorders or tuberculosis, however, an internist may be better placed to serve as team leader.

SCIENTIFIC SATYAGRAHA

We understand that this is easier said than done. Teamwork requires a balance between confidence competence and expressive empathy, and between an individualistic and team-based collaborative style. We should be able to avoid the feeling of intellectual arrogance, and replace it with a scientific search for greater knowledge. This can be termed 'scientific satyagraha', or a Gandhian search for the truth. Once we incorporate this in our thoughts and behavior, a robust and resilient foundation for better health will be ready.

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■■■■

Study Links Gabapentinoids Prescription to Higher Risks of Drug Misuse and Trauma

A recent study published in the journal *Pain* revealed a concerning link between the prescription of gabapentinoids and heightened risks of drug misuse, overdose, and significant trauma among patients prescribed these medications.

For the study, researchers collected data from anonymized GP records. They compared the rates of adverse events—including substance misuse, overdose, and significant injury—between patients prescribed gabapentinoids and those who were not.

The findings showed that patients prescribed gabapentinoids faced elevated risks of adverse events if they exhibited certain predisposing factors. For instance, smokers, individuals with a history of substance misuse or overdose, or those grappling with mental health conditions were particularly vulnerable. Furthermore, the risk intensified for patients concurrently prescribed other drugs impacting the central nervous system, indicating potential interactions amplifying these risks.

(*Source: https://medicalxpress.com/news/2024-04-patients-gabapentinoids-drug-misuse-overdose.html*)

ORIGINAL RESEARCH

Clinical Spectrum of Recurrent Urinary Tract Infections: A Single-Center Study

DURGA DEORUKHKAR*, HARDIK SHAH†, DILIP KIRPALANI‡, SHRIRANG BICHU#, ASHOK KIRPALANI¥

ABSTRACT

A retrospective observational study was undertaken to evaluate the clinical profile of recurrent urinary tract infections (UTIs) in a tertiary care hospital. Patients <18 years, kidney-transplant recipients, those on immunosuppressive agents and pregnant patients were excluded. Patients with ≥2 episodes of culture positive UTIs were included. Demographic details, investigations and treatment were recorded. Out of total 48 patients, 18 were female and 30 male. The common manifestations were acute pyelonephritis (52%), emphysematous pyelonephritis (20%) and cystitis (25%). Extended-spectrum beta-lactamase (ESBL)-producing *Escherichia coli* (48%) was the most frequent organism isolated followed by *Klebsiella* spp. (29%) and *Pseudomonas* spp. (23%). Recurrent episodes of UTI with same organisms were noted in 62% patients. Death occurred in 12.5% patients due to septic shock. Renal calculi (24%) and double J (DJ) stent placement (30%) were associated with recurrent UTIs, though this was not statistically significant. Resistance to higher antibiotics (colistin, carbapenems, piperacillin-tazobactam, cefoperazone-sulbactam, third-generation cephalosporins) (65.4%, r = 0.81), diabetes (62.5%, r = 0.79), urological procedure (39.5%, r = 0.68), prior hospitalization (75%, r = 0.84), history of UTI prior to the study period (44%, r = 0.72) and need for per urethral catheter (PUC) beyond 7 days (35%, r = 0.74) had significant correlation with recurrent UTIs.

Keywords: Recurrent urinary tract infections, urinary tract infections, multidrug-resistant microbes

Urinary tract infections (UTIs) are one of the most frequent community-associated and health care-derived infections that drive antibiotic usage and hospitalizations around the world. The prevalence of UTI in the general population is 11%, while elderly women (age >65 years) exhibit a higher prevalence at 20%[1]. Uropathogenic *Escherichia coli* (*E. coli*) (UPEC) is the dominant infectious agent in both uncomplicated and complicated UTIs. *Enterococcus* spp. and *Candida* spp. are substantially more common in complicated infections, while *Staphylococcus saprophyticus* (*S. saprophyticus*) is rare[1].

Recurrent UTI is described ≥2 infections in 6 months or ≥3 infections in 1 year[1]. From the clinical perspective, the second episode of UTI can be considered as a recurrence and requires a diligent approach to diagnosis and management.

In this retrospective observational study, we aimed to evaluate the clinical spectrum of recurrent UTIs in a tertiary care hospital and identify etiological factors contributing to this entity.

The objectives were to also study the microbiological spectrum and antimicrobial resistance patterns of organisms causing recurrent UTIs and evaluate the associated significant risk factors.

MATERIALS AND METHODS

A retrospective observational single-center study in a tertiary care hospital in Mumbai, India was conducted from 1st January 2021 to 31st December 2021. Indoor patients aged >18 years, with ≥2 episodes of culture-positive UTIs, were included. Patients <18 years, kidney-transplant recipients, those on immunosuppressive agents and pregnant patients were excluded. Demographic details, clinical symptoms, signs, drug history including use of sodium-glucose co-transporter type 2 (SGLT2) inhibitors, radiological and laboratory data including urine and blood cultures, of all patients were recorded in the Case Record Form. The details of

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treatment including urological interventions received and outcomes in hospital were noted. Clinical history and details of treatment of prior hospitalization with UTI were also recorded. Bacterial isolates from urine and blood culture were identified by biochemical profiling using VITEK-2 System, an automated microbiology bacterial identification and antimicrobial susceptibility system. The extended-spectrum beta-lactamase (ESBL) test was done using VITEK-2 ESBL test. Pearson correlation coefficient was used as a statistical method to determine association.

The study was conducted with approval from Institutional Ethics Committee.

RESULTS

Forty-eight patients satisfied the inclusion criteria; of these, 37.5% were female and 62.5% were male. Their mean age was 57.8 ± 11.2 years. Fever (79%), dysuria (60%) and flank pain (50%) were the most common symptoms. The common manifestations of UTI were acute pyelonephritis (52%), emphysematous pyelonephritis (20%) and cystitis (25%). Recurrent episodes of UTI with same organism were noted in 62% patients and 12.5% patients died due to septic shock.

ESBL *E. coli* (48%) was the most frequent organism isolated followed by *Klebsiella* spp. (29%) and *Pseudomonas* spp. (23%) (Fig. 1). The antimicrobial resistance pattern was as follows: colistin (8%), carbapenems (72%), piperacillin/tazobactam (80%), cefoperazone/sulbactam (75%), aminoglycosides (72%), fluoroquinolones (80%), third-generation cephalosporins (92%) and penicillins (95%) (Fig. 2).

Renal calculi (24%), DJ stent placement (30%), use of SGLT2 inhibitors (8.3%) did not correlate statistically with recurrent UTI; however, resistance to higher antibiotics (64.5%, r = 0.81), diabetes (62.5%, r = 0.79), urological procedure (39.5%, r = 0.68), prior hospitalization (75%, r = 0.84), history of UTI prior to the study period (44%, r = 0.72) and need for per urethral catheter (PUC) beyond 7 days (35%, r = 0.74) had statistically significant correlation with recurrent UTIs.

Figure 3 shows the risk factors that had statistically significant association with recurrent UTIs.

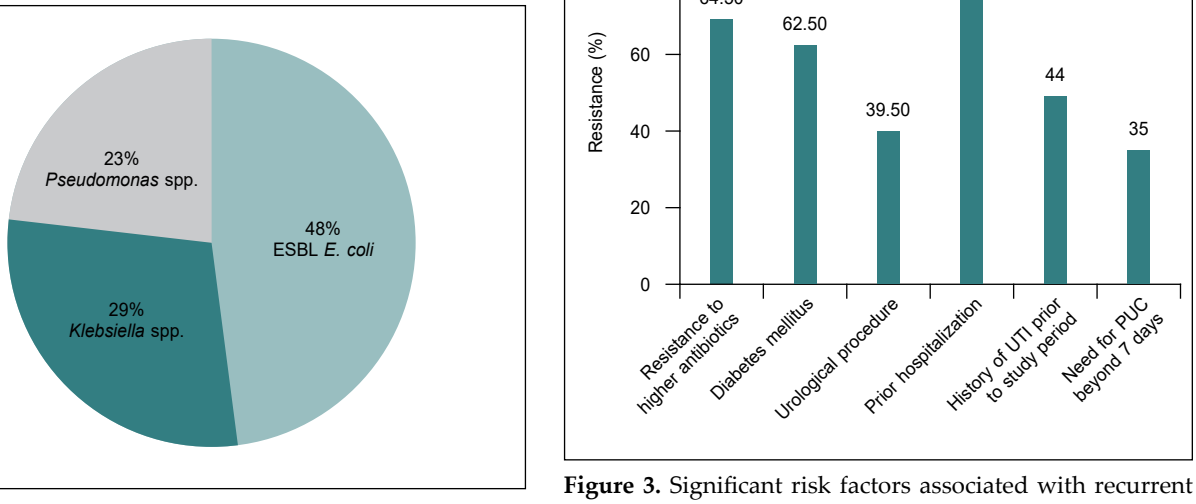

Figure 1. Microbiological spectrum of recurrent UTI.

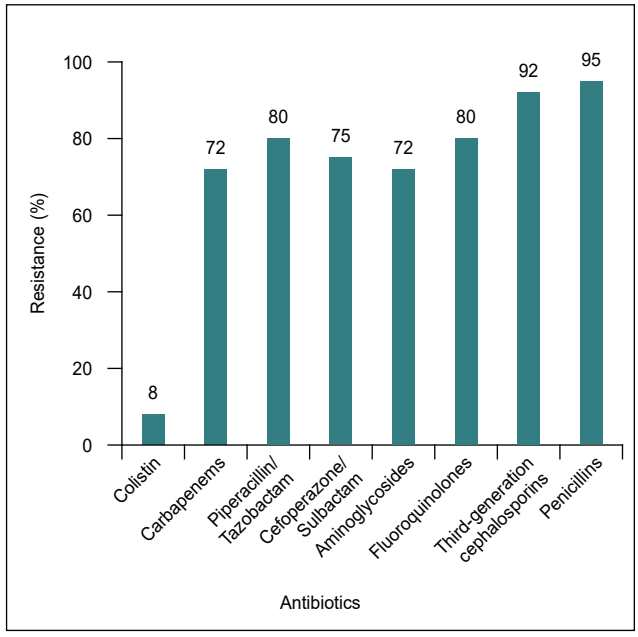

Figure 2. Antimicrobial resistance pattern.

Figure 3. Significant risk factors associated with recurrent UTIs.

DISCUSSION

Urinary tract infections are among the most common infections in all age groups, which can have a wide presentation from simple cystitis to very severe pyelonephritis. Recurrent UTIs, as one of the most common problems in nephrology and urological clinics, significantly increase health care costs and bear a negative impact on the patients' quality of life. The incidence of recurrent UTIs may be as high as 44%[1]. After a first episode of an uncomplicated UTI, at least 1 second episode will occur in 27% of women in the next 6 to 12 months[2]. The clinical presentation and pathogenesis of recurrent UTIs is similar to sporadic UTI.

The pathogenesis of recurrent UTI might include two mechanisms-bacterial factors and deficiency in host defense mechanism.

The bacterial factors that contribute to recurrent UTIs are described below.

Gastrointestinal tract functions as a reservoir for uropathogens, which are repeatedly reintroduced into the urinary tract via contamination of the periurethral surface and subsequent retrograde ascension[3].

Strain-specific bacterial virulence factors such as flagella/pili, adhesins, extracellular polysaccharides, lipopolysaccharides, toxins, ureases, proteases and iron-scavenging siderophores, biofilm formation may also have a role in pathogenesis of recurrent UTIs.

A subpopulation of bacterial cells ("persistors") in the biofilm, are known to reversibly reduce their metabolic activity, adopting a dormant state that can evade host defenses as well as treatments that target active metabolic pathways or activities such as cell division[4].

Bacterial resistance and resilience: The overuse of antibiotics has led to emergence of strains with specific genetic traits allowing them to survive and proliferate in the presence of a single or even a class of antimicrobial compounds[5,6].

Mean age of the study group was 57.8 ± 11.2 years with a relatively younger and predominantly male (62.5%) population, contrary to other studies that had an older and predominantly female population[1,7]. Fever (79%), dysuria (60%) and flank pain (50%) were the most common symptoms similar to the presentation in the study by Hase et al[8].

The most frequent organism isolated in our study was ESBL *E. coli* (48%) followed by *Klebsiella* spp. (29%) and *Pseudomonas* spp. (23%). In a recent study of 477 patients assessing risk factors and efficacy of low-dose prophylactic antibiotic therapy in adult patients with recurrent UTIs, the most common uropathogens isolated in urine culture were *E. coli* (49%), *Klebsiella pneumoniae* (21%), *Enterococcus faecalis* (9.2%)[9]. Multidrug-resistant (MDR) organisms are now frequently implicated in recurrent UTIs.

Figure 4 and Table 1 explains the mechanisms for multidrug resistance and describes the coding genes, corresponding enzymes and implicatory organisms in drug-resistant UTIs.

ESBLs are variants of beta-lactamases that confer resistance to the extended-spectrum cephalosporin antibiotics such as cefotaxime, monobactams and aztreonam. The reason for this resistance is that ESBLs are encoded by plasmids, which also carry resistance genes for other antibiotics[6]. In a cross-sectional study of 427 patients assessing the prevalence and risk factors of ESBL-producing uropathogens, the prevalence was 38.4% with *E. coli* being the most frequent uropathogen[11]. Patients with recurrent UTI had 5 times higher relative risk of having ESBL-producing uropathogens (odds ratio [OR], 4.7) followed by previous antibiotic use (OR 3.07), hemodialysis (OR 2.92), chronic kidney disease (OR 2.69) and diabetes mellitus (OR 1.87)[11].

In our study, *E. coli*, *Klebsiella* and *Pseudomonas* spp. showed resistance to carbapenems (72%), piperacillin/tazobactam (80%), cefoperazone/sulbactam (75%), aminoglycosides (72%), fluoroquinolones (80%), third-generation cephalosporins (92%) and penicillins (95%). Resistance to higher antibiotics was seen in 64.5% (r = 0.81) of the study population.

In a study assessing antibiotic resistance of uropathogens in hospitalized patients, *K. pneumoniae* were resistant to amoxicillin + clavulanic acid (75.0%), piperacillin + tazobactam (76.2%), cefotaxime (76.2%), cefuroxime (81.0%), ciprofloxacin (81.0%) and trimethoprim + sulfamethoxazole (81.0%). Carbapenems were effective against all *E. coli* and *Proteus mirabilis*. Some *K. pneumoniae* isolates (13.6%), two from internal and one from nephrology wards, produced metallo-beta-lactamases (MBLs). *E. coli* (22.6%), *K. pneumoniae* (81.8%) and all *Enterococcus faecium* were MDR organisms. Some *E. coli* (26.2%), *K. pneumoniae* (63.6%) and *P. mirabilis* (14.3%) isolates produced ESBL. Vancomycin-resistant *E. faecium* was also found[12].

Our study reiterates the escalating antimicrobial resistance in this region and the difficulty in the choice of empiric therapy. It also underlines the importance of sending appropriate cultures before antibiotic initiation to aid in better outcome.

	Amber class A	Amber class B	Amber class C	Amber class D
Enzymes	• ESBLs including CTX-M, SHV • Carbapenemases KPC	• Metallo-beta-lactamases including IMP, NDM	• Cephalosporinases AmpC	• Oxacillinases
Organisms commonly affected	• *E. coli* • *K. pneumoniae* • *K. oxytoca* • *P. mirabilis* • *S. marcescens* • *Enterobacter* spp.	• *E. coli* • *K. pneumoniae* • *K. oxytoca* • *S. marcescens* • *Enterobacter* spp.	• Chromosomal AmpC • *Enterobacter* spp. • *C. freundii* • *S. marcescens* • Plasmid AmpC • *K. pneumoniae* • *E. coli*	• *A. baumannii* • *P. aeruginosa*
Implications for detection and treatment	• Inhibited by clavulanic acid • Remains susceptible to carbapenems • Chromosomal genes may be inducible • Inhibited by clavulanic acid	• Remain susceptible to aztreonam • NDM producers typically have additional resistance genes	• Chromosomal or plasmid-mediated • Chromosomal genes may be inducible • Also resistant to aztreonam • Remain susceptible to: □ Carbapenems □ Fourth-generation cephalosporins e.g., cefepime □ Avibactam	• Highly diverse group of enzymes • Some also hydrolyze carbapenems

Figure 4. Amber classification of selected beta-lactamases[10].

ESBL = Extended-spectrum beta-lactamases; CTX-M = Cefotaxime-Munich; SHV = Sulfhydryl variable; KPC = *Klebsiella pneumoniae* carbapenemase; IMP = Imipenem; NDM = New Delhi metallo-beta-lactamase; AmpC = Ampicillinase C.

Adapted from: Mahony M, McMullan B, Brown J, Kennedy SE. Multidrug-resistant organisms in urinary tract infections in children. Pediatr Nephrol. 2020;35(9):1563-73.

Table 1. Mechanisms of Resistance of Other Antibiotics[10]

Antibiotic class	Mechanism of resistance	Organisms
Aminoglycosides	Target site mutation - production of 16S rRNA methylases	*E. coli* *K. pneumoniae* *Acinetobacter* spp.
Quinolones	Drug modification - production of aminoglycoside-modifying enzymes Phosphotransferases (APH) Acetyltransferases (AAC) Nucleotidyltransferases (ANT) Target site mutation - DNA gyrase and topoisomerase IV	*E. coli* *K. pneumoniae* *A. baumannii* *P. aeruginosa* *E. coli* *Klebsiella* spp. *P. aeruginosa*
Trimethoprim or trimethoprim-sulfamethoxazole	Pentapeptide repeats - Qnr Overproduction of enzymes Dihydropteroate synthase (DHPS) Dihydrofolate reductase (DHFS)	*E. coli* *Klebsiella* spp. *E. coli*

Adapted from: Mahony M, McMullan B, Brown J, Kennedy SE. Multidrug-resistant organisms in urinary tract infections in children. Pediatr Nephrol. 2020;35(9):1563-73.

Recent rise in the use of SGLT2 inhibitors has been met with a surge in the incidence of genitourinary tract infections as demonstrated in a retrospective cohort study of 253 diabetics on SGLT2 inhibitors, where the 3- and 6-month incidences of UTIs were 1.98% and 13.57%, respectively[13]. In our study, use of SGLT2 inhibitors (8.3%) was associated with recurrent UTI though this was not statistically significant.

Similarly, renal calculi (24%) and DJ stent placement (30%) were associated with recurrent UTI though not statistically significant. Diabetics comprised 62.5% of our study group that was higher as compared to the cohort studied by Nabi[14] (39.6%).

In our study, resistance to higher antibiotics (64.5%, r = 0.81), diabetes (62.5 %, r = 0.79), urological procedure (39.5%, r = 0.68), prior hospitalization (75%, r = 0.84),

history of UTI prior to the study period (44%, r = 0.72) and need for PUC beyond 7 days (35%, r = 0.74) had significant correlation with recurrent UTI. In a study assessing risk factors and efficacy of low-dose prophylactic antibiotics in 250 adult patients with recurrent UTIs, diabetes mellitus, chronic renal disease, use of immunosuppressive drugs, renal transplant, any form of urinary tract catheterization, immobilization, neurogenic bladder, history of urinary incontinence and urological procedures showed statistically significant association[9].

A limitation of our study is that it only included patients who had to be hospitalized in a tertiary care hospital for recurrent UTI. This precludes community-acquired UTI, which may be recurrent but does not need hospitalization. Additionally, a susceptible population of kidney transplant recipients and those on immunosuppressive medication were not included in the study.

CONCLUSION

Our study thus highlights the constantly growing epidemic of recurrent UTIs and associated risk factors even in those subgroups of patients who ordinarily are not susceptible to recurrent UTI. Resistance to higher antibiotics, urological interventions, diabetes, prior hospitalization, history of UTI prior to study period, need for PUC beyond 7 days contribute to the rising incidence of recurrent UTIs. The associated morbidity takes a heavy toll on the patient's well-being and the health infrastructure. Appropriate and pre-emptive redressal of the underlying etiological factors could assist in reducing the incidence of recurrent UTI. Precise knowledge of the antibiotic resistance pattern of the local microflora and uropathogens is essential to curb the menace of MDR UTI. Thus, close follow-up of patients with risk factors after their first episode of UTI, adoption of antimicrobial and nonantimicrobial preventive strategies and antibiotic stewardship is the need of the hour before this epidemic reaches alarming proportions.

