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ISSN 0971-0876

IJCP
A Medical Communications Group
www.ijcpgroup.com

Indian JOURNAL of CLINICAL PRACTICE

Volume 28, Number 8 January 2018, Pages 701–800 **Single Copy Rs. 300/-**

Peer Reviewed Journal

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Indian JOURNAL of CLINICAL PRACTICE

Volume 28, Number 8, January 2018

Published, Printed and Edited by
Dr KK Aggarwal, on behalf of
IJCP Publications Ltd. and
Published at
E - 219, Greater Kailash Part - 1
New Delhi - 110 048
E-mail: editorial@ijcp.com

Printed at
New Edge Communications Pvt. Ltd., New Delhi
E-mail: edgecommunication@gmail.com

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H3N2 Aussies Flu, a Near Epidemic in Australia, UK and USA; H1N1 in Rajasthan, India

The flu is rapidly spreading across the US, UK and Australia. Not only did it start early, but it seemed to occur all over the country more or less simultaneously.

The predominant flu strain is H3N2. Vaccine effectiveness typically ranges from 40% to 60% in a good year. Preliminary estimates from last year show the vaccine was 40% effective in the US, similar to 2014-2015. But concerns have been raised about this year's vaccine after an editorial published recently in the *New England Journal of Medicine* said it was only 10% effective against H3N2 in Australia.

Additionally, years in which H3N2 is the predominant influenza strain tend to have higher death rates, with approximately 20,000 deaths in the 2012-2013 and 2014-2015 seasons when H3N2 predominated.

Good news is that H3N2 flu is quite susceptible to the available flu medications, like Tamiflu, also known as oseltamivir. Remember, it is most helpful if taken within 48 hours of the start of the flu. It can take up to 2 weeks for the body to build up defenses against the virus.

It is especially important for pregnant women to get the vaccine. There is dual benefit for the pregnant woman to get vaccinated. Not only will she get protection, but she'll also pass those antibodies along to her infant, which will protect them for the first 6 months of life when the infant is too young to get the vaccine. And the vaccine is safe for pregnant women and the fetus.

For those who contract the flu, it could make symptoms less severe. Next, make sure to wash hands carefully to limit the spread of the virus and try to avoid close contact with sick people.

People who get sick should also keep up with fluids - and seek medical attention if they start to feel worse or develop shortness of breath, worsening congestion or cough.

PUBLIC HEALTH CONCERNS

- Trace the first case of H3N2 in India.
- High risk people to consider vaccinations.
- Do not allow any person suffering from flu to enter public places.
- Give compulsory off to people suffering from flu.
- Learn cough etiquettes and respiratory hygiene.

■■■■

AMERICAN FAMILY PHYSICIAN

Colorectal Cancer Screening and Surveillance

MATTHEW W. SHORT, MILES C. LAYTON, BETHANY N. TEER, JASON E. DOMAGALSKI

ABSTRACT

Colorectal cancer is the third most common cancer in men and women. The incidence and mortality rate of the disease have been declining over the past two decades because of early detection and treatment. Screening in persons at average risk should begin at 50 years of age; the U.S. Preventive Services Task Force recommends against routine screening after 75 years of age. Options for screening include high-sensitivity fecal occult blood testing annually, flexible sigmoidoscopy every five years with high-sensitivity fecal occult blood testing every three years, or colonoscopy every 10 years. In 2012, the U.S. Multi-Society Task Force on Colorectal Cancer updated its surveillance guidelines to promote the appropriate use of colonoscopy resources and reduce harms from delayed or unnecessary procedures; these guidelines provide recommendations for when to repeat colonoscopy based on findings. Adenomatous and serrated polyps have malignant potential and warrant early surveillance colonoscopy. Patients with one or two tubular adenomas that are smaller than 10 mm should have a repeat colonoscopy in five to 10 years. Repeat colonoscopy at five years is recommended for patients with nondysplastic serrated polyps that are smaller than 10 mm. Patients with three to 10 adenomas found during a single colonoscopy, an adenoma or serrated polyp that is 10 mm or larger, an adenoma with villous features or high-grade dysplasia, a sessile serrated polyp with cytologic dysplasia, or a traditional serrated adenoma are at increased risk of developing advanced neoplasia during surveillance and should have a repeat colonoscopy in three years. More than 10 synchronous adenomas warrant surveillance colonoscopy in less than three years. Colonoscopy may be repeated in 10 years if distal, small (less than 10 mm) hyperplastic polyps are the only finding.

Keywords: Colorectal cancer, high-sensitivity fecal occult blood testing, flexible sigmoidoscopy, colonoscopy, adenoma, serrated polyp

Colorectal cancer is the third most common cancer in men and women. Despite a reduction in incidence and mortality over the past two decades from early detection and treatment, an estimated 137,000 new diagnoses and 50,000 deaths were expected in 2014.[1-3] Screening and surveillance detect cancer in its early stages when symptoms are not typically present.[1] Approximately 30% of patients have nonmodifiable risk factors that increase their risk of colorectal cancer,[4] including a family or personal history of colorectal cancer or advanced adenomas, personal history of inflammatory bowel disease, and personal history of hereditary polyposis syndromes.[1] Modifiable risk factors include obesity, inactivity, smoking, and heavy alcohol use.[5]

This article reviews the 2012 U.S. Multi-Society Task Force on Colorectal Cancer consensus guidelines for surveillance of persons with colonoscopy findings, which aim to promote the appropriate use of colonoscopy resources and reduce harms from delayed or unnecessary procedures.[6]

COLORECTAL CANCER SCREENING

The U.S. Preventive Services Task Force and other organizations recommend that colorectal cancer screening begin at 50 years of age in persons at average risk.[7-10] The American College of Gastroenterology recommends that black persons receive initial screening at 45 years of age because of an increased incidence of colorectal cancer in this population, although no

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Source: Adapted from Am Fam Physician. 2015;91(2):93-100.

Table 1. Colorectal Cancer Screening Recommendations in Asymptomatic Adults at Average Risk

Organization	Screening test and interval	Patient age
U.S. Preventive Services Task Force*[7]	The following options are equally acceptable High-sensitivity FOBT annually Flexible sigmoidoscopy every 5 years with high-sensitivity FOBT every 3 years Colonoscopy every 10 years	Start at 50 years; individualize after 75 years
American College of Gastroenterology†[8]	Preferred Colonoscopy every 10 years Fecal immunochemical test annually (if colonoscopy is declined) Alternative, prevention Flexible sigmoidoscopy every 5 to 10 years Computed tomography colonography every 5 years Alternative, cancer detection High-sensitivity FOBT annually Stool DNA test every 3 years	Start at 50 years, or 45 years in blacks
American Cancer Society, U.S. Multi-Society Task Force, American College of Radiology‡[9]	Tests that detect adenomas and cancer Flexible sigmoidoscopy every 5 years Colonoscopy every 10 years Double-contrast barium enema every 5 years Computed tomography colonography every 5 years Tests that primarily detect cancer High-sensitivity FOBT annually Fecal immunochemical test annually Stool DNA test, interval uncertain	Start at 50 years

Note: Table 2 summarizes screening recommendations based on risk factors.

FOBT = Fecal occult blood testing.

*Recommendations also apply to those with first-degree relatives with colorectal cancer or adenomas, but the guideline notes that earlier screening is reasonable in those with a first-degree relative who developed colorectal cancer at a young age. Recommendations exclude those with inherited syndromes or inflammatory bowel disease.

†A family history of small tubular adenomas in first-degree relatives is not considered to increase the risk of colorectal cancer. Patients with a family history of colorectal cancer in a single first-degree relative at 60 years or older can be screened on the same schedule as average-risk persons.

‡Guidelines are not for those with a personal or family history of colorectal cancer or adenomas, inflammatory bowel disease, or high-risk genetic syndromes.