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RESEARCH ARTICLE

Navigating Choices: A Questionnaire-based Study on Usage of Antiplatelet Therapies in Management of Acute Coronary Syndrome in India

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ABSTRACT

Background: Percutaneous coronary intervention (PCI) is a common invasive cardiac procedure used to treat acute coronary syndrome (ACS). The main objective of anticoagulant therapy in PCI is to minimize the risk of plaque rupture and decrease the formation of blood clots. Understanding clinicians' prescription patterns is crucial for optimizing treatment strategies for patients with ACS who have undergone PCI. **Methods:** It was a cross-sectional, questionnaire-based, noninterventional study which included questionnaire responses from 136 cardiologists, regarding usage of antiplatelets in ACS management. **Results:** Ticagrelor and aspirin dual antiplatelet therapy (DAPT) is favored by 54% cardiologists in managing ACS patients who have undergone PCI, regardless of the presence or absence of type 2 diabetes mellitus (T2DM). Further, 78% of the participants preferred long-term DAPT over short-term and medium-term alternatives. Forty percent respondents preferred a 1-month triple antithrombotic therapy (TAT) for PCI patients with atrial fibrillation. Additionally, the study emphasized the importance of considering factors like age, bleeding history, hemoglobin, and creatinine clearance in determining the optimal antithrombotic strategy. **Conclusion:** This study contributes valuable insights into the real-world practices of health care practitioners, paving the way for more informed and personalized ACS management strategies in Indian patients.

Keywords: Percutaneous coronary intervention, acute coronary syndrome, dual antiplatelet therapy, ticagrelor

Acute coronary syndrome (ACS) is a complication arising from coronary artery disease (CAD) and is one of the primary causes of mortality worldwide. The combined impact of CAD and ACS results in approximately 7 million annual deaths globally. Percutaneous coronary intervention (PCI) is a nonsurgical, invasive method that aims to relieve coronary artery blockage while improving blood flow to ischemic tissues[1]. India faces significant public health and clinical issues due to ACS, which is the most prevalent cause of mortality and morbidity in the country. India has one of the highest ischemic heart diseases (IHD) burdens globally, resulting in 1.54 million deaths and 36.99 million disability-adjusted life years in 2017[2]. In more recent development, the Global Burden of Diseases Collaboration has reported an increase in age-standardized mortality rates for cardiovascular diseases in South Asia, including India, ranging from 248.6 to 350.9 per 1,00,000 persons in 2021[3].

The use of dual antiplatelet therapy (DAPT) in patients experiencing ACS and undergoing PCI, involving

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the combination of aspirin with another antiplatelet agent, has emerged as a fundamental aspect of PCI treatment[4]. Patients with ACS undergoing PCI face a heightened risk of thrombotic events attributable to disrupted atherosclerotic plaques and the presence of implanted stents. DAPT is a strategic measure to resolve the risks related to stent thrombosis and major adverse cardiovascular events[5,6]. The DAPT consists of aspirin and a P2Y12 receptor inhibitor, such as clopidogrel, prasugrel, or ticagrelor. Aspirin inhibits platelet activation and aggregation, while the P2Y12 inhibitors contribute to more potent and specific antiplatelet effects[7]. The critical decision of selecting the appropriate P2Y12 inhibitor is contingent upon the patient's clinical characteristics and bleeding risk.

Little is known about usage of DAPT in real-world settings in managing ACS in India. We aimed to comprehensively assess the usage of DAPT in ACS management across the country. Based on the findings of the study, we aim to provide in-clinic recommendations for the use of DAPT in patients with medically managed ACS or ACS patients who have undergone PCI.

METHODOLOGY

The study was pan-India, cross-sectional, questionnaire-based, noninterventional, observational study involving health care professionals (HCPs) managing ACS patients. The survey tool was developed after thorough research and comprised of 8 multiple-choice response questions to be rated as per options provided. It aimed to collect data on the choice of DAPT in patients who have undergone PCI, with or without diabetes, duration of DAPT, factors affecting duration of DAPT, utilization of low-dose ticagrelor, etc. The data was collected digitally from the clinicians through case report form (CRF) via an individual login. The data collected was checked for quality, supervised independently by an investigator, and reviewed by 2 investigators.

Descriptive statistics were used, and the analysis was performed using SPSS 23.0 and Microsoft Excel. For all the variables, estimates were calculated using the total number of responses per question as the denominator. A simple percentage was calculated for all the variables.

Based on the study findings, recommendations were formulated and validated as good practice points by the experts participating in the development of the manuscript.

RESULTS

One hundred thirty-six survey participation invitations were issued to HCPs to participate in the survey digitally. Scoring a 100% response rate, all 136 HCPs returned the response.

Which DAPT is Your Preferred Choice in Patients of ACS Undergone PCI? (With/Without T2DM)

Response: The study respondents mentioned the use of ticagrelor and aspirin combination as their preferred choice (54.1%) in ACS patients who have undergone PCI (with or without T2DM) as depicted in Figure 1.

Which DAPT is Your Preferred Choice in Medically Managed Patients of ACS? (With/Without T2DM)

Response: Clopidogrel and aspirin combination was the most preferred choice, opted by 43.4% as extremely likely and 26.5% as likely option in medically managed

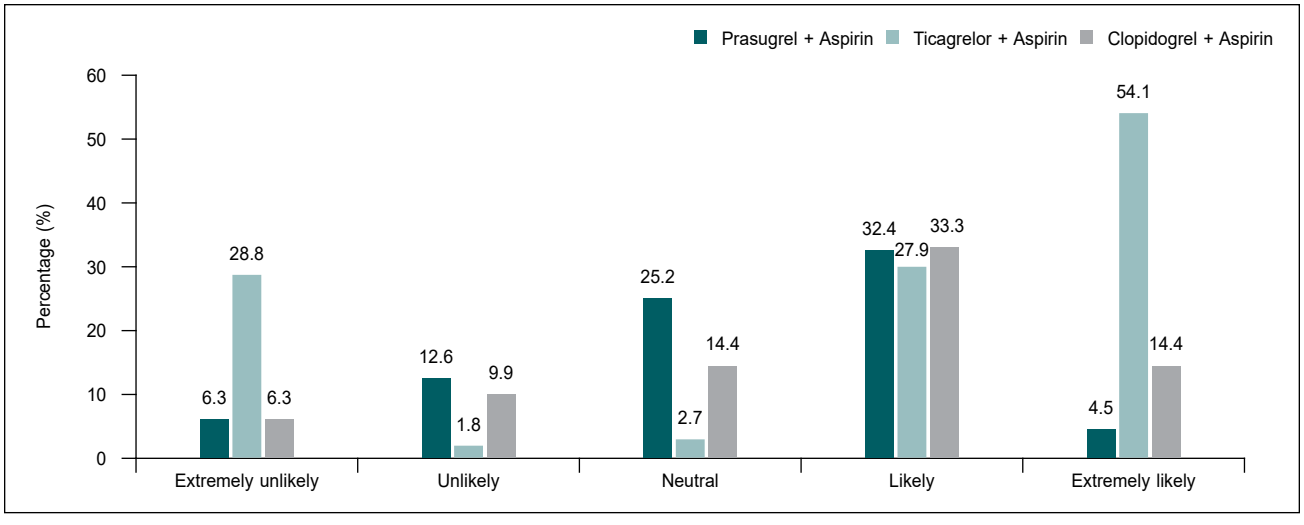

Figure 1. Preferred therapy for ACS patients who have undergone PCI (with/without T2DM).

patients of ACS (with/without T2DM), followed by 30.9% of the participating cardiologists selecting ticagrelor and aspirin combination as the extremely likely choice (Fig. 2).

What is Your Most Preferred DAPT Duration Strategy (up to 1-year Post-PCI)?

Response: It was observed that the standard DAPT regimen of 1 year was the preferred choice among more than 78% of the participating cardiologists compared to short-term and medium-term regimens (Fig. 3).

What is the Most Common APT Strategy >1-year Post-PCI?

Response: 44.4% participating cardiologists preferred clopidogrel + aspirin as the most common APT strategy >1-year post-PCI, followed by 27.3% choosing combination of ticagrelor 60 mg BD + aspirin as the extremely likely option as shown in Figure 4. It was interesting to note that despite the guidelines suggesting ticagrelor 60 mg BD post 1 year of PCI, 42.4% of the participants chose the option to be an extremely unlikely one.

Will You Prefer Ticagrelor 60 mg in Patients having Low Bleeding Risk and Multiple Ischemic Risk Factors?

Response: More than 50% of the participating cardiologists were not sure and around 59% participating cardiologists disagreed that they would prefer ticagrelor 60 mg in patients having low bleeding risk and multiple ischemic risk factors as depicted in Figure 5.

What is the Usual Duration of TAT in PCI Patients with Atrial Fibrillation?

Response: Among the participating cardiologists, most of the doctors (45.3%) preferred the triple antithrombotic therapy (TAT) in PCI patients with atrial fibrillation for 1 month (Fig. 6).

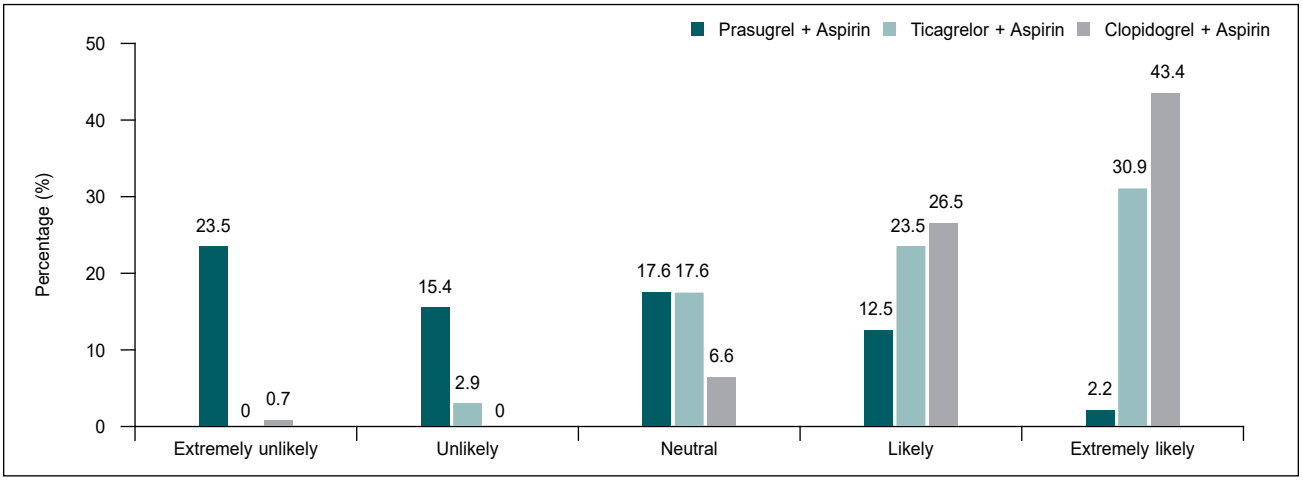

Figure 2. Preferred therapy for medically managed ACS patients (with or without T2DM).

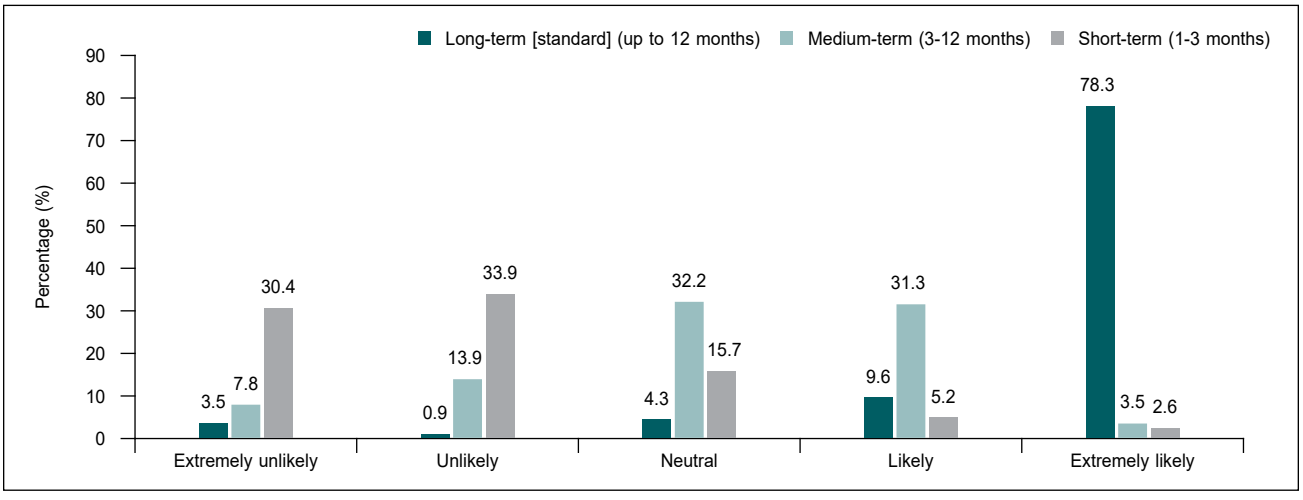

Figure 3. Preference of physicians for the duration of DAPT therapy in patients with ACS who have undergone PCI.

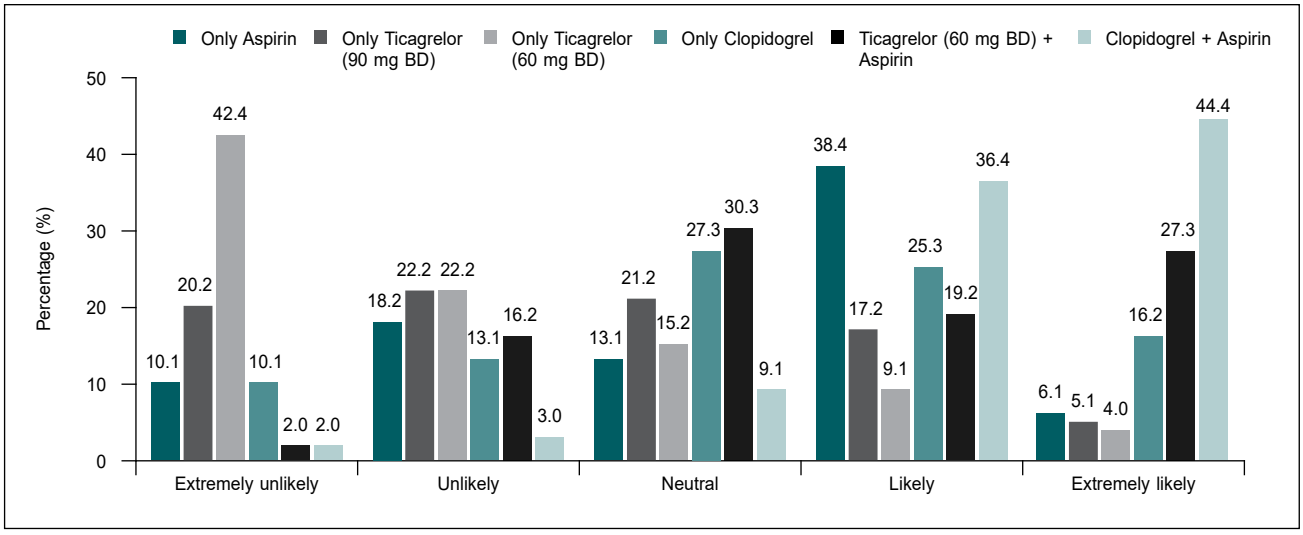

Figure 4. Most common APT strategy >1-year post-PCI.

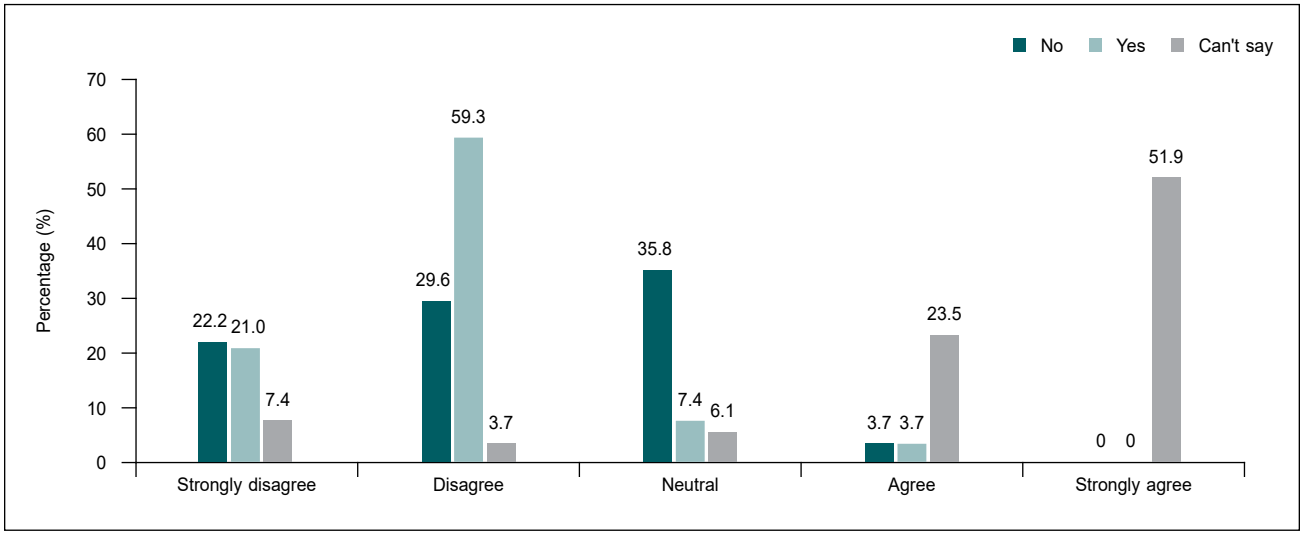

Figure 5. Preference rate for opting ticagrelor 60 mg BD in patients having low bleeding risk and multiple ischemic risk factors.

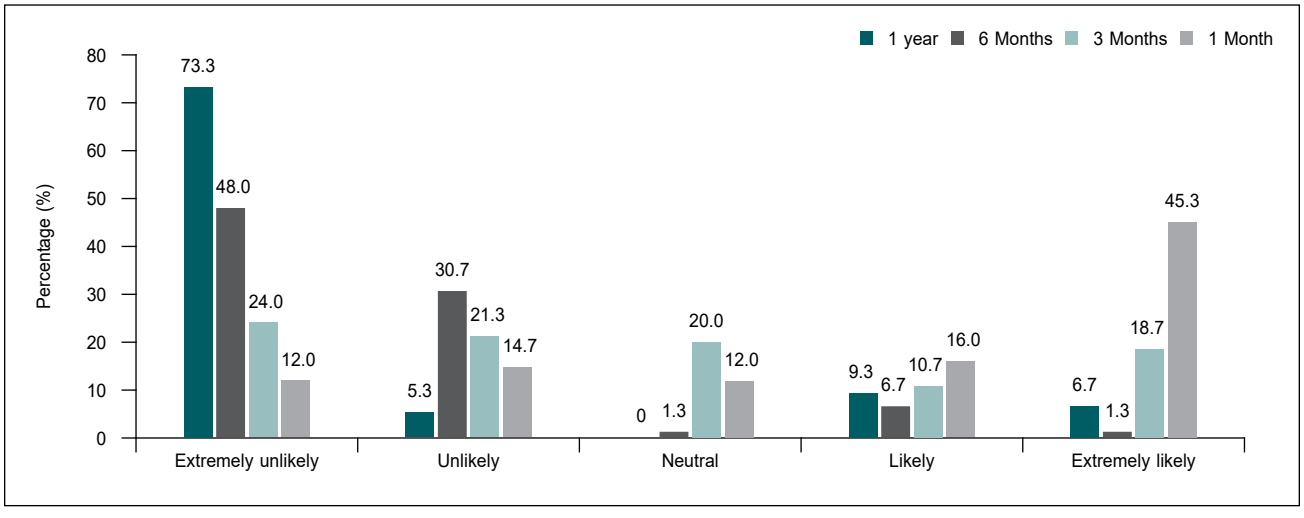

Figure 6. Preferred duration of TAT.

Additionally, the study also observed that over 50% of cardiologists believed that age is a crucial factor in deciding the duration of a DAPT regimen. It also emphasized that history of prior bleeding, hemoglobin, creatinine clearance and liver function test were more important in determining the optimal antithrombotic strategy when compared with left ventricular ejection fraction and WBC.

DISCUSSION

The findings of our study reported ticagrelor to be the preferred option in the treatment of patients with ACS treated with PCI, while still clopidogrel and aspirin combination seem to be preferred by majority of the doctors in the medically managed cases and treatment of patients post 1 year of PCI. The results led to a class I recommendation for their use in individuals with ACS, with or without ST-segment elevation[8,9]. Large-scale clinical trials (NCT00097591, NCT00391872) have unequivocally shown that ticagrelor and prasugrel outperform clopidogrel in inhibiting platelet aggregation, leading to a significant reduction in the occurrence of ischemic events[10-12]. A study by Sawhney et al (2019), demonstrated the use of ticagrelor in various real-world settings for different types of ACS management strategies in India. It reported that majority of patients diagnosed with ST-segment elevation myocardial infarction (STEMI) who underwent PCI were prescribed ticagrelor[1]. A similar picture is observed in the current study.

A meta-analysis by Tan et al (2017) indicated that ticagrelor may reduce the occurrence of the composite end point involving cardiovascular death, myocardial infarction, and stroke, along with reducing platelet reactivity in patients with T2DM experiencing ACS. Given the divergent platelet reactivity observed between T2DM patients and the general ACS population, it is advisable to exercise caution when incorporating ticagrelor into clinical applications[13]. Ticagrelor also exhibited lower all-cause mortality in patients with ACS, myocardial infarction, or stroke, compared to clopidogrel, and its overall tolerance was favorable, without increasing major bleeding rates[9].

The results of the TWILIGHT trial have revealed that ticagrelor monotherapy following a brief DAPT regimen proves to be an effective and safe strategy to prevent bleeding in high-risk patients undergoing PCI with drug-eluting stents[14,15]. It is important to mention that while the recommendation for ticagrelor use extends to high-risk cases undergoing PCI as well as those with stable angina, its benefits persist irrespective of the chosen therapeutic approach, whether medical, invasive, or surgical[16].

The PEGASUS-TIMI 54 trial showed that extended use of DAPT with either doses of 60 mg and 90 mg of ticagrelor significantly reduced ischemic events and major adverse cardiovascular events compared to aspirin alone[17,18]. PLATO trial demonstrated that a 12-month course of ticagrelor was more effective than clopidogrel in reducing the primary composite end point of myocardial infarction, stroke, or cardiovascular death. Ticagrelor also exhibited a lower all-cause mortality compared to clopidogrel and its overall tolerance was favorable, without an increase in the rate of overall major bleeding, but with an increased risk of nonprocedure-related bleeding relative to clopidogrel[9,19]. In our study also, the cardiologists preferred the standard DAPT, extending up to 1 year following a PCI.

The latest guidelines from the American College of Cardiology/American Heart Association regarding the duration of DAPT following PCI using drug-eluting stents strongly recommend maintaining DAPT for a minimum of 12 months after experiencing an ACS and for at least 6 months after revascularization in cases of stable IHD[20]. In the PEGASUS trial, adjunctive ticagrelor therapy significantly reduced ischemic recurrences on top of aspirin, albeit at the expense of increased bleeding complications. Low-dose ticagrelor seems an appealing strategy to optimize ischemic and hemorrhagic risk in elevated-risk patients with stable CAD undergoing PCI[21]. In a study conducted by Sharma et al (2020), the results showed that ticagrelor 60 mg twice daily is recommended for duration of up to 3 years in high-risk patients[17]. In the present study, however, ticagrelor 60 mg BD was shown to be extremely unlikely to be used post 1 year of PCI. The study also reported that cardiologists did not prefer using ticagrelor 60 in patients with low bleeding risk and multiple ischemic risk factors. In a study by Calderone et al (2020), it was observed that among patients with a history of myocardial infarction (1-3 years prior) and cardiovascular risk factors, ticagrelor caused a significant reduction in ischemic events compared to a placebo, however, with an increased risk of bleeding. Notably, the ticagrelor 60 mg twice-daily regimen showed the most favorable safety profile[22].

In an observational study involving 568 unselected patients who underwent PCI, researchers found that a 1-month duration of TAT yielded comparable rates of ischemic events, bleeding events, and overall clinical outcomes compared to longer durations. Consequently,

shortening TAT to 1 month could be a viable option for patients at high risk of bleeding. However, these findings need validation through prospective studies that evaluate TAT regimens of predetermined lengths, customized to the ischemic and bleeding risks of individual patients[23].

In another network meta-analysis, data from 12,329 patients concluded that short-term TAT offers advantages in reducing bleeding events to varying extents. The findings suggest that short-term TAT should be considered as the default approach, unless there exists a notable risk of stent thrombosis that justifies extending the duration of TAT appropriately[24].

In the initial month following PCI, there is a higher risk of thrombotic complications. Hence, it is sensible to employ TAT for 1 month in patients with a high thrombotic risk and a relatively low risk of bleeding. However, extending TAT beyond this 1-month period after PCI is not advisable[5,25].

The responses obtained in the current research are in sync with the earlier research and guideline recommendations.

RECOMMENDATIONS

Recommendations for the management of ACS patients who are medically managed and who may have undergone PCI (with or without T2DM)

- **Recommendation 1:** Ticagrelor and aspirin combination is the preferred therapy of choice in ACS patients who have undergone PCI (with or without T2DM).
- **Recommendation 2**. DAPT is preferred to be used over the long-term (up to 1-year post-PCI).
- **Recommendation 3**: The precise risk of bleeding and ischemic events should be assessed before determining the optimal antithrombotic strategy for individual patients.
- **Recommendation 4**: The duration of TAT in PCI patients with atrial fibrillation should be 1 month.
- **Recommendation 5**: The major factors which decide the duration of DAPT are age, history of prior bleeding, hemoglobin, and creatinine clearance in the Indian settings.

CONCLUSION

This study highlights the usage patterns of DAPT in the management of ACS among HCPs in India. The study reveals a preference for a ticagrelor and aspirin combination in ACS patients who have undergone PCI, mostly for period of 1 year. Multiple trials have demonstrated the greater efficacy of ticagrelor in reducing the ischemic events compared to clopidogrel, and the cardiologists seem to view it as a valuable option besides clopidogrel. The recommendations underscore the importance of assessing factors like age, bleeding history, hemoglobin, and creatinine clearance for determining the optimal antithrombotic strategy. The study contributes valuable insights into the real-world practices of health care practitioners, paving the way for more informed and personalized ACS management strategies in Indian patients.

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REVIEW ARTICLE

Role of Sodium Alginate in Gastroesophageal Reflux Disease: An Overview

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ABSTRACT

Sodium alginate helps manage and treat heartburn and gastroesophageal reflux disease (GERD). This article discusses the structure, mechanism of action and clinical application. A brief review of the literature is carried out.

Keywords: Gastroesophageal reflux disease, sodium alginate

Gastroesophageal reflux disease (GERD) is a digestive disorder that occurs when gastric contents, which are acidic stomach juices or food and fluids, reflux from the stomach into the esophagus. This irritates the stomach lining, leading to heartburn and regurgitation occurring two or more times a week[1]. The symptoms can occur in the daytime but have a higher impact at night due to loss of usual physiological function associated with sleep and supine position[2]. In India, 22.2% of people suffer from heartburn[3]. The prevalence of GERD ranges from 7.6% to 30%, and less than 10% of GERD patients in India have erosive esophagitis[4].

The typical symptoms of GERD are heartburn, regurgitation and water brash/hypersalivation, while the atypical symptoms are nausea, eructation/belching, bloating, slow digestion, early satiety, vomiting, epigastric pain, precordial chest pain, early and nocturnal awakening and nightmares, hoarseness, pharyngeal pain, cough, wheeze and chronic rhinosinusitis. The alarming symptoms of GERD include dysphagia, odynophagia, epigastric mass, gastrointestinal tract bleeding and lymphadenopathy[5]. Patients with GERD have significantly poor health-related quality of life (HRQoL). The rate and intensity of acid complaints or gastrointestinal symptoms significantly influence the quality of life. The presence of gastrointestinal symptoms is associated with reduced work productivity[6].

Treatment goals and strategies of GERD are based on (a) effective and rapid relief of symptoms and improvement in HRQoL for patients; (b) healing of esophageal mucosal damage, preventing the relapse of erosive esophagitis and reducing the development of other serious complications; (c) preventing the repeated reflux of gastric contents into the esophagus and reduce the damaging effect of gastric acid[6,7].

MECHANISMS OF ACTION OF VARIOUS DRUGS FOR TREATMENT OF GERD

Antacids

Antacids reduce the acid reaching the duodenum by neutralizing the acid present in the stomach[8]. They also offer rapid and short-term relief[9]. The easily available antacids and serotonergic or dopaminergic receptor activators offer only short-term relief of symptoms[9].

Proton Pump Inhibitors

Proton pump inhibitors (PPIs) bind and inactivate the hydrogen potassium ATPase in the parietal cells of gastric mucosa. They are rapid-acting and produce a considerable but dose-dependent elevation of gastric pH[4]. PPIs do not significantly change the size and position of acid pockets, nor do they displace them to a more distal location. Acid pockets persist even after treatment with PPIs[10]. The long-term continuous use of PPIs and prokinetics is associated with chronic side effects, which limit their use. Safety implications with PPIs include increased risk of diseases, such

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as hospital- and community-acquired pneumonia, *Campylobacter enteritis*, *Clostridium difficile*-associated disease and fractures[11]. Despite high efficacy, failure to respond to PPIs has now become the most common presentation in gastrointestinal practice[12].

Prokinetics

Since it is a known fact that the pathogenesis of GERD is a disordered function of the lower esophageal sphincter, the use of a prokinetic agent in such patients seems logical[13]. Prokinetics activate serotonergic or dopaminergic receptors to increase esophageal and gastric peristalsis, which aids in esophageal clearance[9,14]. This is particularly crucial for individuals with GERD characterized by transient lower esophageal sphincter relaxation (TLESR), which refers to spontaneous lower esophageal sphincter relaxation unrelated to swallowing and plays a pivotal role in GERD patients.

In GERD patients, symptom relief through acid-suppressive therapy usually obviates the need for additional treatments or diagnostic procedures. Acid-suppressive therapy, such as PPIs, alleviates symptoms, fosters esophageal healing and mitigates potential complications. However, addressing the underlying cause of TLESR may become necessary to sustain remission and deter relapses. In situations where acid-suppressive therapy falls short of yielding a complete response, including a prokinetic agent may be advantageous[15].

Additionally, prokinetics alone may not be sufficient for significant relief in GERD patients. When used in conjunction with PPIs, prokinetics reduce the frequency of reflux episodes, resulting in more substantial improvements in symptom scores[16].

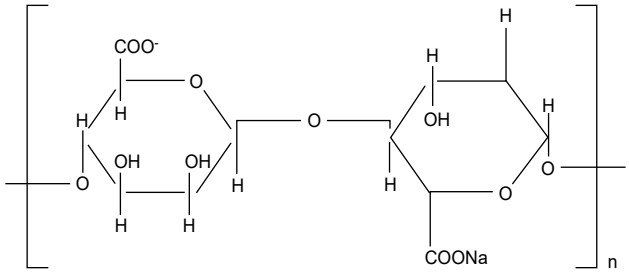
Histamine Receptor Antagonists

The histamine receptor antagonists competitively and reversibly block histamine type 2 (H_2) receptors, thereby decreasing gastric acid secretion. They are safe and significantly more effective than antacids. Acid suppression therapy with histamine receptor antagonists, though effective, has slower onset of action and is relatively ineffective in most patients[6]. Patients continue to use acid-reducing medications regularly and have no significant differences in grade of esophagitis and impact on quality of life[9,13].

Alginates

Alginates precipitate to form a gel, which then floats in the stomach and displaces postprandial gastric acid pocket, thus physically blocking the refluxate from entering the esophagus. It may also coat and protect the esophageal mucosa[9]. The acid pocket is a phenomenon that occurs in both healthy individuals and in patients suffering from esophageal hypersensitivity after a meal. Acid pockets are unbuffered acidic regions formed near the gastroesophageal squamocolumnar junction during postprandial period. This region escapes the buffering effect of meals, remaining highly acidic (median pH 1.6) compared with the body of stomach (pH 4.7) and thus is termed acid pocket. It plays an important role in causing acid reflux by shortening the lower esophageal sphincter after a meal or during transient hiatus herniation[17].

Structure of sodium alginate



Sodium alginate is a basic polysaccharide derived from alginic acid. It is composed of 1,4-β-D-mannuronic and L-guluronic acid. It is obtained from brown algae and contains 30% to 60% alginic acid. The conversion of alginic acid to sodium alginate allows its solubility in water, which assists in its extraction[18]. The floating ability of alginate depends on the amount of carbon dioxide generated, amount of carbon dioxide entrapped in gel and the molecular properties of alginate, i.e., molecular weight and the ratio of D-mannuronic and L-guluronic acid. The addition of calcium to the alginate crosslinks with an alginate-containing acid polymer, that aids in floating with greater viscoelastic strength. On the other hand, the combination of aluminum and alginate reduces floating ability. The magnesium-alginate antacid formulation also remains floating in the stomach for only 1 hour[19].

Modes of action

Alginates act by the following modes.

Prevention of gastric reflux: Alginates prevent gastric reflux by suppressing gastric reflux, and preventing postprandial reflux. The G-block structure of sodium alginate reacts with the acid in the stomach, thus producing a low-density gel that floats on top of stomach contents. This forms a physical barrier that suppresses gastric reflux. The physical barrier formed by alginate eliminates or displaces the acid pocket, preventing postprandial acid reflux[20].

Inhibition of pepsin and bile acids: Alginates inhibit pepsin and bile acids by reflux of pepsin and bile acids and by relieving symptoms, such as regurgitation and heartburn. Pepsin and bile acids are believed to be a major etiological factors associated with the development of gastroesophageal complications, i.e., Barrett's esophagus and esophageal adenocarcinoma. Alginate relieves symptoms by removing both pepsin and bile acids from gastric refluxate, thus limiting their diffusion and aiding relief[18,20].

Mucosal protection: Alginates protect the mucosa firstly by reflux prevention and secondly by their bioadhesive potential. They play a major role in protecting esophageal mucosa by reducing risk of inflammation via prevention of reflux of gastric contents. Alginates form an adherent viscous layer when it comes in contact with the esophageal mucosa and demonstrate bioadhesive potential[20].

Sodium alginate has a rapid onset of action, within 1 hour of administration, when compared to other antacids[21]. The mode of action of alginate is physical and does not depend on absorption into the systemic circulation. On ingestion, alginate reacts rapidly with gastric acid to form an alginic acid gel, which has a near neutral pH and floats on the stomach contents and thus quickly and effectively prevents the impending gastroesophageal reflux. Alginate formulations require three chemical reactions to take place simultaneously: transformation to alginic acid, sodium bicarbonate reacting to form carbon dioxide and calcium carbonate releasing free calcium ions to bind with alginic acid providing strength to float. In severe cases, the float itself may be refluxed into the esophagus, in preference to the stomach contents, and exert a demulcent effect. The sodium alginate was found to be retained in the stomach for up to 4 hours, thus preventing acid reflux for a longer duration[22].

Alginate-containing formulations are safe, well-tolerated and comparable to the other antireflux medications such as omeprazole, ranitidine and other nonalginate antacids. Additionally, there have been no reports of any significant adverse events associated with alginate antacids. Alginate very rarely causes immune system disorders in the form of anaphylactic and anaphylactoid reactions and hypersensitivity reactions such as urticaria and respiratory effects like bronchospasm[23-26].

Uses of alginate

The floating ability of sodium alginate above the acid pocket aids in preventing acid reflux. Alginate therapy successfully led to a reduction in regurgitation compared to patients in the placebo group[23]. A randomized, double-blind placebo control trial suggested that the alginate-antacid combination (n = 212) compared to placebo (n = 212), is an effective treatment option in patients with reflux symptoms[7].

In obese patients, the alginate-antacid combination was more effective than control in suppressing gastric reflux after a late-night supper[23]. Sodium alginate was effective in patients suffering from heartburn and epigastric pain due to its faster onset of action, thus providing long-term relief of symptoms[27]. Sodium alginate, compared with anhydrous magaldrate was found to be quick in relieving heartburn symptoms and/or acid regurgitation[28].

Due to its localizing and acid neutralizing effect, the alginate-antacid combination was significantly more effective in reducing gastric reflux events[29]. The alginate-antacid combination is also effective in reducing postprandial esophageal acid exposure[30].

Adding sodium alginate to PPI therapy was significantly more effective in attaining a complete resolution of heartburn and heartburn-free days compared to PPI therapy alone[31]. Alginates were also effective in step-down or cessation of PPI therapy[11,20].

In patients, the addition of alginate with H_2 receptor antagonists was observed to be more effective in alleviating gastric acid reflux. Gastric reflux events were significantly reduced with sodium alginates compared to cimetidine[32].

Need of Alginate-antacid Combination

PPIs are considered the first-line approach for endoscopic healing and symptomatic relief in patients with GERD. Still, a substantial subgroup of patients, around 30%, continue to experience reflux symptoms despite adequate dosing[12,20]. Either because of general unease with open-ended pharmacotherapy or because of the intermittent nature of reflux symptoms, prefer to address reflux symptoms with PRN medication. The problem has been the limited efficacy of this approach; antacids neutralize gastric acid in a short time frame after ingestion, but the effect is soon overcome by meal-stimulated acid secretion[30].

On the other hand, treatment with the combination of alginate and antacid decreases the severity and frequency of heartburn, leading to complete resolution of symptoms[20]. The combination potentially targets postprandial symptoms because of its localized acid-neutralizing action in the proximal stomach, while maintaining effective alginate float[7]. The alginate-antacid

combination decreases burden of reflux symptoms, especially in PPI-unresponsive patients. The oral suspension of alginate that contains antacids, such as calcium carbonate, sodium bicarbonate and magnesium hydroxide, is used[20].

It should be given only on medical advice in children under 12 years of age. In adults and children over 12 years, 10-20 mL after meals and at bedtime is given. No dosage modification is required in elderly persons and patients with hepatic impairment, and can be safely administered. Alginate should be cautiously administered in renal insufficiency patients if a highly restricted salt diet is necessary. In patients with diabetes, sugar-free formula can be administered. Alginate is considered a safe treatment of choice for GERD during pregnancy[12,20].

CONCLUSION

Sodium alginate is useful in treating GERD, more so when combined with antacids and PPIs.

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Study Reveals Increased Cancer Risk among *BRCA1* and *BRCA2* Carriers in Asian Population

In the largest study to date, researchers investigated breast and ovarian cancer risks among *BRCA1* and *BRCA2* carriers within the Asian population. This study published in *The Lancet Regional Health—Western Pacific* highlighted the genetic predispositions and evolving cancer trends in Asian communities. Examining clinical data from 572 families in Singapore and Malaysia with *BRCA1* and *BRCA2* mutations, researchers focused on individuals aged 20 to 79, representing Chinese, Indian, and Malay ethnicities. Among the 1,121 *BRCA1* carriers studied, 144 were diagnosed with breast cancer and 65 with ovarian cancer. Of the 1,275 *BRCA2* carriers, 152 were diagnosed with breast cancer and 19 with ovarian cancer. Statistical analysis was employed to estimate cancer risks, considering factors such as ethnicity, location, and birth cohort.

The findings showed the increased cases of breast cancer among carriers, particularly among cohorts born after 1960. This upward trend was attributed to urbanization and shifts in reproductive patterns. It was observed that the estimated incidence of breast cancer peaked at age 55 across all ethnicities, followed by a decline.

Moreover, it was found that the incidence of cancer among *BRCA1* and *BRCA2* carriers in Singapore mirrored that of Western populations. Comparative analysis revealed that the cumulative risks for Chinese *BRCA1* and *BRCA2* carriers in Singapore resembled those of Asians in the United States. In contrast, Indian carriers' risks were akin to Asians in the UK. However, these risks were notably higher compared to their counterparts in Malaysia. Similarly, the graphical representation of cumulative risks depicted striking similarities and disparities across different ethnicities and geographic locations. Chinese carriers in Singapore exhibited comparable risks to East Asians in the United States, whereas Indian carriers paralleled the risks of South Asians in the United Kingdom.

(*Source: https://www.news-medical.net/news/20240426/Largest-study-of-BRCA1-and-BRCA2-carriers-refines-cancer-risk-estimates-in-Asian-population.aspx*)

CLINICAL STUDY

Clinical Outcomes of Slow versus Rapid Enteral Feeding Advancement in Very Low Birth Weight Neonates at a Tertiary Care Center

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ABSTRACT

Background: In India, every year around 3.5 million babies are born premature, accounting for almost 13% of total live births in the country as compared to 5% to 7% incidence in the West. Preterm is defined as babies born before 37 weeks of pregnancy. The rapidity of feed volume increments involves controversies like faster weight gain, shorter hospital stays, the risk of necrotizing enterocolitis and vice versa. **Methods:** The present study was a randomized controlled trial conducted from June 1, 2018 to October 31, 2019. All infants in the study were randomized to slow and rapid feeding protocols by a stratified block randomization sequence of 2, 4, 6 blocks. Group 1 or the slow advancement group included 64 newborns babies and Group 2 or the rapid advancement group included 69 newborns babies. **Results:** The average weight gain in Group 1 was 4.41 ± 0.9 g and in Group 2 it was 6.33 ± 1.3 g, the difference was statistically significant ($p < 0.02$). Sixty out of 64 newborns regained birth weight within 16.87 ± 0.9 days in Group 1, while 64 out of 69 newborns regained birth weight within 13.63 ± 0.9 days in Group 2. The difference was statistically significant. Increment in the mean occipitofrontal circumference per week was 0.29 ± 0.27 cm Group 1, while in Group 2 it was 0.42 ± 0.05 cm; the difference was statistically significant. Mean average length increment per week was found to be 0.55 ± 0.04 cm and 0.69 ± 0.05 cm in Group 1 and Group 2, respectively, the difference was statistically significant ($p < 0.005$). The mean duration of hospital stay was 27.47 ± 3.33 days in Group 1 while in Group 2, the duration of stay was 23.15 ± 2.22 days, the difference was statistically significant. **Conclusion:** Our study supports enteral nutrition by rapid enteral feeding regimen in stable preterm neonates with very low birth weight.