Information from references 7 through 9.

patient-oriented outcome studies currently support this recommendation.[8,11]

The U.S. Preventive Services Task Force recommends against routine screening after 75 years of age because the potential benefits of screening may be outweighed by harms and competing causes of mortality; physicians and patients should individualize screening decisions after this age.[7] Similarly, the U.S. Multi-Society Task Force believes the decision to continue surveillance should be based on a patient's estimated risk, benefit, and comorbidities.[6] Table 1 summarizes screening recommendations for asymptomatic adults at average risk.[7-9] Patients with a positive test result should undergo full visualization of the colon with colonoscopy.

Screening recommendations for patients with a family history of colorectal cancer vary based on the relative's relationship to the patient, findings, and age when the cancer was diagnosed (Table 2).[8] Patients with a first degree relative who has had colorectal cancer or an advanced adenoma (i.e., an adenoma that is 10 mm or larger, has villous elements, or has high-grade dysplasia) diagnosed before 60 years of age, or two first-degree relatives with colorectal cancer or an advanced adenoma diagnosed at any age, should receive a

Table 2. Colonoscopy Screening Recommendations Based on Risk Factors

Risk factor	Age to initiate screening	Interval if normal (years)
Single first-degree relative with colorectal cancer or an advanced adenoma diagnosed at ≥ 60 years of age	50 years (may start at 45 years in blacks)	10
Single first-degree relative with colorectal cancer or an advanced adenoma diagnosed at < 60 years of age	40 years or 10 years younger than affected relative's age when diagnosed, whichever is earlier	5
Two first-degree relatives with colorectal cancer or an advanced adenoma diagnosed at any age	40 years or 10 years younger than the youngest affected relative's age when diagnosed, whichever is earlier	5

Note: An advanced adenoma is defined as an adenoma that is 10 mm or larger, has villous elements, or has high-grade dysplasia.

Information from reference 8.

screening colonoscopy every five years starting at 40 years of age or 10 years younger than the relative's age when diagnosed, whichever is earlier. Patients who have one first-degree relative who has had colorectal cancer or an advanced adenoma diagnosed at 60 years of age or older can be screened on the same schedule as average-risk individuals.

Guidelines for follow-up surveillance colonoscopy are summarized in Table 3.[6,8,12]

COLON POLYPS

A colon polyp is a growth protruding into the lumen from the colonic mucosa. The two main categories of polyps are neoplastic and non-neoplastic. Hyperplastic polyp is the most common non-neoplastic polyp. Common neoplastic polyps include adenomas and serrated polyps.

Hyperplastic Polyps

Hyperplastic polyps (Figure 1), which account for up to 50% of sigmoid and rectal polyps, are typically small, sessile polyps that measure 1 to 5 mm in size.[13] Because small (less than 10 mm) hyperplastic polyps in the rectum and sigmoid rarely exhibit dysplasia or develop into colon cancer, colonoscopy may be repeated in 10 years if they are the only finding. No increased risk has been shown three years after baseline colonoscopy in patients with hyperplastic polyps and coexisting adenomas.[14] Therefore, small, distal hyperplastic polyps do not alter colonoscopy surveillance guidelines.

Adenomas

Adenomas are polyps that have malignant potential and require early surveillance colonoscopy.[15] They are classified by their glandular histology and level of dysplasia, which determine their malignant potential and interval for repeat colonoscopy. Tubular adenomas (Figures 2 and 3) account for 80% of adenomas and have a malignant transformation rate at diagnosis of 4.8%. Tubulovillous and villous adenomas (Figure 4) are less common but have more malignant potential (19.0% for tubulovillous, 38.4% for villous).[16]

Although all adenomas are dysplastic, the degree of dysplasia is classified as low or high grade. High-grade dysplasia (Figure 5) suggests that the polyp is evolving toward malignancy. An adenoma that is 10 mm or larger, has villous elements, or has high-grade dysplasia, or the presence of three or more adenomas during a single examination, has a strong association with advanced neoplasia on future colonoscopies.[6,17-19]