Keywords: Very low birth weight, nutrition, feeding, enteral feeding, preterm

Globally, every year, an estimated 15 million babies are born preterm (before 37 completed weeks of gestation). Preterm birth complications are the leading cause of death among children under 5 years of age, responsible for approximately 1 million deaths in 2015[1].

In India, every year almost 3.5 million babies are born premature, accounting for nearly 13% of total live births in the country as compared to 5% to 7% incidence in the West. Preterm birth is defined as babies born alive before 37 weeks of pregnancy are completed. There are subcategories of preterm births, based on gestational age[2]. Complications of prematurity include necrotizing enterocolitis (NEC), feed intolerance, exaggerated physiological jaundice, sepsis and prolonged hospital stay, etc. The duration of hospital stay may be reduced if feed can be rapidly built up thereby significantly reducing morbidity and mortality in these newborns. The appropriate goals of low birth weight feed include ensuring adequate short-term growth, preventing feeding-related morbidities, optimizing long-term outcomes including its impact on adult-onset diseases (e.g., coronary artery disease [CAD], diabetes mellitus, etc.). Over the last 2 decades, the concept of minimal enteral nutrition has evolved and is defined as starting a small amount of enteral feeding (exact volume not defined) usually 5-25 mL/kg as soon as possible after birth. This approach has numerous positive impacts on the development and maturation of gut function, hormonal and digestive enzyme surge[3,4]. Numerous studies have shown the beneficial effects of minimal enteral nutrition; however, none have demonstrated an

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increase in the incidence of NEC. However, larger trials are required regarding safety in very immature and critically ill babies[5,6].

The rapidity of increments in feed volume has been beset with controversies. A more rapid increase should result in faster weight gain and a shorter hospital stay. The proponents of slow feed advancements have cited the risk of NEC in their defense, while those in favor of rapid advancements have cited better growth in their defense. Controlled trials prior to the 1990s had observed an association between rapid feed advancement and increased risk of NEC[4,6]. However, many randomized controlled trials have not demonstrated any increased risk of NEC[7-11]. The lack of effect on NEC could be a result of differences in study design, improved neonatal care resulting in a decrease in NEC risk factors, and a shift in feeding protocols. The present study was aimed to compare the effects of slow rates of enteral feed advancement versus rapid advancement on the incidence of NEC in very low birth weight (VLBW) infants and to compare the effects of slow enteral feed advancement versus rapid advancement on the weight of VLBW infants. The *primary outcome* was the duration to reach full enteral feeds (days). The *secondary outcomes* were to study the incidence of feed intolerance, to find duration of hospital stay (days), to calculate average weight gain, length and head circumference and to find incidence of NEC.

MATERIALS AND METHODS

The present randomized controlled trial included 133 stable newborn babies, having a birth weight between 1,000 to 1,500 g, admitted in neonatal intensive care unit (NICU) in the Department of Pediatrics, SMS Medical College, and Attached Group of Hospitals, Jaipur during a period of 16 months from June 1, 2018 and October 31, 2019 after obtaining informed written consent of parents. Newborns with major congenital cardiac or other malformations contraindicating initiation of enteral feeds as per existing guidelines; with hypotension requiring dopamine ≥10 μg/kg/min or more than one inotrope support, persistent metabolic acidosis (pH <7.25 or base deficit of ≥10 mmol/L for >4 hours), abdominal distension, gastrointestinal bleeding and absent bowel sounds were excluded. All infants in the study were randomized into slow and rapid feeding protocols by a stratified block randomization sequence of 2, 4, 6 blocks. The slow advancement group (Group 1) comprised of 64 newborn babies and the rapid advancement group (Group 2) included 69 newborn babies. Both the study group newborns were thoroughly examined clinically on daily basis. The patients were monitored for weight gain, time to achievement of full feed, the occurrence of complications like NEC and sepsis. The findings and data were recorded on a predesigned proforma (Fig. 1).

The serial weight of the baby was recorded daily. Serial data of the length were recorded weekly. Abdominal girth was measured by using a nonstretchable tape, at the level, just above the umbilicus. Serial data of abdominal girth were recorded daily.

Feeding protocol: All neonates of both the groups were given gastrointestinal priming feeding (Trophic feeding) on Day 1 with expressed breast milk (EBM) at the rate of 10 mL/kg/day. All newborns were given feeding through a nasogastric tube.

Group 1 (Slow advancement group): All infants were given gastrointestinal priming feeding on Day 1 with EBM at the rate of 10 mL/kg/day, thereafter the feeds increased by 15-20 mL/kg/day till the maximum volume of 180 mL/kg/day was achieved.

Group 2 (Rapid advancement group): All infants in Group 2 were also given gastrointestinal priming as in Group 1 infants. The feed was advanced by 30-40 mL/kg/day till the maximum volume of 180 mL/kg/day was achieved.

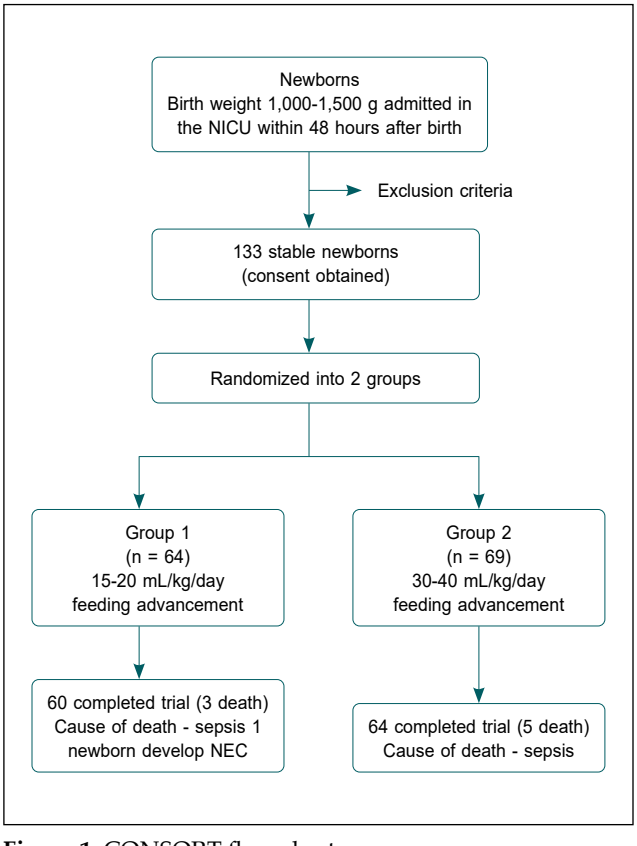

Figure 1. CONSORT flow chart.

All stable VLBW neonates were thoroughly examined clinically daily and the finding were duly recorded on a predesigned proforma.

The pre-feed abdominal girth was measured. If pre-feed abdominal girth increased >2 cm between consecutive feeds, then gastric aspiration was done. If the pre-feed gastric aspirate volume was >30% or 3 mL/kg (whichever is greater) then the further increment of feed was deferred for the next 24 hours and one feed was omitted. If gastric aspirate volume was >50% of pre-feed, the feeding was discontinued temporarily for the next 24 hours.

During this period, the baby was investigated for evidence of sepsis and NEC. If sepsis was confirmed, the feed was discontinued and if sepsis screen was negative, feed was restarted at half the volume of last feed. In the event of the occurrence of severe sepsis or NEC, the patient was excluded from this study and managed for this complication.

RESULTS

In these VLBW babies, feed intolerance was observed clinically in relation to abdominal distension and gastric residue. We found that there was no statistically significant difference between the slow and rapid advancement groups. Both the time for reaching full-feed and duration of regaining birth weight were less in rapid advancement group than in slow advancement group. In the present study, total 133 VLBW babies were included.

In Group 1, 36 babies (56.25%) were male and 28 (43.75%) were female and 60 (93.75%) were appropriate-for-gestational age (AGA) and 4 (6.25%) were small-for-gestational age (SGA).

In Group 2, 43 (62.31%) were male and 26 (37.68%) were female and 65 (94.20%) were AGA and 4 (5.79%) were SGA.

The overall mean gestational age of newborns in Group 1 was 31.8 ± 0.3 weeks and that of Group 2 newborns was 31.9 ± 0.3 weeks. It was 31.63 ± 0.32 and 32.8 ± 2.04 weeks in Group 1 AGA and SGA newborns, while it was 31.89 ± 0.29 and 32.8 ± 1.36 weeks in Group 2 AGA and SGA newborns.

The mean birth weight of Group 1 newborns was 1,270.06 ± 38.2 g and those in Group 2 was 1,293.1 ± 36.2 g. It was 1,269.58 ± 38.58 and 1,299.69 ± 36.39 g in Group 1 AGA and SGA newborns, while it was 1,299.69 ± 36.39 and 1,263 ± 245.5 g in Group 2 AGA and SGA newborns (Table 1).

The mean time of starting minimal enteral feed in Group 1 was 25.6 ± 3.9 hours and 21.7 ± 3.8 hours in Group 2. It was 28.15 ± 5.42 and 27.0 ± 31.4 hours in Group 1 AGA and SGA newborns; while in Group 2 it was 21.35 ± 3.98 and 22.8 ± 21.12 hours in AGA and SGA newborns.

The mean time to achieve full feeds was 11.37 ± 1.36 days in Group 1, while in Group 2 was 6.59 ± 0.62 days. It was 10.75 ± 1.55 and 12.4 ± 8.76 days in Group 1 AGA and SGA newborns, while in Group 2 it was 6.63 ± 0.66 and 7.2 ± 3.44 days in AGA and SGA newborns. Feeding was interrupted in about 4.68% newborns in Group 1 and in 5.79% in Group 2.

The mean time of regaining birth weight was 16.87 ± 0.9 days in Group 1, while it was 13.63 ± 0.9 days in Group 2 (Table 2). It was 13.87 ± 1.88 and 16.0 ± 1.96 days in Group 1 AGA and SGA newborns, while in Group 2 it was 13.03 ± 1.16 and 11.0 ± 8.0 days in AGA and SGA newborns.

The average weight gain in Group 1 was 4.41 ± 0.9 g and 6.33 ± 1.3 g in Group 2 (Table 2). It was 3.61 ± 0.86 and 2.175 ± 2.09 g in Group 1 AGA and SGA newborns,

Table 1. Socio-demographic Profile

Variable	Group 1 (n = 64)	Group 2 (n = 69)	P value
Male:Female	36:28	43:26	>0.05
Birth weight (in grams)	1,270.06 ± 38.2	1,293.1 ± 36.2	0.39
Gestational age (In weeks)	31.8 ± 0.3	31.9 ± 0.3	0.42
AGA:SGA	60:4	65:4	>0.05

Table 2. Outcome Measures in Both Groups

Outcome	Group 1 (n = 64)	Group 2 (n = 69)	P value
Average weight gain per day (grams)	4.41 ± 0.9	6.33 ± 1.3	0.02
Regain of birth weight (days)	16.87 ± 0.9	13.63 ± 0.9	0.005
Average occipitofrontal circumference increment per week (cm)	0.29 ± 0.27	0.42 ± 0.05	<0.005
Average length increment per week (cm)	0.55 ± 0.04	0.69 ± 0.05	<0.005
Duration of hospital stay (Days)	27.47 ± 3.33	23.15 ± 2.22	0.03

while it was 5.66 ± 1.29 and 4.04 ± 6.22 g in AGA and SGA newborns in Group 2.

The mean occipitofrontal circumference increment per week was 0.29 ± 0.27 cm Group 1, while in Group 2, it was 0.42 ± 0.05 cm (Table 2). It was 0.28 ± 0.03 and 0.32 ± 0.14 cm in Group 1 AGA and SGA newborns, while in Group 2 AGA and SGA newborns, it was 0.42 ± 0.06 and 0.32 ± 0.18 cm, respectively.

The mean length increment per week was found to be 0.55 ± 0.04 cm and 0.69 ± 0.05 cm in Group 1 and Group 2, respectively (Table 2). It was 0.53 ± 0.05 and 0.56 ± 0.03 cm in Group 1 AGA and SGA newborns, while it was 0.70 ± 0.05 and 0.54 ± 0.28 cm in Group 2 AGA and SGA newborns.

The mean duration of phototherapy was 92.04 ± 9.22 hours in Group 1 and it was 77.42 ± 7.54 hours in Group 2. It was 67.7 ± 12.8 and 67.2 ± 48.97 hours, respectively in Group 1 AGA and SGA newborns, while in Group 2 it was 62.28 ± 9.6 in AGA and 76.8 ± 64.6 hours SGA newborns.

In Group 1, NEC was found in 1 baby, while none of the newborns in Group 2 suffered from NEC.

In Group 1, sepsis was found in 3 babies, while it was seen in 5 babies in Group 2.

The mean duration of hospital stay was 27.47 ± 3.33 days in Group 1 while in Group 2, the duration of stay was 23.15 ± 2.22 days (Table 2). It was 27.9 ± 3.5 and 25.2 ± 14.86 days in Group 1 AGA and SGA newborns, while in Group 2 it was 23.37 ± 2.31 and 19.4 ± 9.48 days in AGA and SGA newborns.

Four newborns in Group 1 had adverse outcomes (expired/NEC), while 5 newborns in Group 2 had adverse outcomes (expired).

DISCUSSION

In the present study, study subjects included 64 newborns in Group 1 and 69 newborns in Group 2. The profile of patients was almost similar to that seen in other studies[7-13]. In the present study, 93.75% newborns were AGA and 6.25% newborns were SGA in Group 1, while 94.2% were AGA and 5.80% newborns were SGA. In a study conducted by Krishnamurthy et al, in 80% newborns in Group 1 were AGA and 20% were SGA, while in Group 2, 72% newborns were AGA and 28% newborns were SGA[14]. In a study conducted by Karagol et al, 65.21% newborns were AGA and 34.79% newborns were SGA in Group 1, while 63.04% newborns were AGA and 36.96% newborns were SGA in Group 2[8].

In a study conducted by Krishnamurthy et al, the mean gestational age in Group 1 was 31.1 ± 1.2 weeks and 30.8 ± 1.1 weeks in Group 2[14]. While in the study conducted by Karagol et al, the mean gestational age in Group 1 was 28.2 ± 1.1 weeks and in Group 2, it was 28.3 ± 1 weeks[8].

In the present study, mean birth weight in Group 1 was 1,270.06 ± 38.2 g and in Group 2 was 1,293.1 ± 36.2 g. It was 1,269.58 ± 38.58 and 1,268 ± 250.6 g in Group 1 AGA and SGA newborns, while it was 1,299.69 ± 36.39 and 1263 ± 245.5 g in Group 2 AGA and SGA newborns. While in study conducted by Karagol et al, mean birth weight was in Group 1 was 984.3 ± 217.1 g and in Group 2 was 951.6 ± 196.4 g. The difference was because Karagol et al had selected newborns with weight ranging from 750 to 1,250 g[8]. The birth weight in the study conducted by Caple et al in 2004 was 1,000 to 2,000 g and <1,250 g in the study by Salhotra and Ramji in 2004 Krishnamurthy et al in 2010 reported a mean birth weight of 1,306.0 ± 129.2 g and 1,261.4 ± 121.6 g in Groups 1 and 2, respectively, which was similar to our study[7,13,14].

In the present study, the mean time of starting minimal enteral feed in Group 1 was 25.6 ± 3.9 hours and 21.7 ± 3.8 hours in Group 2. It was 28.15 ± 5.42 and 27.0 ± 31.4 hours in Group 1 AGA and SGA newborns whiles in Group 2 it was 21.35 ± 3.98 and 22.8 ± 21.12 hours in AGA and SGA newborns. In Karagol et al, the mean time of starting minimal enteral feed was 36.4 (8-17) hours in Group 1 and 35.8 (11-22) hours in Group 2[8]. In our study, trophic feeding in almost all babies were started within 24 hours, while in Karagol et al, the average time of starting trophic feeds was 24 to 48 hours.

In present study, the volume increments in Group 1 ranged from 1,520 mL/kg/day, while in Group 2, the increment in volume was 30-40 mL/kg/day. In Karagol et al, the volume increment in Group 1 was 20 mL/kg/day and 30 mL/kg/day in Group 2[8]. In Rayyis (1999)[12], the volume increment was 15 mL/kg/day in Group 1 and 35 mL/kg/day in Group 2. It was 20 mL/kg/day (Group 1) and 35 mL/kg/day (Group 2) in Caple et al (2004)[13]; 15 mL/kg/day (Group 1) and 30 mL/kg/day (Group 2) in Salhotra and Ramji in 2004[7] and 20 mL/kg/day (Group 1) and 30 mL/kg/day (Group 2) in the study by Krishnamurthy et al[14].

In the present study in Group 1 were given gastrointestinal priming feeding for first 24 hours with EBM at the rate of 10 mL/kg/day 4-hourly thereafter the feeds increased by 15-20 mL/kg/day till maximum achievement that was 180 mL/kg/day and similarly all

the infants of Group 2 were also given gastrointestinal priming as Group 1 infants and feeds were advanced by 30-40 mL/kg/day till maximum of 180 mL/kg/day was achieved. Salhotra and Ramji in 2004[7], and Krishnamurthy et al in 2010[14] and Karagol et al in 2013[8] also used the same maximum advancement of 180 mL/kg/day.

The method of feeding in the present study was nasogastric tube feeding similar to the other trials[9,11,12,14].

Caple et al in 2004[13] used full strength commercial formula or human milk for feeding infants, Salhotra and Ramji in 2004[7] used human milk for feeding infants; Krishnamurthy et al[14] used EBM and formula milk, while Karagol et al[8] used EBM and formula milk for feeding. In the present study, we used EBM for the feeding of all infants.

In the present study, feeding was interrupted in 6.25% newborns in Group 1, whereas in Group 2, feeding was interrupted in 5.79%, newborns, which was statistically not significant. In Salhotra and Ramji in 2004[7], feeding was interrupted in 65.38% in Group 1 and in 51.62% in Group 2; in Krishnamurthy et al in 2010[14], feeding was interrupted in 24% in Group 1 and 16% in Group 2 newborns, while in Karagol et al in 2013[8], feeding had to be interrupted in 28% newborns in Group 1 and 23.9% in Group 2.

In the present study, no association was found between advancement of feed and feed intolerance. Salhotra and Ramji in (2004)[7], Caple et al (2004)[13] and Krishnamurthy et al (2010)[14] also reported no significant difference in feed intolerance with slow and rapid advancements of feeds. It further strengthened the belief that adverse events related to rapid advancement of feeding were not so common as previously feared.

In present study, the fast advancement group reached full enteral feeds significantly earlier (mean 6.59 ± 0.62 days) than in the slow advancement group (mean 11.37 ± 1.36 days), which was statistically highly significant. It was 10.75 ± 1.55 and 12.4 ± 8.76 days in AGA and SGA newborns in Group 1, while it was 6.63 ± 0.66 and 7.2 ± 3.44 days in Group 2 AGA and SGA newborns. In Karagol et al, the mean duration to reach full enteral feed in Group 1 was 18.1 ± 5.8 days and 15.5 ± 8.4 days in Group 2[8]. In Salhotra and Ramji in 2004, the fast advancement group (30 mL/kg/day) attained full enteral feeds of 180 mL/kg/day by the 10th day and the slow advancement group (15 mL/kg/day) by the 15th day (mean 14.8)[7]. In Rayyis et al, the rapid advancement group (35 mL/kg/day) attained full enteral feeds of 180 mL/kg/day by the 11th day and the slow advancement group (15 mL/kg/day) by the 15th day[12]. In Krishnamurthy et al, the median time taken to reach full enteral feed was 9 days in Group 1 and 7 days in Group 2[14]. But in the present study, the rapid advancement group (30-40 mL/kg/day) reached full feed by the 6.59 days (mean), while slow advancement group (15-20 mL/kg/day) reached full feed by 11.37 days (mean). Our results were similar to the studies by Salhotra and Ramji in 2004[7] and Krishnamurthy et al in 2010[14] in reaching full feeds early by rapid advancement of feeds without complications.

In the present study, the mean time to regain birth weight was shorter in the rapid advancement group (13.63 ± 0.9 days) compared to the slow advancement group (16.87 ± 0.9 days); this difference was statistically significant ($p < 0.005$). It was 13.87 ± 1.88 and 16.0 ± 1.96 days in Group 1 AGA and SGA newborns while in Group 2 it was 13.03 ± 1.16 and 11.0 ± 8.0 days in AGA and SGA newborns.

Salhotra and Ramji in 2004[7] also showed early regain of birth weight in slow advancement feeding group in 23 days, while in rapid advancement group, regain in birth weight occurred in 18 days. In the study conducted by Krishnamurthy et al, median time to regain birth weight was 22 days in Group 1 while it was 16 days in Group2[14]. This study also supports our results of early regain of birth weight. Similar results were observed by Karagol et al[8]. In which, mean time of regaining birth weight was in Group 1 19.3 (14-17) days and in Group 2 was 16.0 (12.3-20) days.

In our study, the average increment in length per week was 0.55 ± 0.04 cm in Group 1 and 0.69 ± 0.05 cm in Group 2. It was 0.53 ± 0.05 and 0.56 ± 0.03 cm, respectively in Group 1 AGA and SGA newborns, while it was 0.70 ± 0.05 and 0.54 ± 0.28 cm in Group 2 AGA and SGA newborns.