Serrated Polyps

Sessile serrated polyps are thought to be the principal precursor of hypermethylated gene cancers; 20% to 30% of colorectal cancers can arise from this pathway.[6] These polyps are often difficult to detect during colonoscopy because they can be flat and indiscrete, and have adherent mucus[6,20] (Figures 6 and 7). All sessile serrated polyps require early follow-up colonoscopy; those that have cytologic dysplasia, are 10 mm or larger, or are located proximal to the sigmoid colon may be associated with a higher risk of developing cancer.[6]

COLONOSCOPY SURVEILLANCE AFTER POLYPECTOMY

Patients who have adenomas are more likely to have additional adenomas or colorectal cancer on subsequent examinations.[6] Endoscopic follow-up of patients with adenomas is referred to as a surveillance colonoscopy. The presence of low- or high-risk adenomas determines the surveillance interval.[6]

Table 3. Guidelines for Follow-up Surveillance Colonoscopy

Initial colonoscopy findings	Follow-up interval
Normal[8]	
No polyps or normal biopsy results	10 years
Hyperplastic polyps[6]	
Small (< 10 mm) hyperplastic polyps in rectum or sigmoid	10 years
Low-risk polyps[6]	
1 or 2 small (< 10 mm) tubular adenomas	5 to 10 years
Small sessile serrated polyp (< 10 mm) without dysplasia	5 years
High-risk polyps[6]	
3 to 10 tubular adenomas	3 years
Tubular adenoma or serrated polyp that is ≥ 10 mm	
Adenoma with villous features or high-grade dysplasia	
Sessile serrated polyp with cytologic dysplasia	
Traditional serrated adenoma	
Other circumstances[6]	
More than 10 adenomas	< 3 years
Serrated polyposis syndrome*	1 year
Following piecemeal removal of a large (> 15 mm) sessile adenoma or serrated polyp	Consider repeat in < 1 year if question of residual polyp
Following curative resection of colorectal cancer[12]	1 year after resection, then 3 and 5 years if normal

*Criteria for serrated polyposis syndrome: at least 5 serrated polyps proximal to the sigmoid with 2 or more that are > 10 mm, any serrated polyp proximal to sigmoid with a family history of serrated polyposis syndrome, or > 20 serrated polyps of any size throughout the colon.

Information from references 6, 8, and 12.

Low-risk Polyps

Low-risk polyps include one or two small (less than 10 mm) tubular adenomas or serrated polyps without cytologic dysplasia. Patients with low-risk tubular adenomas should have a repeat colonoscopy in five to 10 years. Evidence suggests that a surveillance interval of more than five years for low-risk tubular adenomas is reasonable in most patients; however, a five-year interval is prudent if the bowel preparation is inadequate or the cecum is not reached during colonoscopy.[17,18,21,22] Repeat colonoscopy at five years is recommended for patients with nondysplastic serrated polyps that are smaller than 10 mm.[20]

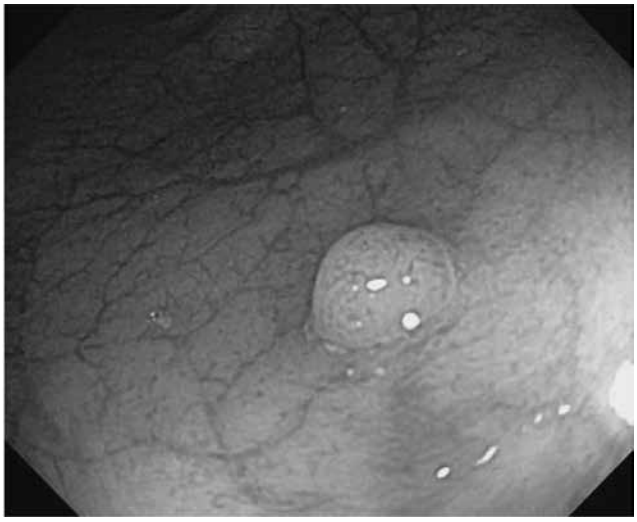

Figure 1. Hyperplastic polyp.

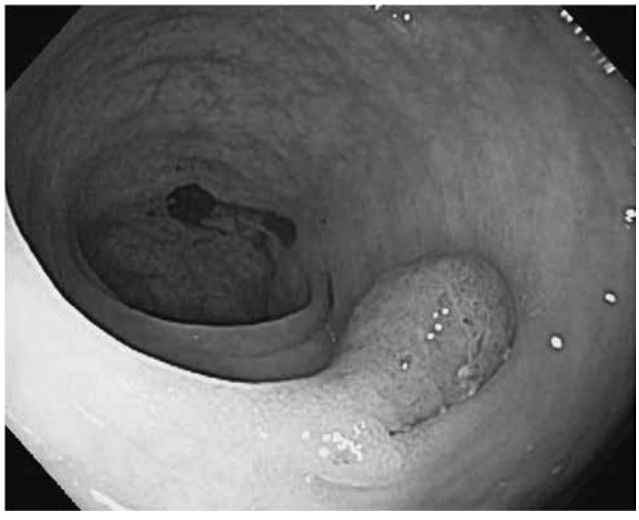

Figure 2. Tubular adenoma (pedunculated).

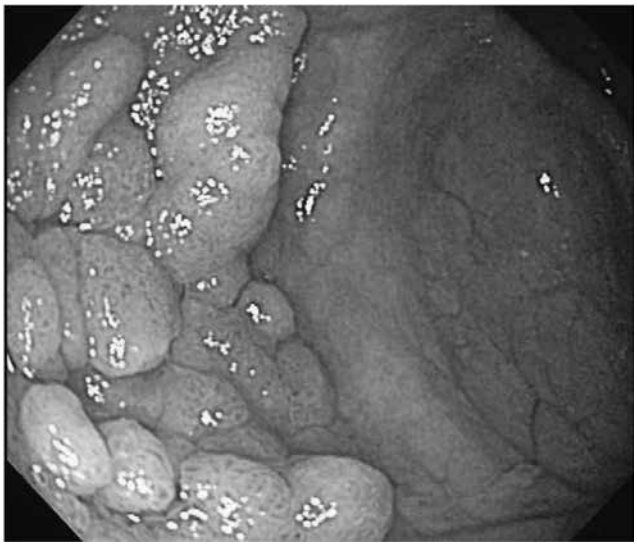

Figure 3. Tubular adenoma (sessile).

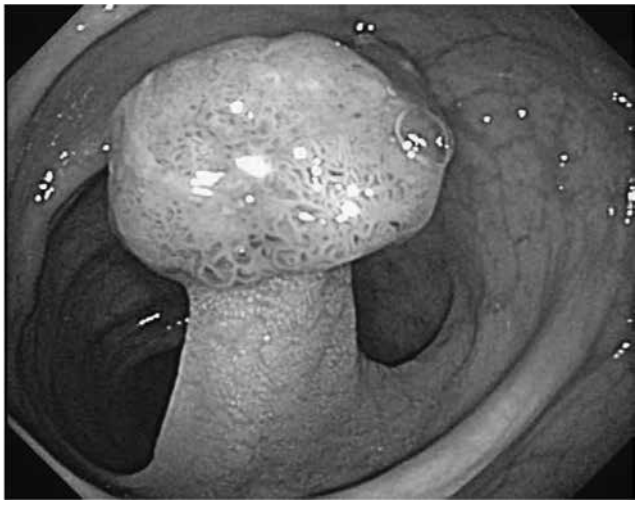

Figure 4. Tubulovillous adenoma.