The mean duration of phototherapy was 92.04 ± 9.22 hours in Group 1, and 77.42 ± 7.54 hours in Group 2. This difference was due to slow enterohepatic circulation in slow advancement group, and in Group 1 AGA and SGA newborns, the mean duration of phototherapy was 67.7 ± 12.8 and 67.2 ± 48.97 hours, while in Group 2 AGA and SGA newborns, it was 62.28 ± 9.6 and 76.8 ± 64.6 hours.

In the present study, mean increment in occipitofrontal circumference per week was 0.29 ± 0.27 cm in Group 1, while in Group 2 it was 0.42 ± 0.05. It was 0.28 ± 0.03 and 0.32 ± 0.14 cm in Group 1 AGA and SGA newborns, and in Group 2 AGA and SGA newborns, it was 0.42 ± 0.06 and 0.32 ± 0.18 cm.

In present study, average weight gain per day was 4.41 ± 0.9 g in Group 1 and 6.33 ± 1.3 g, respectively. According to gestational age, in Group 1 it was 3.61 ± 0.86 and 2.17 ± 2.09 g in AGA and SGA newborns, while it was 5.66 ± 1.29 and 4.04 ± 6.22 g in Group 2 AGA and SGA newborns.

In the present study, the incidence of culture proven sepsis in Group 1 was 3.12% and 4.34% in Group 2. In Salhotra and Ramji 2004[7], 38.46% newborns in Group 1 and 18.51% in Group 2 developed sepsis. In Krishnamurthy et al in 2010[14], sepsis was seen in 10% and 8% of Group 1 and Group 2 patients, respectively. In Karagol et al (2013)[8] sepsis was seen in 13.04% in Group 1 and 6.52% newborns in Group 2, respectively.

In the present study in Group 1 (slow advancement group), 1 male AGA newborn developed NEC. None of the newborns in the rapid advancement group developed NEC. Earlier studies have shown almost equal incidence of NEC in male and female newborns. In Caple et al in 2004[13], 2.38% newborns in Group 1 and 5.40% in Group 2 developed NEC. In Salhotra and Ramji (2004)[7], 7.40% newborns in Group 2 developed NEC compared to none in Group 1. The incidence of NEC in Krishnamurthy in 2010[14] was 2% in Group 1 and 4% in Group 2, which showed similar ratio of NEC patients as present study. In Karagol et al[8], 10.86% newborns in Group 1 and 8.69% newborns in Group 2 developed NEC. These studies show that is not a common adverse event in relation to feed advancement.

In the present study, mean duration of hospital stay was 27.47 ± 3.3 days in Group 1 and 23.15 ± 2.2 days in Group 2; it was 27.9 ± 3.5 and 25.2 ± 14.86 in Group 1 AGA and SGA newborns, and 23.37 ± 2.31 and 19.4 ± 9.48 in Group 2 AGA and SGA newborns. In Karagol et al[8], the mean duration of hospital stay was 26.2 ± 1.1 days in Group 1 and 21.5 ± 1.3 days in Group 2.

The adverse events related to rapid advancement of feeding, i.e., gastric residuals, abdominal distension and feeding interruption were comparable in the slow advancement and rapid advancement group. The benefits of rapid advancement of feeds were early regaining of birth weight, shorter hospital stay and early achievement of full feed. Similar conclusion was also found in earlier studies by Salhotra and Ramji in 2004[7] and Caple et al in 2004[13] and Krishnamurthy et al 2010[14].

Feed intolerance (abdominal distension, gastric residue, feed interruption) related to advancement of feeding were almost equal in slow advancement and rapid advancement group indicating that rapid advancement of feeding is beneficial in VLBW babies and refutes the old fear about the rapid advancement of feeding in low birth weight and premature babies.

CONCLUSIONS

In conclusion, rapid advancement of feeding up to 40 mL/kg/day is safe and well-tolerated in VLBW babies, including SGA and AGA. It leads to early regaining of birth weight and reduces the total duration of hospital stay of newborns, which can indirectly decrease the risk of hospital-acquired infections and other complications. It fulfills the required nutrition and prevents undernutrition and future growth retardation of VLBW babies.

It lessens the physical and psychological stress of parents and reduces the extra work load of the medical personnel and hospitals and also cuts short the financial burden on hospitals, families and heath personnel by shortening hospital stay in developing countries like India. But further long-term studies are required with large numbers of premature and low birth weight babies, to recommend universal rapid advancement of feeding in these babies.

Declarations

Funding: None of the authors has taken any financial support from anyone.

Conflicts of interest/Competing interests: None.

Availability of data and material: Yes.

Code availability: Not applicable.

Authors' contributions: RKM & DRB drafted the study design, collected data, contributed in statistical analysis and inference of results. RM & JS supervised the entire work, drafted the study design, collected data, contributed in statistical analysis and inference of results. CKM did critical analysis of all data, counseled the parents and hypothesized the study, drafted the study design, collected data, contributed in statistical analysis and inference of results. RKM, DRB, JS, CM & RM drafted the conclusions, reviewed the literature, drafted the study design, collected data, contributed in statistical analysis and inference of results.

Ethics approval: Taken.

Consent to participate: Consent of parents was taken.

Consent for publication: Yes.

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Machine Learning Unveils Potential Link between Gut Metabolites and Alzheimer's Disease

In a study published in *Cell Reports*, researchers used machine learning to predict how metabolites originating in the gut interact with receptors found in both the gut and the brain to determine the potential role of the microbiome in the pathogenesis of Alzheimer's disease. Researchers from Cleveland Clinic conducted a comprehensive evaluation, including over 1 million potential pairs of metabolites and receptors.

They initiated a genetic analysis to investigate the relationships between 408 receptors and Alzheimer's disease. They predicted the protein shapes encoded by these receptors, utilizing artificial intelligence resources, providing crucial insights into the binding regions' configurations.

The results showed the predominant lipid or lipid-like metabolites among the identified binding pairs. Moreover, by exploring the microbiome composition associated with Alzheimer's disease, researchers pinpointed two metabolites—agmatine and phenethylamine—abundantly produced by *Bacteroides fragilis* and *Ruminococcus*, respectively.

Furthermore, they investigated the impact of these metabolites on the neurons of individuals with Alzheimer's disease. Using induced pluripotent stem cells, researchers observed a significant reduction in levels of tau proteins—a hallmark of Alzheimer's disease—upon exposure to agmatine and phenethylamine.

(*Source: https://www.medicalnewstoday.com/articles/ai-helps-researchers-uncover-gut-brain-interactions-in-alzheimers#Open-access-resource-for-Alzheimers-researchers*)

CASE REPORT

An Interesting Case of Pulmonary Tuberculosis with Hypoxemic Respiratory Failure Mimicking Interstitial Lung Disease

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ABSTRACT

Hypoxemic respiratory failure is a rare presentation of active pulmonary tuberculosis (TB). Though tuberculous acute respiratory distress syndrome (ARDS) is well documented in medical literature, non-ARDS respiratory failure is seldom reported in active pulmonary TB. We herein report a case, which posed a diagnostic dilemma as it clinically mimicked interstitial lung disease. Imaging showed unilateral localized smooth interlobular septal thickening along with consolidation without significant mediastinal lymphadenopathy. To the best of our knowledge, this rare radiological finding has not been reported in medical literature as being associated with hypoxemic respiratory failure in pulmonary TB patients.

Keywords: Pulmonary TB, TB, hypoxemic respiratory failure, interlobular septal thickening

Pulmonary tuberculosis (TB) has been recognized as a scourge of humanity since antiquity. The disease continues to ravage much of the developing world and is still the most common infection causing death. One-fourth of the world population is estimated to be infected with *Mycobacterium tuberculosis*, although the distribution is heterogeneous[1]. TB has a myriad of clinical presentations making its diagnosis challenging.

Here we present a rare case of a patient who presented with type 1 respiratory failure and was clinically suspected to have interstitial lung disease but got microbiologically diagnosed with pulmonary TB and improved with antitubercular medications. This case report emphasizes the importance of a high degree of clinical suspicion for pulmonary TB in endemic countries like India.

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CASE REPORT

A 74-year-old male farmer with a history of working in a cotton mill for 12 years, never-smoker, presented with complaints of breathlessness on exertion for the last 4 months. The breathlessness was insidious in onset and progressed from Grade 0 on the Modified Medical Research Council (mMRC) dyspnea scale to Grade IV. He gave a history of dry cough for the past 10 years with no diurnal, seasonal or postural variation. There was no history of fever, hemoptysis, weight loss, wheezing, chest tightness, joint pains, rash or Raynaud's syndrome. He had no other medical comorbidities or history of previous TB or severe coronavirus disease 2019 (COVID-19) infection. On evaluation, he was found to have tachycardia (heart rate - 110/min), tachypnea (respiratory rate - 35/min), hypoxemia (oxygen saturation of 72% at room air); the blood pressure was 136/84 mmHg. The patient had pallor with no evidence of clubbing, icterus or peripheral lymphadenopathy.

On auscultation, there were fine end-inspiratory crackles in bilateral lower lung zones with a predominance in the left lower regions of the chest. Arterial blood gas evaluation revealed respiratory alkalosis along with moderate hypoxemia (pH - 7.479, pCO_2 - 26.9 mmHg, pO_2 - 52.9 mmHg, HCO_3 - 24 mmol/L and lactate - 1.2 mmol/L). He was given supplemental oxygen through a face mask at 10 L/min.

On further evaluation, he had a hemoglobin level of 9.9 g/dL, total leukocyte count of 10,500 cells/μL with a differential cell count showing 87% neutrophil, 7% lymphocytes, 3% eosinophils, 3% monocytes and platelets of 1.53 lakh/cu mm. Serum biochemistry revealed urea - 41 mg/dL, creatinine - 0.81 mg/dL, aspartate aminotransferase (AST) - 103 IU/L, alanine aminotransferase (ALT) - 85 IU/L, sodium - 130 mEq/L, potassium - 4.3 mEq/L, total protein - 6.4 g/dL and albumin - 2.1 g/dL.

Chest radiography demonstrated a hyperinflated lung field with reticular opacities in the right upper zone, left upper and middle zones with nonhomogenous air space opacities and features of volume loss in the form of rib crowding in the left upper and middle zone (Fig. 1).

Gram stain and Ziehl-Neelsen (ZN) stain done on induced sputum were negative. The viral markers for human immunodeficiency virus (HIV) and hepatitis B virus (HBV) were negative. High-resolution computed tomography (HRCT) of the chest taken for further evaluation of the patient revealed bilateral apical emphysematous changes with interlobular septal thickening in the left lingula and left lower lobe with consolidation in the left lower lobe with no significant mediastinal lymphadenopathy (Fig. 2).

He underwent videobronchoscopy and bronchoalveolar lavage (BAL) was taken from the left lower lobe superior segment. Cartridge-based nucleic acid amplification test (CB-NAAT) done on BAL revealed high levels of *M. tuberculosis* with no rifampicin resistance. BAL Gram stain and ZN stain were negative.

He was diagnosed with microbiologically-confirmed pulmonary TB and was put on first-line antitubercular drugs. He responded well to treatment and was weaned off supplemental oxygen after 6 weeks of starting antitubercular therapy.

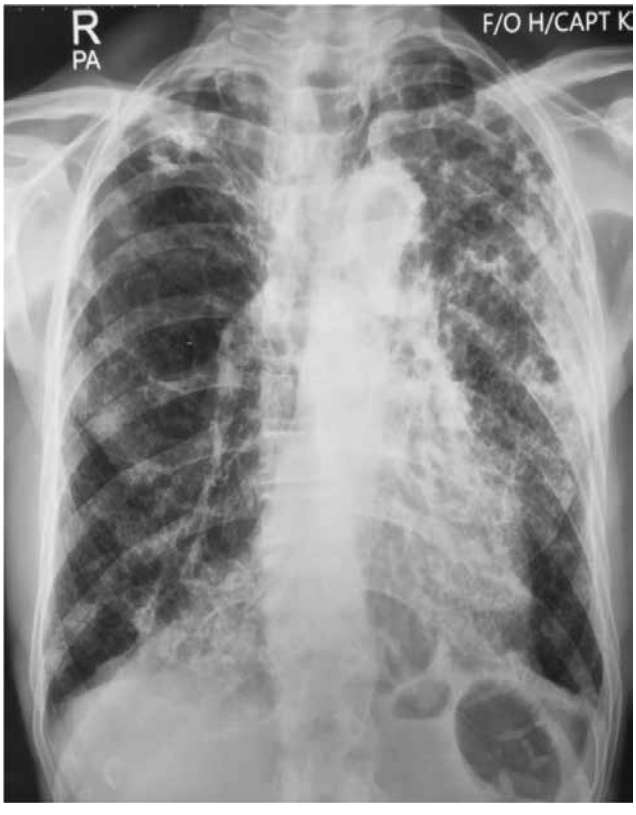

Figure 1. Chest radiography (PA view) demonstrating a hyperinflated lung field with reticular opacities in the right upper zone, left upper and middle zone. Left upper and middle zone shows rib crowding along with nonhomogenous air space opacities.

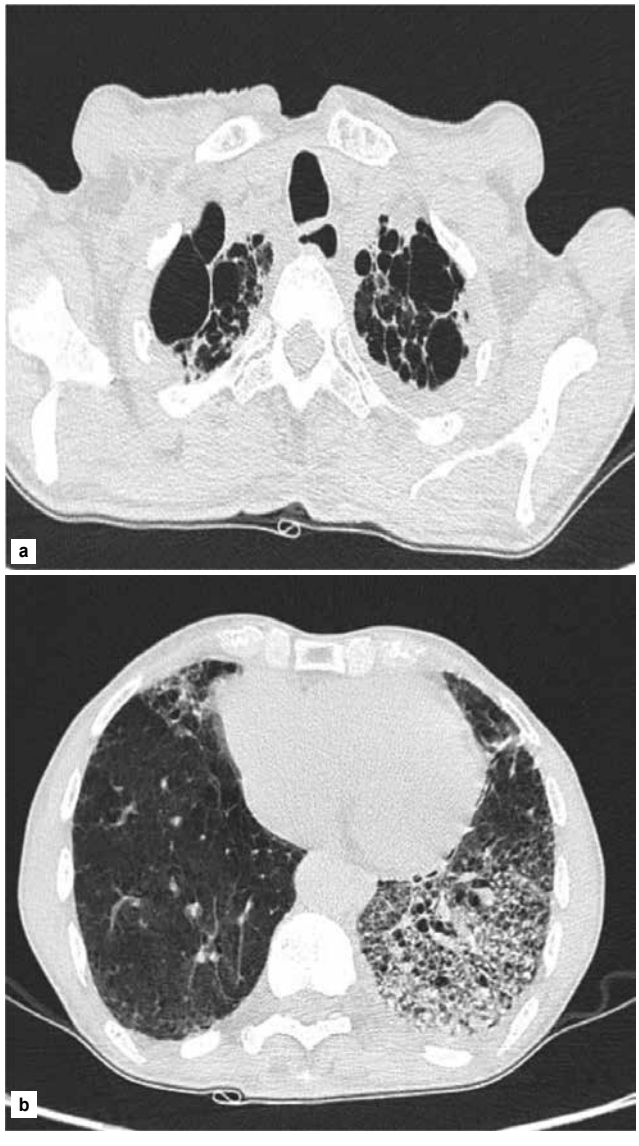

Figure 2. HRCT of the chest demonstrating (**a**) bilateral apical emphysematous changes (**b**) interlobular septal thickening in the left lingula and left lower lobe with consolidation in the left lower lobe.

DISCUSSION

India bears the highest burden of TB with an incidence of 210 per 1,00,000 population in 2021[2]. Acute hypoxemic respiratory failure is a rare presentation of pulmonary TB with an incidence of only 1.7% and mortality nearing 53%[3,4].

Our patient was clinically suspected to have acute exacerbation of interstitial lung disease as he had history of significant exposure to cotton dust, chronic dry cough with progressive dyspnea, fine crackles on auscultation and hypoxemia. He had no history of exposure to an active pulmonary TB case, no fever or significant weight loss. Chest radiography prompted us to further evaluate the patient for infective etiology of hypoxemic respiratory failure but the HRCT of the patient added to the existing diagnostic dilemma. CB-NAAT performed on the patient's BAL was crucial in diagnosing the patient.

Even though TB ARDS has been documented in medical literature[5], our patient with unilateral localized radiological lesions did not satisfy Berlin's criteria for ARDS. Bronchogenic pulmonary TB, extensive parenchymal consolidation, bilateral smooth interlobular septal thickening and miliary TB have been reported as causes of acute respiratory failure[6,7]. Our patient had unilateral localized interstitial involvement in the form of interlobular septal thickening along with consolidation, which to the best of our knowledge has not been reported in medical literature as a cause of hypoxemic respiratory failure in pulmonary TB. Interlobular septal thickening demonstrates a lymphatic spread of disease, which is usually associated with enlarged regional lymph nodes. Its absence in our case makes it an extremely rare presentation.

Chronic obstructive pulmonary disease (COPD) is a known risk factor for respiratory failure in active pulmonary TB[8]. Our patient, even though not spirometrically diagnosed with COPD, had extensive bilateral upper lobe emphysematous changes, which might have predisposed him to develop respiratory failure. In non-miliary pulmonary TB, the most dominant mechanism causing hypoxemia is the destruction of pulmonary parenchyma caused by the inflammatory response against the bacillary antigen of *M. tuberculosis*[9]. Given the destructive inflammatory response, corticosteroids have been used along with antitubercular drugs for managing TB ARDS. Their use in pulmonary TB with non-ARDS respiratory failure is controversial. Our patient was managed with first-line antitubercular drugs and was successfully weaned off oxygen within 6 weeks of initiation of therapy.

CONCLUSION

Pulmonary TB can have a myriad of clinical presentations. The clinicians should have high suspicion, especially in endemic countries like India. Unilateral interlobular septal thickening with hypoxemic respiratory failure, though rare, is a possible presentation of pulmonary TB.

Compliance with Ethical Standards

The authors have no conflict of interest to disclose. Informed written consent of the patient was taken for the publication of his medical information.

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CASE REPORT

Arrhythmia in Adult Congenital Heart Disease

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ABSTRACT

This case report highlights the significance of a multidisciplinary approach in the management of patients with repaired membranous ventricular septal defect (VSD) who develop postoperative arrhythmias. We present the case of a young female who experienced symptomatic episodes of supraventricular tachycardia following VSD repair. Through electrophysiological study and radiofrequency ablation, multiple tachycardia substrates were identified and successfully ablated. This report underscores the importance of combining surgical repair, electrophysiological evaluation and intervention to achieve optimal outcomes in this specific patient population.

Keywords: Arrhythmia, adult congenital heart disease, electrophysiological study, radiofrequency ablation

Congenital heart disease (CHD) encompasses a wide spectrum of structural abnormalities affecting the cardiovascular system. Advances in medical and surgical interventions have significantly improved survival rates among individuals with CHD. However, the long-term consequences and associated complications of repaired CHD remain an ongoing challenge.

In this case report, we present a unique clinical scenario involving a patient with repaired ventricular septal defect (VSD) who presented with recurrent arrhythmias. The investigation of this case led to the identification of a multiple tachycardia substrate and coronary sinus diverticulum, a rare anatomical variant, as the underlying etiology for the arrhythmic manifestations. We describe the diagnostic and therapeutic interventions employed, which resulted in successful resolution of the patient's symptoms.

CASE REPORT

A 17-year-old girl was referred to our arrhythmia center for electrophysiological study for recurrent paroxysmal episodes of regular palpitations. She had medical history of recently repaired VSD. Physical examination, transthoracic echocardiography (TTE) and biochemical tests were unremarkable. There was no family history of cardiac arrhythmia. Baseline electrocardiogram (ECG) showed sinus rhythm, pre-excited QRS with delta wave polarity suggestive of left posterior accessory pathway (Fig. 1).