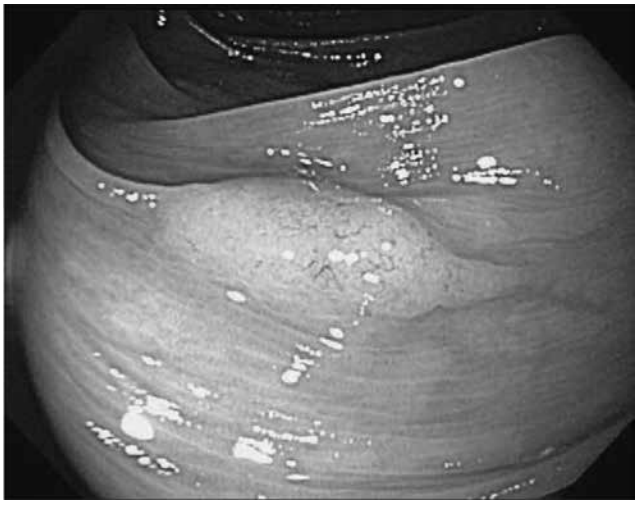

Figure 6. Sessile serrated polyp.

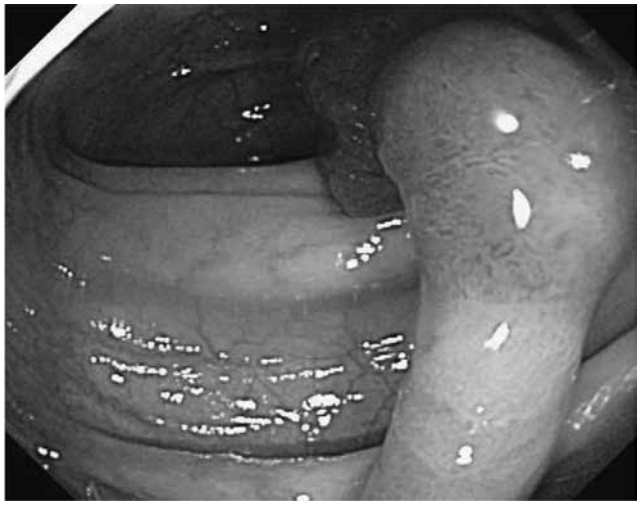

Figure 5. Tubular adenoma with high-grade dysplasia.

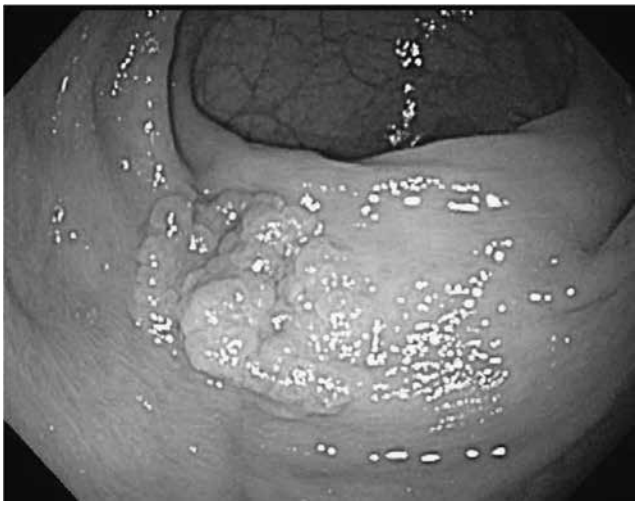

Figure 7. Traditional serrated adenoma.

High-risk Polyps

High-risk polyps include three to 10 tubular adenomas found during a single colonoscopy, at least one tubular adenoma or serrated polyp that is 10 mm or larger, at least one adenoma with villous features or high-grade dysplasia, a sessile serrated polyp with cytologic dysplasia, or a traditional serrated adenoma. Surveillance colonoscopy is recommended at three years for high-risk polyps.[6,17,18]