After written informed consent, patient was taken for electrophysiological study. Two quadripolar diagnostic catheters were advanced under fluoroscopy to His bundle region and right ventricular apex. One decapolar catheter was advanced into the coronary sinus. During the electrophysiological study at baseline, atrial-His bundle (AH) and His-ventricular (HV) intervals were 85 ms and 3 ms in sinus rhythm, respectively. There were no atrioventricular (AV) conduction abnormalities. A narrow complex tachycardia (tachycardia cycle length [TCL] = 400 ms) was easily induced during catheter placement with following features: initiation of the tachycardia with a critical AH interval, fixed 1:1 ventriculoatrial (VA) conduction, concentric retrograde activation with VA interval of 37 ms, a post-pacing interval (PPI, 576 ms)–TCL (406 ms) >115 (170 ms) and ventricular overdrive pacing resulted in a VAHV response. His synchronized and early premature ventricular contraction (PVC) did not reset the tachycardia. His synchronized premature atrial contraction (PAC) also failed to reset the tachycardia. The tachycardia was reproducible and consistent (Fig. 2). After confirming the diagnosis of typical AV nodal re-entrant tachycardia (AVNRT) a decision was taken for slow pathway ablation. Using a steerable ablation catheter, with the help of intracardiac electrograms (EGMs) and using fluoroscopy, the region of the slow

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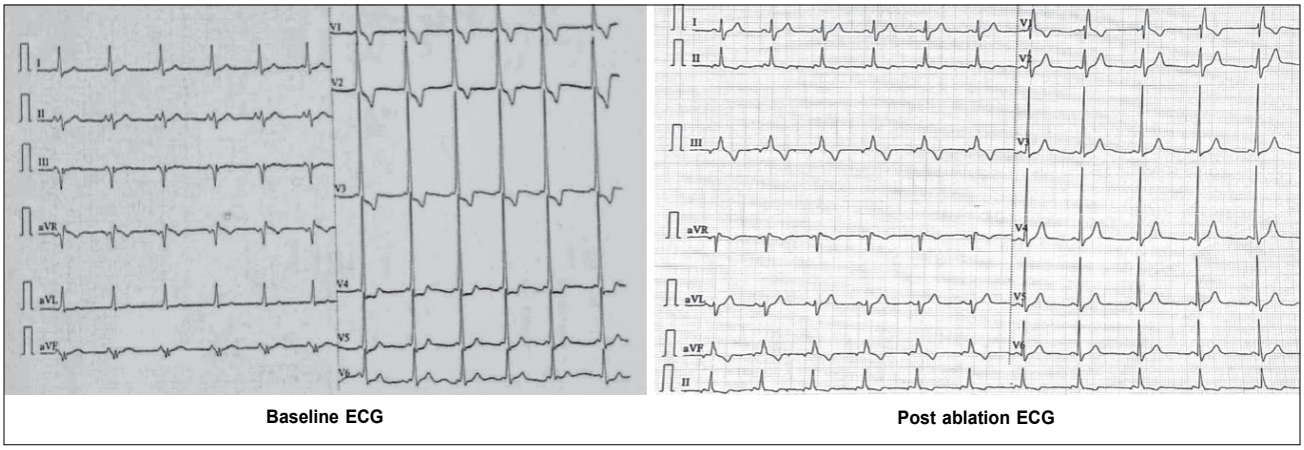

Figure 1. ECG (left) at baseline diagnostic of posteroseptal accessory pathway, ECG (right) after successful ablation of pathway with memory T waves in inferior leads.

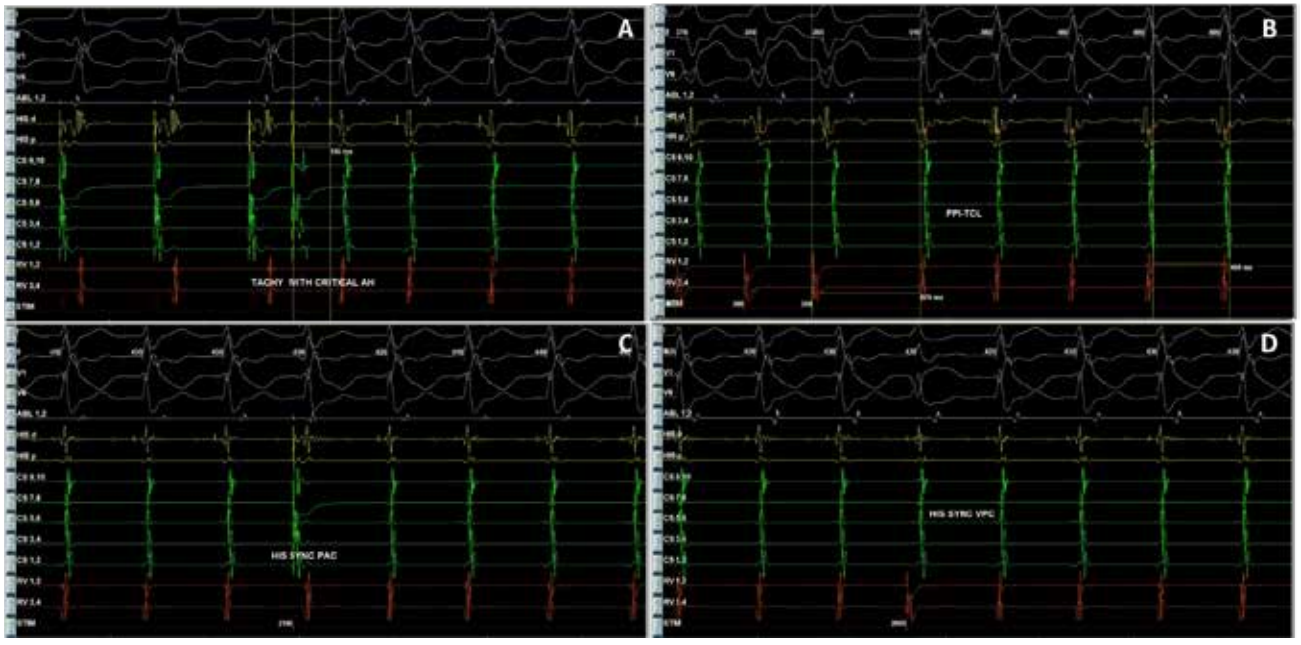

Figure 2. Intracardiac EGMs showing tachycardia induction with AH jump **(A)**, RV overdrive pacing **(B)**, and response of His synchronous PVCs **(C)** and PACs **(D)** diagnostic of typical slow-fast AVNRT.

pathway was identified. Radiofrequency applications were made in the region of the slow pathway while constantly monitoring temperature, impedance, ECG and intracardiac EGMs, monitoring for fast junctional conduction and radiofrequency energy was halted if there was evidence of VA block. Radiofrequency ablation resulted in a junctional rhythm with intact AV conduction, which is a typical response. The AV nodal slow pathway was successfully modified (Fig. 3).

Later on, during programmed atrial stimulation with burst pacing, patient developed another broad complex tachycardia (TCL = 220 ms) with 1:1 AV relationship. The tachycardia was hemodynamically unstable and led to ventricular fibrillation and required direct current cardioversion (DCCV) with 200J (Fig. 4). With the help of steerable ablation catheter, earliest atrial activation during ventricular pacing and earliest ventricular signal in sinus rhythm was mapped at the septal tricuspid annulus (RA mapping) and septal mitral annulus (LA mapping). Afterwards coronary sinus angiogram was taken, which showed a coronary sinus diverticulum near the decapolar coronary sinus 5-6 electrodes (Fig. 5). Radiofrequency applications were delivered at the neck of diverticulum that leads to disappearance of pre-excitation (Fig. 6). Afterwards aggressive programmed stimulation done on and off with isoproterenol that did not induce any atrial arrhythmias.

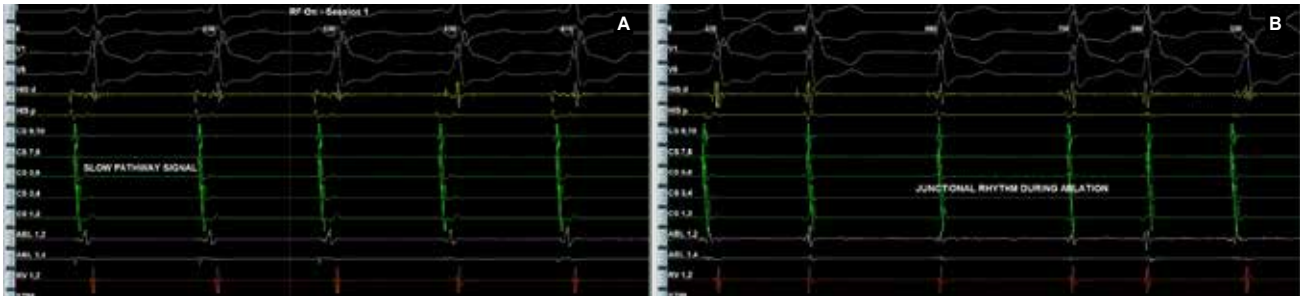

Figure 3. Slow pathway signals **(A)** at rightward inferior extension showed fused signals because of underlying pathway. Junctional rhythm **(B)** in response of radiofrequency energy.

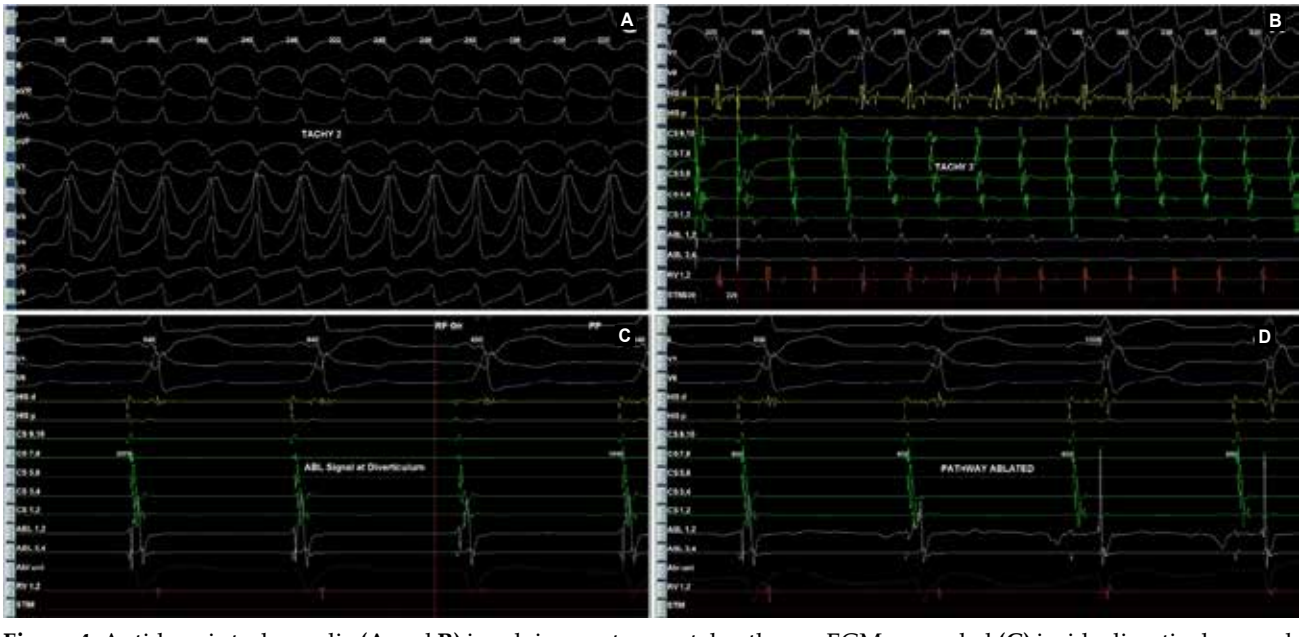

Figure 4. Antidromic tachycardia **(A** and **B)** involving posteroseptal pathway. EGMs recorded **(C)** inside diverticulum neck that was ablated successfully **(D)**.

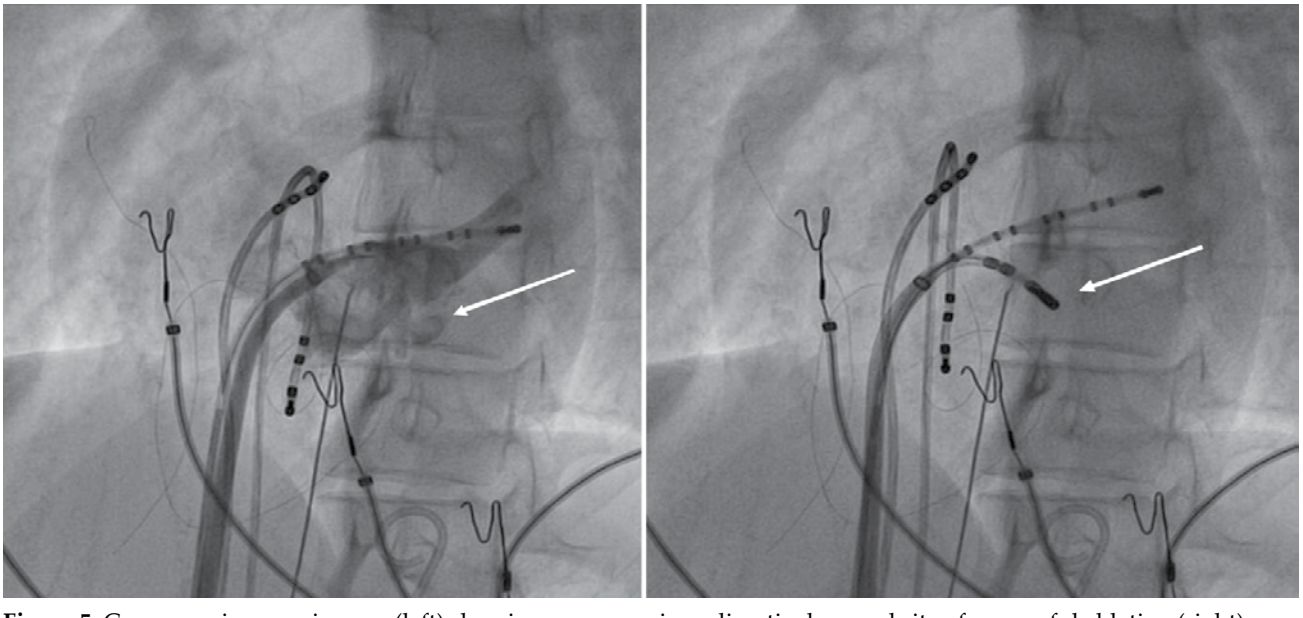

Figure 5. Coronary sinus angiogram (left) showing coronary sinus diverticulum and site of successful ablation (right).

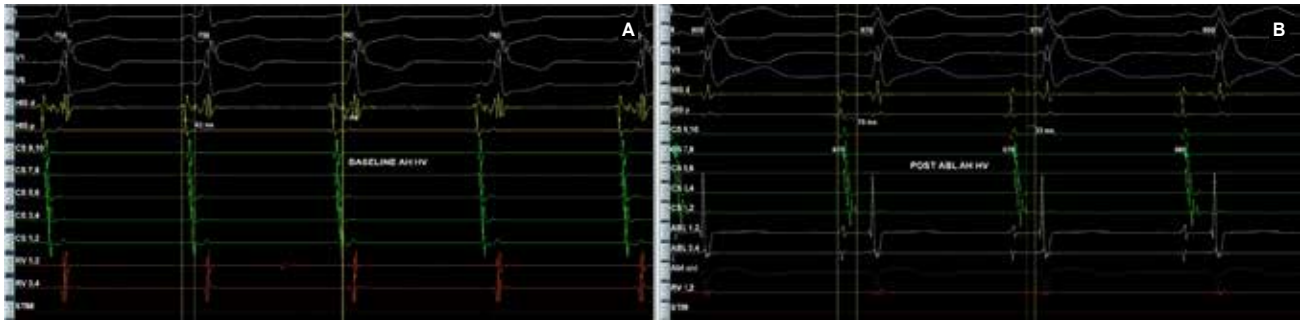

Figure 6. Intracardiac intervals baseline **(A)** showed HV interval of 3 ms that was normalized **(B)** after successful accessory pathway ablation.

During the follow-up, the patient remained free of symptoms and was not required to take antiarrhythmic agents. We did not find any conduction trouble on the ECG during the follow-up.

DISCUSSION

Coronary sinus diverticula are rare congenital anomalies. These are venous pouches at the pericardial aspect of posterior ventricular septum with neck draining into the proximal coronary sinus. They also contain accessory pathway at the neck of diverticula. Radiofrequency catheter ablation appears to be safe and curative in this setting. These diverticulae may be associated with other congenital cardiac abnormalities like membranous VSD and subaortic membranes[1-6].

Surgical series suggest they may be present in 6% to 9% of patients with posteroseptal accessory pathways with symptoms severe enough to warrant surgery[7]. In patients undergoing transesophageal echocardiography (TEE) following failed attempts at ablation of a posteroseptal accessory pathway, coronary sinus diverticulae were identified in 13% of cases. So, it is reasonable to do a coronary sinus venogram in case of posteroseptal or left posterior accessory pathway.

The posteroseptal accessory pathway is responsible for AV reciprocating tachycardia. Orthodromic re-entrant tachycardia mediated by posteroseptal pathway mimicking AVNRT, can be differentiated by different pacing maneuvers. However, the two may co-exist as seen in our case. Secondly, it is important to note that when accelerated junctional rhythm occurs during slow pathway ablation, the presence of retrograde atrial activation is reassuring, yet when a retrograde accessory pathway is present, the reassurance would be potentially false.

CONCLUSION

It is important to predict the accessory pathway location from the delta wave polarity. In patients with left posterior and posteroseptal accessory pathways coronary sinus venogram is recommended to identify coronary venous anomaly. Multiple arrhythmias can co-exist, so one needs to identify all the possible substrates.

Acknowledgment

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Conflict of interest: None.

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An Interesting Case of Chromonychia in an Immunosuppressed Individual

RAJESH RAJAGOPALAN

A 28-year-old unmarried promiscuous bisexual man with a history of human immunodeficiency virus (HIV) infection for past 2 years on triple drug regimen (efavirenz/emtricitabine/tenofovir disoproxil fumarate) but highly irregular, now on antituberculosis treatment (ATT) for pulmonary tuberculosis for past 4 months, presented with linear pigmented band on right middle finger nail for past 8 months. There was no history of trauma. He denied pain or tenderness. Otherwise he felt well and reported no other systemic symptoms except occasional dry cough. General physical and systemic examinations were unremarkable.

On local examination, there was a linear black discoloration of right middle finger nail with no discoloration of periungual skin (Hutchinson's sign was negative). Nails on the left hand were distally orangish red due to henna pigmentation (Fig. 1 a and b). Nail clippings for potassium hydroxide (KOH) mount were negative for fungal hyphae. A diagnostic nail biopsy was deferred as onychoscopy confirmed the diagnosis. His Venereal Disease Research Laboratory (VDRL) and other viral markers were unremarkable. Patient was assured and as his CD4 cell count was very low (18 cells/mm^3), his regimen was changed to 3-drug regimen containing dolutegravir/emtricitabine/tenofovir alafenamide. He was asked to continue ATT.

Figure 1 a and b. Longitudinal black band involving solitary digit.

1. What is the most likely underlying diagnosis?

A. Benign longitudinal melanonychia

B. Drug-induced pigmentation

C. Onychomycosis due to molds

D. Nail matrix nevus

E. Subungual melanoma

Answers:

A. **Benign longitudinal melanonychia – correct**. Melanonychia striata is the commonest morphological pattern[1]. Longitudinal brown-black band extends proximally from nail matrix or cuticle to distal free edge of the nail plate.

B. **Incorrect**. Drugs such as antiretroviral therapy (ART) (zidovudine)[2] or cancer chemotherapeutics usually causes diffuse black pigmentation of multiple nails. Exogenous pigments can also cause melanonychia, but they usually do not form regular linear bands.

C. **Incorrect.** More than one nail involvement with KOH mount revealing fungal hyphae. Often nails are dull, brittle with subungual hyperkeratosis/periungual inflammation. Longitudinal melanonychia is more common with dermatophytes like *Trichophyton rubrum* while diffuse pigmentation is seen with molds such as *Scytalidium, Aspergillus niger* and *Alternaria.*

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D. **Incorrect**. Nail matrix nevus and constitutional nail pigmentation (racial) are the most common causes of nail melanosis. Melanonychia in such cases result from nail matrix melanocyte proliferation with (nevus) or without nest formation (lentigine). Nail matrix nevi are commonly seen in childhood (congenital or acquired).

E. **Incorrec**t. Involvement of nail matrix by malignancy though rare is seen. Dermoscopy of the hyponychium and periungual tissues permits discovering the micro-Hutchinson sign, a periungual pigmentation. Despite its rarity, when melanoma of the nail unit occurs, it may portend a poorer prognosis and lower survival than melanoma of other sites[3].

2. All the following are correct about this condition except:

A. Longitudinal melanonychia is a rare clinical condition.

B. Mostly characterized by the presence of longitudinal, demarcated and pigmented bands on the nail unit.

C. Etiology is generally classified as melanocytic activation or melanocytic hyperplasia.

D. It is important to distinguish malignant melanoma from benign melanonychia as prognosis is different.

E. History, physical examination, onychoscopy and nail biopsy are obtained or performed to help determine the diagnosis.

Answer:

A. It is not rare but quite common in dark-skinned races, especially in people of African descent. The incidence in whites is very low at around 1%.

3. All the following are true about this condition except:

A. The thumbnails, index fingernails and great toenails are the most affected.

B. Mostly benign; very few cases turn out to be nail melanoma.

C. It can appear before, during or sometimes after pregnancy[4,5].

D. Laugier-Hunziker, Peutz-Jegher, Touraine syndromes are sometimes associated with this condition.

E. Hutchinson's sign is not pathognomonic of subungual melanoma.

Answer:

E. If the melanin pigment extends into the skin and soft tissue surrounding the nail plate, such as the eponychium, hyponychium or lateral grooves; it is identified as a positive Hutchinson's sign, which is considered to be almost pathognomonic of subungual melanoma and usually requires attention and further examination[6,7].