The U.S. Multi-Society Task Force recommends surveillance colonoscopy earlier than three years in some situations. Patients with more than 10 synchronous adenomas warrant surveillance colonoscopy in less than three years. *MUTYH* mutation analysis or genetic consultation should also be considered to evaluate for *MUTYH*-associated polyposis, an autosomal recessive disease associated with increased risk of colorectal cancer.[23] The U.S. Multi-Society Task Force has also released guidelines on the genetic evaluation and management of Lynch syndrome, an autosomal dominant condition and the most common cause of inherited colorectal cancer.[24] Patients diagnosed with serrated polyposis syndrome should have surveillance colonoscopy in one year because of a significant risk of colorectal cancer.[6,25] A repeat colonoscopy should be considered in less than one year for a large (more than 15 mm) sessile adenoma or serrated polyp removed by piecemeal resection if there is concern about incomplete removal. A repeat colonoscopy in two to six months is no longer required for a polyp removed by piecemeal resection if the endoscopist is certain that the resection was complete.[6]

The second surveillance interval relies on findings from the baseline and first surveillance colonoscopy (Figure 8).[6] Patients with a history of low-risk adenomas

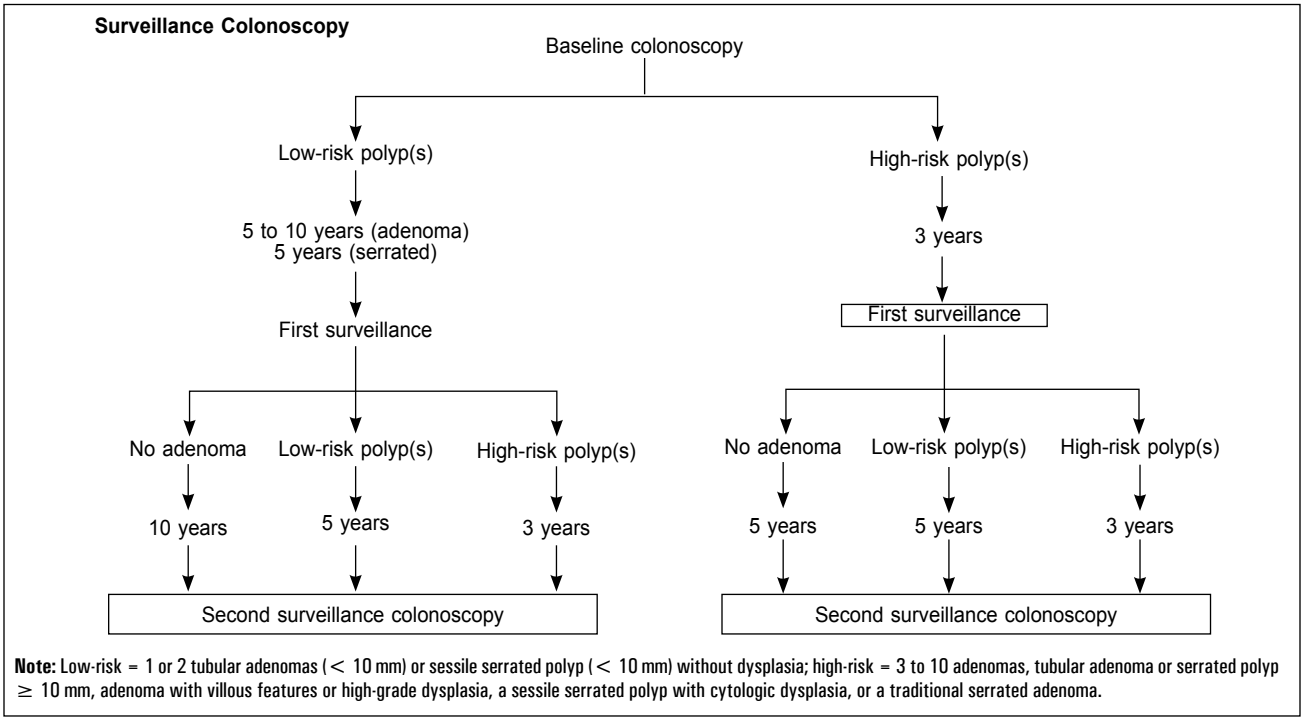

Figure 8. Algorithm for surveillance colonoscopy.
Information from reference 6.