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BRIEF COMMINICATION

Adolescent Obesity and Type 2 Diabetes Mellitus: Synaptics and Heuristics

MEENAKSHI VERMA*, DAVINDER SINGH BATTH†, MOHAN T SHENOY‡, SUNEET K VERMA#

ABSTRACT

The adolescent population is the foundation for a Nation's progress. Their shoulders therefore must be emboldened with health and dignity to ensure a developed Nation. However, the multitude of prevailing epidemics have left nostone unturned to enfeeble their strength. Type 2 diabetes mellitus (T2DM) and obesity stand amongst the top shotguns. There is a dire need to execute preventive as well as therapeutic actions to contain the epidemic, for which one must be well versed with the attributable risk factors. In this article, we will understand the synaptics of adolescent obesity and T2DM and what strategies are recommended by the health authorities to prevent and overcome this rising epidemic.

Keywords: Adolescent obesity, diabetes mellitus, adolescent health, healthy lifestyle, motivation, obesity

Until recently, young children and adolescents almost never got type 2 diabetes (T2DM), which is why it used to be called as 'adult-onset diabetes'. The majority of cases of diabetes mellitus among this population were immune-mediated type 1a diabetes. However, over the past two decades, the incidence of T2DM among the adolescents has shown a dramatic rise. In a systematic review of literature on the incidence of T2DM among children and adolescents from 25 countries/territories, Wu et al estimated ~41,600 new cases of youth-onset T2DM globally in 2021[1].

Most of these cases were irrefutably preventable. Youth with T2DM have more rapid disease progression resulting in earlier and more severe micro- and macrovascular complications compared to both adult-onset T2DM and youth-onset type 1 diabetes (T1DM)[2]. Such complications include but are not limited to atherosclerotic cardiovascular disease, stroke, myocardial infarction and sudden death, renal insufficiency and chronic renal failure, limb-threatening neuropathy and vasculopathy, and retinopathy leading to blindness[3]. Moreover, the available treatment options for children and adolescents with T2DM are more limited than for adult patients.

SYNAPTICS OF ADOLESCENT OBESITY AND TYPE 2 DIABETES MELLITUS

Insulin resistance is the major risk factor for T2DM at all ages. In adolescent population, the exogenous factor responsible for most cases of insulin resistance is obesity which, when coupled with relative insulin deficiency particularly the physiologic insulin resistance of puberty, leads to the development of overt T2DM. A systematic review and meta-analysis of 53 studies including 8,942 participants found that 75.27% of children with T2DM had obesity, and 77.24% had obesity at diagnosis[4].

The increasing frequency, earlier onset and greater severity of childhood obesity in the past 50 years together with increasingly sedentary lifestyles and an increasing frequency of intrauterine exposure to diabetes are important drivers of the epidemic of youth-onset T2DM[5].

STRATEGIES TO CONTROL ADOLESCENT OBESITY AND PREVENT TYPE 2 DIABETES MELLITUS

The following strategies should be implemented to help an adolescent child with obesity lead a healthy lifestyle and prevent the onset and progression of T2DM as per Table 1.

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Table 1. Strategies to Control Adolescent Obesity and Prevent Type 2 Diabetes Mellitus

Physical activity	• How much • How often • Parents' role
Family-based approach	• Food choices • Lifestyle
Screening	• Whom to screen • When to screen • How often to screen • Role of genetic testing • Diagnostic criteria • Confirming diabetes type

PHYSICAL ACTIVITY

There is no denying the fact that adolescent population is overburdened with today's education trends. But a good education is of no worth if the body is not in synchronization with the mind. One of the constants in approach towards a healthy body is physical activity. One must make conscious efforts to inculcate the habits of involving themselves into one or the other physical activities.

- A daily moderate to vigorous physical activity of 30 to 60 minutes, either at once or in 2 to 3 sessions, at least 5 days per week (and strength training on at least 3 days per week), aiming to achieve 7% to 10% decrease in excess weight, is recommended[6].
- Parents should appreciate even a small amount of progress shown by their child.
- Engage the child into a fitness or sport activity.
- Active family outings must be planned every fortnight to keep the children away from screens, especially during the weekends.
- Involving the children in household chores in the form of fun activities helps to keep them moving on daily basis.

FAMILY-BASED APPROACH

Family is a child's first school. The journey towards a healthy body would not be difficult for a child with obesity if the whole family commits to a healthy lifestyle. Bringing the following lifestyle changes in the family is as mandatory as sending the child to school for good education. Table 2 illustrates the suggestions that could be included in family-based approach.

Table 2. Suggestions that can be Included in the Family-based Approach in Adolescent Obesity and Type 2 Diabetes Mellitus

- Eliminate or gradually reduce sugar intake for everyone in the family
- Include more of fruits and vegetables in the plate
- Adopt healthier alternatives of favorite foods
- Involve kids in food shopping and preparation
- Teach the children to read food labels
- Demonstrate and encourage them to eat slowly
- Discourage TV or gadgets while eating
- Have family meals more often
- Reward them with praises instead of food
- Serve smaller portions and let them to ask for seconds

SCREENING

Risk-based screening for prediabetes and/or T2DM is recommended in the adolescents having one or more of the following risk factors[5].

- **Risk Factors**
  - Body mass index (BMI) >85th percentile for age and sex, weight for height >85th percentile or weight >120% of ideal for height.
  - Genetics/epigenetics manifested as a strong family history of T2DM in first- or second-degree relatives.
  - Offspring of a pregnancy complicated by gestational diabetes mellitus (GDM)
  - Minority race/ethnicity (Native American, African American, Latino, Asian American, Pacific Islander).
  - Small-for-gestational-age birth weight.
  - Physiologic insulin resistance of puberty.
  - Having signs of insulin resistance or conditions associated with insulin resistance like acanthosis nigricans, hypertension, dyslipidemia, polycystic ovary syndrome.
- **Time of screening:** After the onset of puberty or after 10 years of age, whichever occurs earlier.
- **Frequency of screening:** Every 3 years, until the diagnosis is established or refuted.
- **Role of genetic testing:** Testing for monogenic forms of diabetes (Maturity-onset diabetes of the young [MODY], Donohue syndrome and Rabson-Mendenhall syndrome) should be considered as

well, especially if impaired insulin sensitivity and reduced insulin secretion are present in otherwise healthy youth with a family history of T2DM[7].

- **Diagnostic criteria for overweight and obesity:** The Indian cut-off levels as per Indian Academy of Pediatrics (IAP) are as below[8]:
  - Overweight: BMI ≥23 kg/m^2
  - Obesity: BMI ≥27 kg/m^2
  - Extreme obesity: BMI ≥120% of the 95th percentile or ≥35 kg/m^2.
- **Diagnostic criteria for diabetes in adolescents[9]:**
  - Prediabetes: HbA1c level of 5.7 to <6.5 or fasting glucose ≥100 but <126 mg/dL or 2-hour plasma glucose ≥140 but <200 mg/dL.
  - Diabetes: HbA1c level of >6.5 or fasting glucose ≥126 mg/dL or 2-hour plasma glucose ≥200 mg/dL or random plasma glucose >200 mg/dL in a patient with classic symptoms of hyperglycemia or hyperglycemic crisis.
  - Confirming diabetes type:
    - Clinical signs helpful in distinguishing T2DM from T1DM are obesity and signs of insulin resistance.
    - Children and adolescents with overweight/obesity in whom the diagnosis of T2DM is being considered should have a panel of pancreatic autoantibodies tested to exclude the possibility of autoimmune T1DM.
    - Genetic evaluation to exclude monogenic diabetes should also be based on clinical characteristics and presentation.
    - The distinction between these forms of diabetes in youth with obesity has important implications for treatment, since Ab$^+$ youth (with phenotype of T2DM) present more like individuals with T1DM, progressing to insulin requirement more rapidly, and are at risk for other autoimmune disorders. Therefore, measurement of pancreatic autoantibodies (GAD-65 and insulinoma-associated protein 2) is recommended in all youth with clinical characteristics of T2DM[10].

TAKE HOME MESSAGE

- One should suspect and screen and be aware of Indian cut-offs for obesity.
- Support family-based, school-based and community-based interventions for prevention of this menace.
- Seek and stick to medical advice, as appropriate.

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Medicolegal Insights

CAN DOCTOR/SURGEON/CONSULTANT BE HELD LIABLE FOR NOT RENDERING A SERVICE OR FACILITY, WHICH IS NOT AVAILABLE IN THE HOSPITAL?

The doctor cannot be held liable for not rendering a facility, which was not available in the hospital. If the hospital knowingly fails to provide some amenities that are fundamental for the patients, then it would certainly amount to medical malpractice; but for the same, the doctor cannot be held liable for medical negligence.

In the matter of **Malay Kumar Ganguly vs. Sukumar Mukherjee & Ors. AIR 2010 SC 1162, the Hon'ble Supreme Court of India** has held that:

"We must bear in mind that negligence is attributed when existing facilities are not availed of. Medical negligence cannot be attributed for not rendering a facility which was not available. In our opinion, if hospitals knowingly fail to provide some amenities that are fundamental for the patients, it would certainly amount to medical malpractice. As it has been held in Smt. Savita Garg (supra), that a hospital not having basic facilities like oxygen cylinders would not be excusable. Therein this Court has opined that even the so-called humanitarian approach of the hospital authorities in no way can be considered to be a factor in denying the compensation for mental agony suffered by the parents. The aforementioned principle applies to this case also in so far as it answers the contentions raised before us that the three senior doctors did not charge any professional fees."

In the matter of **Savita Garg vs. Director, National Heart Institute AIR 2004 SC 5088, the Hon'ble Supreme Court of India** has held that:

"The patients once they are admitted to such hospitals, it is the responsibility of the said hospital or the medical institutions to satisfy that all possible care was taken and no negligence was involved in attending the patient. The burden cannot be placed on the patient to implead all those treating doctors or the attending staff of the hospital as a party so as to substantiate his claim. Once a patient is admitted in a hospital it is the responsibility of the Hospital to provide the best service and if it is not, then hospital cannot take shelter under the technical ground that the concerned surgeon or the nursing staff, as the case may be, was not impleaded, therefore, the claim should be rejected on the basis of non-joinder of necessary parties. In fact, once a claim petition is filed and the claimant has successfully discharged the initial burden that the hospital was negligent, as a result of such negligence the patient died, then in that case the burden lies on the hospital and the concerned doctor who treated that patient that there was no negligence involved in the treatment. Since the burden is on the hospital, they can discharge the same by producing that doctor who treated the patient in defence to substantiate their allegation that there was no negligence. In fact, it is the hospital who engages the treating doctor thereafter it is their responsibility. The burden is greater on the Institution/Hospital than that of the claimant. The institution is private body and they are responsible to provide efficient service and if in discharge of their efficient service there are couple of weak links which has caused damage to the patient then it is the hospital which is to justify the same and it is not possible for the claimant to implead all of them as parties."

IS IT OBLIGATORY FOR HOSPITALS TO PROVIDE COPY OF THE CASE RECORD TO PATIENT OR HIS LEGAL REPRESENTATIVE?

Yes, it is obligatory for doctors, hospitals to provide the copy of the case record or medical record to the patient or his legal representative.

The Medical Council of India (MCI) has imposed an obligation on doctors as per the Indian Medical Council (Professional Ethics, Etiquette & Conduct) Regulations, 2002 notified on 11th March 2002, amended up to December 2010 to maintain the medical record and provide patient access to it.

Maintenance of Medical Records:

1.3.1. Every physician shall maintain the medical records pertaining to his/her indoor patients for a ***period of three years*** *from the date of commencement of the treatment in a standard proforma laid down by the Medical Council of India and attached as Appendix 3.*

1.3.2. If any request is made for medical records either by the patients/authorized attendant or legal authorities involved, the same may be duly acknowledged and documents ***shall be issued within the period of 72 hours.***

With the enforcement of the MCI Regulations, 2002 it is made clear that the patient has a right to claim medical records pertaining to his treatment and the doctors/ hospitals are under obligation to maintain them and provide them to the patient on request.

In **Kanaiyalal Ramanlal Trivedi vs. Dr Satyanarayan Vishwakarma I (1997) CPJ 332 (Guj), The Hon'ble High Court of Gujarat** has held that the hospital and doctor were held guilty of deficiency in service as case records were not produced before the court to refute the allegation of a lack of standard care.

In **Raghunath Raheja vs. Maharashtra Medical Council, AIR 1996 Bom 198, Bombay High Court** upheld the right of patient to medical record very emphatically.

In the matter titled as **P.P. Ismail v K.K. Radha 1999 CPJ 99 (NC), the Hon'ble National Commission for Consumer Dispute Redressal Forum** has held the hospital vicariously liable for the negligent action of the doctor on the basis of the bill showing the professional fees of the doctor and the discharge certificate under the letterhead of the hospital signed by the doctor.

In **S.A. Quereshi vs. Padode Memorial Hospital and Research Centre II 2000. CPJ 463** (Bhopal) it was held that the plea of destroying the case sheet as per the general practice of the hospitals appeared to the court as an attempt to suppress certain facts that are likely to be revealed from the case sheet.

In case of **Dr Shyam Kumar vs. Rameshbhai, Harmanbhai Kachiyal (2006) CPJ 16 (NC), the Hon'ble National Commission of Consumer Dispute Redressal Forum** has held that not producing medical records to the patient prevents the complainant from seeking an expert opinion and it is the duty of the person in possession of the medical records to produce it in the court and adverse inference could be drawn for not producing the records.

In **Medi. Supri. Loknayak Jaiprakash Narayan Hospital & Ors. V/s. K.M. Santosh. F.A. No. 244/2008, decided on 14/03/2016, the National Consumer Disputes Redressal Commission** has observed that it is the primary responsibility of the hospital to maintain and produce patient records on demand by the patient or appropriate judicial bodies. The patient or their legal heirs can ask for copies of the treatment records that have to be provided within 72 hours. The hospital can charge a reasonable amount for the administrative purposes including photocopying the documents. Failure to provide medical records to patients on proper demand will amount to deficiency in service and negligence.

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WHO Report Highlights Alarming Surge in Measles Cases Worldwide

A recent report by the World Health Organization (WHO) highlighted a staggering 88% increase in measles cases globally in 2023 compared to the previous year, marking a concerning trend in infectious disease resurgence.

Presenting the findings at the ESCMID Global Congress in Barcelona, Dr Patrick O'Connor of the WHO emphasized the alarming rise in measles cases, from 1,71,153 in 2022 to 3,21,582 in 2023. The report attributed this surge to the disruption of vaccination efforts during the COVID-19 pandemic.

While reflecting on the progress made towards measles and rubella elimination over the past decade, the report underscored the urgent need for intensified efforts to curb the spread of measles. It highlighted that 2024 is poised to witness further increases in measles cases, with 94,481 cases reported by early April.

Notably, the WHO European Region bore the brunt of these cases, with Yemen, Azerbaijan, and Kyrgyzstan emerging as countries with the highest reported measles incidence worldwide. Of particular concern is the tripling of countries experiencing large or disruptive measles outbreaks, defined as 20 cases per million population continuously over 12 months, from 17 to 51.

However, amidst this concerning trend, the report underscored the vital role of measles vaccination in averting mortality. Globally, vaccination against measles has prevented an estimated 57 million deaths from 2000 to 2022. Notably, in the European region alone, vaccination efforts have resulted in a remarkable 98% reduction in annual measles deaths, from 3,584 in 2000 to 70 in 2022.

(*Source: https://www.daijiworld.com/news/newsDisplay?newsID=1187143*)

HCFI Dr KK Aggarwal Research Fund

Round Table Environment Expert Zoom Meeting on "World Air Quality Report 2023"

March 24, 2024 (Sunday, 12 noon-1 pm)

- The World Air Quality Report 2023 was released on 19th March. This report is based on data from 30,000 monitoring stations across 7,812 locations in 134 countries.
- This report provides a global review of air quality data and is based on only PM2.5 levels. In 2023, air pollution remained a global health catastrophe.
- India is the 3rd most polluted country with average PM2.5 levels of 54.5 μg/mm^3) after Bangladesh (79.9 μg/mm^3), and Pakistan (73.7 μg/mm^3).
- According to the report, Central and South Asia were the worst performers globally and home to all four of the most polluted countries: Bangladesh, Pakistan, India, and Tajikistan.
- South Asia is of particular concern with 29 of the 30 most polluted cities in India, Bangladesh, and Pakistan.
- This is a human caused climate crisis caused by burning of fossil fuels which plays a pivotal role in influencing air pollution levels.
- Climate crisis is also altering the weather patterns leading to changes in wind and rainfall.
- Out of the 50 most polluted cities in the world, 42 are in India.
- Begusarai in India was the most polluted city in India and also in the world with PM2.5 of 119 followed by Guwahati at 105.4.
- Delhi was the 3rd most polluted city with PM2.5 of 102.1; it was also the most polluted capital city.
- Greater Noida and Gurugram also figure in the list of top 15 most polluted cities in India.
- PM2.5 and ultrafine particles (UFPs) are dangerous for human health. Despite several measures being taken to control air quality such as Commission for Air Quality Management in NCR and adjoining areas, National Clean Air Program, lot still needs to be done.
- The World Health Organization (WHO) recommended PM2.5 target of <5 is impossible to achieve in India.
- Even during COVID lockdown, the levels achieved were <25-30.
- Only 10 out of the 134 countries have succeeded in meeting this target: Finland, Estonia, Puerto Rico, Australia, New Zealand, Bermuda, Grenada, Iceland, Mauritius, and French Polynesia.
- About 96% of population in India lives in air quality, which is 7 times higher than the WHO recommended level.
- The report illustrates the international nature and inequitable consequences of the continuing air pollution crisis.
- Local, national and international effort is urgently needed to monitor air quality in under-resourced places, manage the causes of transboundary haze, and cut reliance on combustion as an energy source.
- The monitoring stations work on different principles. The low cost sensors used are not reliable and reproducible.
- Achieving the WHO recommended target is difficult in the Indo-Gangetic Plain. The report does not mention that this is a geographically disadvantaged area. Population weighted annual average has been used, but it has to be vetted with the meteorological conditions such as wind direction, mixing height to get a better picture. Countries cannot be compared based on PM2.5.
- The Ministry of Environment and Forests (MoEF) and Central Pollution Control Board (CPCB) must take note of this data and undertake a thorough analysis. It is time to review and rethink.
- Comparing the Indo-Gangetic Plain with European data is an injustice to India. Particulate matters are very high naturally in most parts of India. Hence, the standards used in the report must be questioned.
- The dust collected by the mechanical sweepers is deposited in the central verge of the roads. With vehicle movements, it against gets resuspended.
- More than the vehicular emissions, road dust is the major polluter.
- Efforts should be made to make the central verge green by planting shrubs such as oleander, nerium, and bougainvillea. They are easy to maintain, hardy and climate resilient.

- The resuspended road dust becomes toxic when mixed with vehicular fumes.
- Road maintenance with proper cleaning including of road sides is important.
- Follow the principle of either green it or pave it for any area of the city.
- Roads need to be graded just as buildings are (green rating).
- In Pakistan, major sources are crop burning and temperatures.
- In North India and Delhi, high levels have been attributed to crop burning, vehicular emissions, and other anthropogenic activities.
- In Bangladesh, brick kilns are the major source.
- The major culprits in Begusarai are the brick kilns and windblown dust.
- Few cities in Karnataka are also highly polluted. Sources for the high pollution levels in these cities need to be studied.
- Identification of exact local sources is important. The report is generic without going into specifics and is not a very detailed analysis.
- We must have our own standards. There should be a uniform monitoring protocol across India.
- A balance must be created between development and environment health. Public-private partnership is essential. The solutions are not being implemented. There is a lack of focus toward improvement.
- This data shows that it is an emergency situation and emergency steps need to be taken.
- Transformative multi-sector action across all regions under the National Clean Air Programme is required for a time-bound reduction in pollution levels. System improvement is the need of the hour.

Participants: Dr MP George, Prof Shivaji Sarkar, Dr SD Singh, Mr Pradeep Khandelwal, Mr Sanjeev Kumar, Mr Neeraj Tyagi, Ms Ruchika Sethi Takkar

Moderator: Dr Anil Kumar

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Groundbreaking Study Reveals Dance and Music Therapies' Potential in Parkinson's Treatment

Researchers from the Jaslok Hospital and Research Centre have revealed the results of a pilot study exploring the efficacy of dance and music-related therapies in delaying the progression of Parkinson's disease (PD).

Parkinson's disease, a neurodegenerative disorder affecting over 10 million people globally, with a significant burden in India and Asia, impairs motor functions and quality of life due to the degeneration of dopaminergic neurons. Despite its prevalence, there is currently no cure for PD, with management relying on treatments such as medications, lifestyle adjustments, and surgery.

Prof (Dr) Paresh Doshi, lead investigator, emphasized the emotional impact of PD diagnosis on patients and highlighted the significance of offering alternative avenues for managing the disease. The study revealed that just 1 hour of dance combined with meditation or music and meditation daily could slow the progression of PD, marking a significant advancement in the field.

The study, which included 28 patients, 15 of whom were in therapy and 13 in the control group, showcased promising results. Disease progression was reduced across multiple parameters, including quality of life, balance, depression, anxiety, memory function, and gait. The study also evaluated the impact on caretakers, an aspect often overlooked in previous research.

Dr Doshi stressed the importance of objective evidence in validating therapeutic interventions, noting the study's adherence to rigorous protocols and the support received from various stakeholders. However, he acknowledged challenges in implementation, particularly in ensuring patient compliance and supervision during therapy sessions.

(*Source: https://health.economictimes.indiatimes.com/news/industry/dance-music-therapy-shows-promise-in-slowing-parkinsons-progression/109642689*)

News and Views

Clinical Outcomes in ARDS Patients with Diabetes

Acute respiratory distress syndrome (ARDS) patients with diabetes have adverse clinical outcomes evident as lower survival rate, longer lengths of stay in the hospital and intensive care unit (ICU) and higher levels of inflammation compared with those who did not have diabetes. These findings from a secondary analysis of data from the Fluids and Catheters Treatment Trial (FACTT) were published in the March 2024 issue of the journal *Respiratory Medicine*[1].

Researchers from the University of Georgia in Augusta, Georgia, USA conducted this secondary analysis of data from the FACTT, which compared two fluid management strategies (conservative and liberal) in patients with ARDS.

For the present study, 173 people with known diabetes and 794 without diabetes from the FACTT were enrolled and outcomes such hospital and ICU stays, days on ventilator till independent breathing and death at 90 days were examined. In-hospital mortality at 90 days was the primary end point of the study. The aim of the study was to investigate the impact of diabetes mellitus on critical care outcomes and explore potential biomarkers associated with these outcomes.

Participants with pre-existing diabetes had a poorer survival rate (61.3%) compared to those without diabetes (72.3%), which was statistically significant ($p = 0.006$). Diabetic subjects also had markedly longer duration of hospitalizations (24.5 vs. 19.7 days; $p = 0.008$) and longer stays in the ICU (14.8 vs. 12.4 days; $p = 0.029$). Between the two groups, there was no discernible difference in the number of ventilator days until unaided breathing (11.7 vs. 10 days; $p = 0.1$).

The study also evaluated plasma chemokines and cytokines using a multiplex test based on human magnetic beads. Analyses showed a nonsignificant trend toward raised levels in diabetic patients compared to nondiabetic patients on both days 0 and 1. Specifically, cytokines tumor necrosis factor alpha (TNF-α), interleukin (IL)-10, and IL-6, and chemokines C-reactive protein (CRP) and monocyte chemoattractant protein-1 (MCP-1) showed elevated levels in participants with diabetes. Of note, levels of lipopolysaccharide-binding protein (LBP) were significantly higher in patients with diabetes versus those without diabetes.

These findings show worse clinical outcomes in ARDS patients with pre-existing diabetes compared to those with no diabetes suggesting a negative impact of diabetes on lung function. Hence, respiratory functions of these patients should be carefully monitored. Further studies, according to the authors, can provide greater insights into the specific mechanisms by which diabetes influences respiratory functions in ARDS and validate this association.

Reference

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Foot Complications in Patients with Diabetic Polyneuropathy and Chronic Kidney Disease

Patients with diabetic polyneuropathy (DPN) and chronic kidney disease (CKD) are at higher risk of developing major adverse foot events (MAFEs) and functional mobility deficits, suggests a study published in the journal *Metabolism and Target Organ Damage*[1]. The risks were evident even in the early stages of CKD and increased further as CKD progressed.

The aim of this study was to ascertain the risk ratios (RR) for MAFEs as well as moderate and severe functional mobility deficits by analyzing medical records of 284 patients with DPN across various stages of CKD.

Foot X-ray reports in the medical records of 152 participants were used to collate data on MAFEs, such as foot fractures, ulcerations, Charcot neuropathic arthropathy, osteomyelitis, and any minor foot amputations (partial/complete toe amputation, partial/complete ray amputation, or transmetatarsal amputation); the modified physical performance test (mPPT) was used to evaluate functional mobility deficits in 132 participants. mPPT scores <22 were defined as severe mobility deficit, while scores ranging from 22 to 29 were considered as moderate mobility deficit. Every stage of CKD was evaluated for both unadjusted and adjusted (age, body weight, race, and glycated hemoglobin [HbA1c]) RR calculations, with stage 1 CKD serving as the reference group.

Across all CKD stages, the RR for diabetic foot ulceration, Charcot neuropathic arthropathy, and neuropathic foot fracture stayed constant. Unlike foot fracture and

Charcot neuropathic arthropathy, instances of ulceration, osteomyelitis, and minor foot amputation were more common in patients with DPN and stages 3, 4, and 5 diabetic kidney diseases. In stage 1 CKD, the frequency of foot ulceration was 6%, whereas it rose to 20% in stage 4 CKD and 24% in stage 5 CKD. Sixteen percent patients with stage 4 CKD had foot osteomyelitis, while 24% with stage 5 CKD had foot osteomyelitis. There was a higher risk of minor amputation in stages 4 and 5 of CKD. The RR of moderate mobility deficit was 7-times higher in CKD stages 3, which increased 12 stimes in Stage 5 CKD. The RR of severe mobility deficit increased fivefold in stage 3, 10-fold in stage 4 and rose steeply by 30-fold in stage 5. Across all CKD stages, an inverse correlation between mPPT scores and MAFE prevalence was found.

According to the authors, this is the first study to determine the risk of MAFEs and functional mobility deficits in patients with DPN and CKD. These findings highlight the importance of proactive foot care and functional mobility assessment in these patients, even in the early stages of CKD (stages 2 and 3) when preventive interventions are possible. As functional mobility decreased, as indicated by lower mPPT scores, the prevalence of MAFEs increased, regardless of CKD stage.

Early detection followed by timely intervention and targeted management strategies may help minimize the risk of foot complications and functional mobility deficits in this population, which, if left untreated, may lead to lower extremity amputation. These findings also call for educating patients about the risks for MAFEs and accompanying functional mobility deficits, which may further aid early recognition of foot complications.

Reference

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Fetal Nuchal Translucency Measurements Cut-offs: Time for a Rethink?

Fetuses with nuchal translucency measurements as low as 2.0 mm have a higher probability of chromosomal abnormalities, suggest a recent study published in *JAMA Network Open*[1]. Fetuses with nuchal translucency measurements of 3.0 to <3.5 mm were 20 times more at risk of having abnormalities versus those with measurements <2.0 mm. The risk was sixfold higher in fetuses with measurements of 2.5-3 mm and more than doubled when the nuchal transparency measurement ranged between 2 and 2.5 mm.

Kara Bellai-Dussault from the School of Epidemiology and Public Health, University of Ottawa, Canada and coauthors conducted this retrospective cohort study to explore how different nuchal translucency measurements correlate with the likelihood of specific cytogenetic outcomes in singleton pregnancies. For this, they used data of all singleton pregnancies with an estimated delivery dates between September 2016 and March 2021 from the Better Outcomes Registry & Network, which serves as the perinatal registry for Ontario, Canada. The reference group for comparison consisted of pregnancies with a nuchal translucency measurement <2.0 mm. Chromosomal anomalies such as Down syndrome, Edwards syndrome, and Patau syndrome were identified through prenatal and postnatal cytogenetic tests conducted in Ontario laboratories. The results of cell-free DNA (cfDNA) screening and clinical assessment at birth were added to the data from cytogenetic testing to identify pregnancies free of chromosomal abnormalities.

Analysis of data revealed that a nuchal translucency of <2.0 mm was present in the majority of the study group (86.9%; n = 3,59,807) out of the 4,14,268 pregnancies that were included in the study. The mean maternal age at the predicted delivery date was 31.5 years. Chromosomal abnormalities were present in 0.5% of this group.

As the nuchal translucency measurement increased, the risk of chromosomal abnormalities increased. For pregnancies with nuchal translucency measurements of 3.0 to <3.5 mm, the adjusted risk ratio (aRR) was 20.33 and the adjusted risk difference (ARD) was 9.94%. When limited to chromosomal abnormalities outside the widely screened aneuploidies (excluding trisomies 21, 18, and 13 and sex chromosome aneuploidies), the aRR was 4.97 and the ARD was 1.40%.

The findings from this cohort study suggest a clear association between higher nuchal translucency measurements and the elevated risk of chromosomal anomalies. Those with nuchal translucency measurements <2.0 mm were at the least risk. The study further indicates that even after excluding the commonly screened chromosomal anomalies, there remains a significantly increased risk of anomalies not frequently checked for by many prenatal genetic screening programs associated with higher nuchal translucency measurements. Overall, this study underscores the importance of nuchal translucency measurements as

a valuable screening tool in prenatal care. Even slight increases in nuchal translucency can potentially signal an elevated risk of chromosomal abnormalities.

A cut-off of 3.0 mm or greater or above the 99th percentile for the crown-rump length in the first trimester has been proposed by the American College of Obstetricians and Gynecologists (ACOG) for further diagnostic testing such as prenatal cfDNA screening or cytogenetic testing[2].

This study, by suggesting that pregnancies with nuchal translucency measurements lower than the 3.0 mm threshold were associated with risk of chromosomal anomalies, may have practice changing implications for prenatal genetic screening.

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2. American College of Obstetricians and Gynecologists' Committee on Practice Bulletins—Obstetrics; Committee on Genetics; Society for Maternal-Fetal Medicine. Screening for Fetal Chromosomal Abnormalities: ACOG Practice Bulletin, Number 226. Obstet Gynecol. 2020;136(4):e48-e69.

Childhood Atopic Dermatitis and Risk of Inflammatory Bowel Disease

Children with atopic dermatitis are at risk of developing inflammatory bowel disease (IBD). However, no such association was noted for other atopic manifestations. These findings were recently published March 21, 2024, in *The Journal of Pediatrics*[1].

This study focused on investigating potential associations between early childhood allergic conditions and the subsequent development of IBD. The study analyzed data from two large, prospective cohort studies in Scandinavia: 9,041 children from the All Babies in Southeast Sweden (1997-1999) and 74,270 from the Norwegian Mother, Father, and Child Cohort Study (2000-2009) who were followed up from birth until 2021 or a diagnosis of IBD. Data on any atopy such as asthma, food allergy, atopic dermatitis and allergic rhinitis by the age of 3 years was obtained from parents through questionnaires. Two or more diagnostic records in the national health registries were used to identify IBD. The adjusted hazard ratio (aHR) for several confounders including parental history of IBD, atopy, educational level, smoking habits, and national origin.

During a follow-up period of over 1,174,756 person-years, a total of 301 patients received the diagnosis of IBD. By the age of 3 years, 31,671 children (38%) developed an atopic manifestation. After adjusting for confounding variables, children with atopic dermatitis at the age of 3 years were more likely to develop IBD (pooled aHR 1.46), ulcerative colitis (pooled aHR 1.78), and Crohn's disease (pooled aHR 1.53). In contrast, neither analyses that explicitly examined early-life food-related allergic symptoms, asthma, or allergic rhinitis were linked to subsequent risk for IBD (pooled aHR 1.20) nor were any atopic manifestations by the age of 3.

This study suggests that although atopic symptoms in early infancy were not generally linked to IBD, children with atopic dermatitis in particular were more likely to develop IBD, indicating that there may be potential common etiological characteristics between atopic dermatitis and IBD. According to the authors, "a deeper understanding could significantly benefit the development of novel treatment approaches capable of effectively addressing both conditions, consequently enhancing patient outcomes". Atopic dermatitis may thus be an indicator of children at risk for developing IBD. Hence, clinicians managing children with atopic dermatitis should be aware of this association and closely monitor them for early recognition of IBD and timely intervention, if required.

Reference

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Why is Spirituality Well-Being–Friendly?

- What you believe in can have a big impact on health and longevity. People with high levels of religious beliefs or spirituality have lower cortisol responses. Cortisol is a hormone the body releases in response to stress.
- Positive thinking produces nearly a 30% drop in perception of pain.
- Spirituality and the practice of religion are associated with a slower progression of Alzheimer's disease.
- Those who regularly attend organized religious activities may live longer than those who don't. Regular participation lowers mortality rate by about 12% a year.
- People who undergo cardiac rehabilitation feel more confident and perceive greater improvements in their physical abilities if they have a strong faith.
- Increased levels of spirituality and religious faith may help substance abusers kick their habit.
- Spirituality stimulates the relaxation response. When the body is relaxed, your heart rate, blood pressure, and breathing rate all go down, which decreases the body's stress response.
- Spirituality can affect immune-system function. Spirituality, faith, church attendance improves immune function in ways that can be measured, like an increase in white blood cells.
- Prayer heals the heart. Positive talking and thinking in the ICU produces better results.
- Spirituality is what brings you peace and safety. It can be achieved through God or Goddess, nature, a beautiful sunset, a meditation, Pranayama, religious meeting, chanting, mind body relaxation, etc. Spirituality is something that can help all the way from promoting wellness to helping with recovery.

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Azithromycin Found Ineffective in Preventing Chronic Lung Disease in Premature Babies

A study published in *The Lancet Respiratory Medicine* delivered definitive findings regarding the efficacy of azithromycin in preventing chronic lung disease in premature infants, dispelling previous uncertainties surrounding its use.

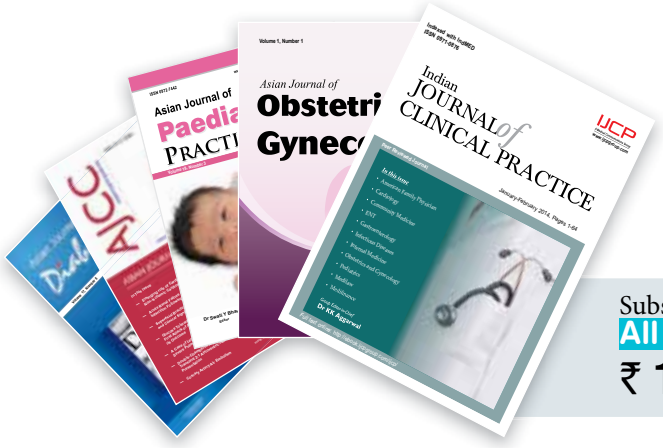
The AZTEC trial, conducted collaboratively by leading institutions across the UK, was the largest clinical study to investigate the potential of azithromycin in this context.

The trial, which included 796 premature babies from 28 neonatal intensive care units, was spearheaded by a partnership between the Cardiff University School of Medicine and the Cardiff University Clinical Trials Research Unit. Additional contributions came from esteemed institutions, including the University of Leicester, Imperial College London, University College London, University of Liverpool, and Newcastle University.

Contrary to prior speculation, the findings demonstrated that early administration of azithromycin does not confer protection against the development of chronic lung disease in prematurely born infants.

This finding emphasized the need for robust clinical trials to ascertain therapeutic interventions' true efficacy and safety profile, particularly in vulnerable populations such as premature babies.

(*Source*: *https://medicalxpress.com/news/2024-04-clinical-trial-azithromycin-chronic-lung.html*)



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Lighter Side of Medicine

HUMOR

HOTEL SECURITY

A friend and I stayed at a Chicago hotel while attending a convention. Since we weren't used to the big city, we were overly concerned about security.

The first night we placed a chair against the door and stacked our luggage on it. To complete the barricade, we put the trash can on top. If an intruder tried to break in, we'd be sure to hear him.

Around 1 AM there was a knock on the door. "Who is it?" my friend asked nervously.

"Honey," a woman on the other side yelled, "you left your key in the door."

UPSET IS UNHEALTHY

The mother of a problem child was advised by a psychiatrist, "You are far too upset and worried about your son. I suggest you take tranquilizers regularly."

On her next visit the psychiatrist asked, "Have the tranquilizers calmed you down?"

"Yes," the boy's mother answered.

"And how is your son now?" the psychiatrist asked.

"Who cares?" the mother replied.

CARPENTER'S DISTANCE

A carpenter was giving evidence about an accident he had witnessed.

The lawyer for the defendant was trying to discredit him and asked him how far away he was from the accident.

The carpenter replied, "Twenty-seven feet, six and one-half inches."

"What? How come you are so sure of that distance?" asked the lawyer.

"Well, I knew sooner or later some idiot would ask me, so I measured it!" replied the carpenter.

INSPIRATIONAL STORY

DO NOT BE JEALOUS

We all have experienced how jealousy can disturb our peace of mind. You know that you work harder than your colleagues in the office, but sometimes they get promotions; you do not. You started a business several years ago, but you are not as successful as your neighbor whose business is only 1 year old. There are several examples like these in everyday life.

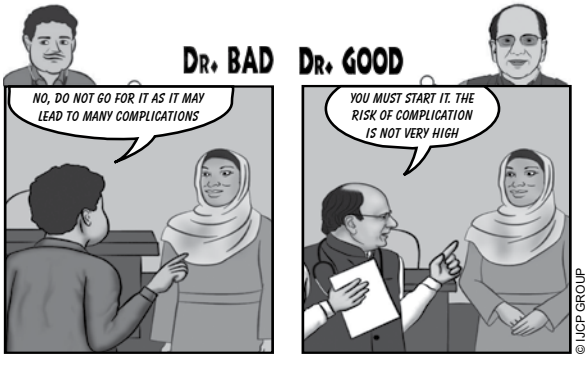
Should you be jealous? No. Remember everybody's life is shaped by his/her destiny, which has now become his/her reality. If you are destined to be rich, nothing in the world can stop you.

If you are not so destined, no one can help you either. Nothing will be gained by blaming others for your misfortune.

Jealousy will not get you anywhere; it will only take away your peace of mind.

Dr. Good and Dr. Bad

SITUATION: A 41-year-old female with T1DM from the past 6 years had HbA1c more than 8%, despite multiple daily injections and thus was advised continuous subcutaneous insulin infusion (CSII).



LESSON: It has been reported that CSII is an effective method for improving HbA1c, particularly in patients with HbA1c more than 8% prior to initiation of CSII. The incidence and progression rates of complications such as retinopathy and albuminuria are low, especially in those with a diabetes duration less than 15 years at the time of commencement of CSII.

J Diabetes Sci Technol. 2017;11(5):924-9.

Indian JOURNAL of CLINICAL PRACTICE

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- Confidence intervals for the measurements should be provided wherever appropriate.

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Discussion

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References

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Paintal AS. Impulses in vagal afferent fibres from specific pulmonary deflation receptors. The response of those receptors to phenylguanide, potato S-hydroxytryptamine and their role in respiratory and cardiovascular reflexes. Q. J. Expt. Physiol. 1955;40:89-111.

Books

Stansfield AG. Lymph Node Biopsy Interpretation Churchill Livingstone, New York 1985.

Articles in Books

Strong MS. Recurrent respiratory papillomatosis. In: Scott Brown's Otolaryngology. Paediatric Otolaryngology Evans JNG (Ed.), Butterworths, London 1987;6:466-470.

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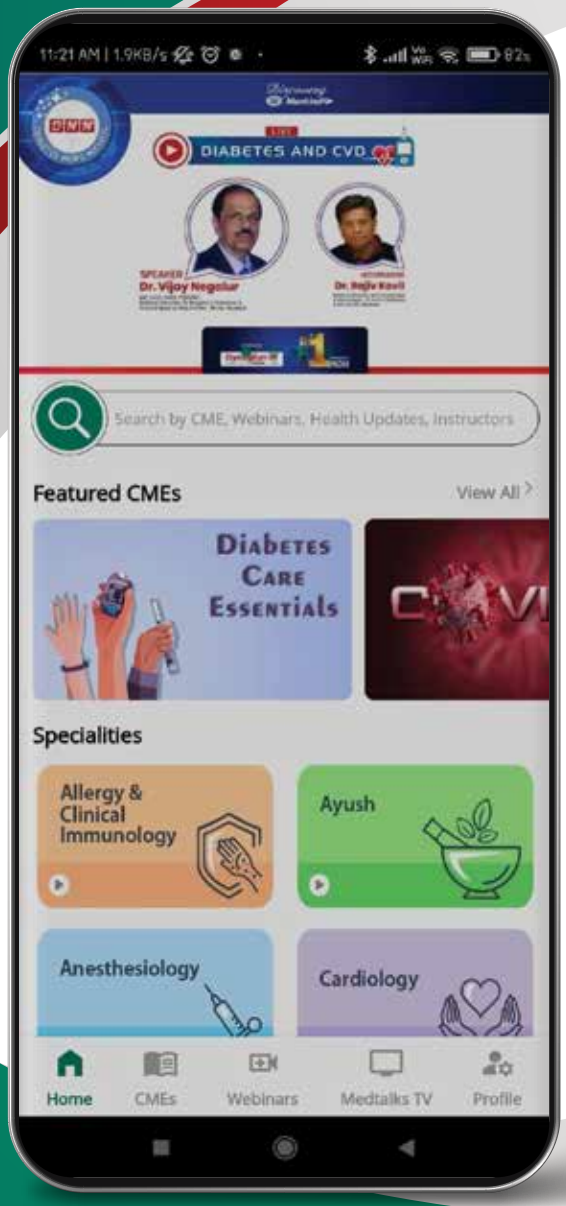

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