and negative findings on their first surveillance colonoscopy are very low risk.[6] Patients with high-risk adenomas on baseline colonoscopy should continue to have shorter follow-up intervals.[26,27]

QUALITY OF COLONOSCOPY

The recommended colorectal cancer screening and surveillance intervals assume that high-quality colonoscopy has been performed. There is a direct relationship between published quality indicators for colonoscopy and interval cancer risk.[28,29] Interval cancers are less likely when colonoscopy is performed by endoscopists with high cecal intubation and high adenoma detection rates.[30,31] High-quality endoscopists are expected to reach the cecum in 95% of screening procedures performed, and detect adenomas in 15% of women and 25% of men undergoing screening colonoscopy after 50 years of age.[28] A repeat colonoscopy should be considered in one year for patients with a poor bowel preparation because this is associated with missed polyps.[6] The use of fecal occult blood testing between surveillance colonoscopies is currently not recommended,[6] but it requires further study.[32,33] If a patient has a positive finding on fecal occult blood testing, the decision to perform an early colonoscopy should be based on the quality of the previous colonoscopy.

SURVEILLANCE AFTER COLORECTAL CANCER

If colorectal cancer is found during colonoscopy, the remainder of the colon should be viewed proximal to the cancer before surgery. If there is an obstructing cancer, computed tomography colonography with intravenous contrast media or a double-contrast barium enema should be used to view the proximal colon followed by a colonoscopy three to six months after resection. After curative resection of the cancer, patients should undergo colonoscopy one, three, and five years after the initial colonoscopy if findings on these surveillance colonoscopies remain normal.[12] Intervals may be shortened after the one-year examination based on adenomatous findings or hereditary causes of colon cancer.

ADHERENCE TO GUIDELINES

Adherence to surveillance guidelines is variable with reports of overutilization in low-risk groups and underutilization in high-risk groups.[34] Following evidence-based guidelines can help reduce the cost and risk of unnecessary procedures, and prevent cancer in high-risk individuals. The Choosing Wisely campaign aims to promote patient-physician conversations by helping patients choose care that is supported by evidence, not duplicative of other tests or

procedures already received, free from harm, and truly necessary.[35] Through Choosing Wisely, the American Gastroenterological Association recommends against repeating colorectal cancer screening (by any method) for 10 years after a negative colonoscopy result, and screening no earlier than five years after removal of a low-risk adenoma in asymptomatic patients.[36]

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Practice Guidelines

ACOG RELEASES GUIDELINE ON GESTATIONAL DIABETES

Up to 7% of pregnancies are complicated by diabetes mellitus, and rates of gestational diabetes are rising worldwide with the increase in obesity and sedentary lifestyle. Gestational diabetes increases the risk of gestational hypertension, preeclampsia, cesarean delivery, and developing diabetes later in life. There is debate about the diagnosis and treatment of gestational diabetes, even with large-scale studies on the subject. The American College of Obstetricians and Gynecologists (ACOG) has released a guideline that provides recommendations based on good-quality research and identifies current gaps in knowledge.

Recommendations

Good and Consistent Evidence

Gestational diabetes should be treated with nutrition therapy. If necessary, medications should also be used to benefit the mother and fetus.

Studies show a significant reduction in serious complications with treatment of gestational diabetes. Nutrition therapy includes nutritional counseling, a personalized nutrition plan, and a moderate exercise program, with the goal of achieving normoglycemia, preventing ketosis, facilitating adequate weight gain, and contributing to fetal well-being.

If target glucose levels cannot be met with nutrition therapy alone, medical therapy should be initiated. There is no conclusive evidence to guide when to start medications. Although insulin has been the standard medical therapy for gestational diabetes, insulin and oral medications (e.g., glyburide, metformin) are equally effective and appropriate for first-line therapy.

Limited or Inconsistent Evidence

All pregnant women should be screened for gestational diabetes using history, clinical risk factors, or glucose screening tests. Screening for gestational diabetes usually occurs at 24 to 28 weeks' gestation. Early screening is recommended in women with risk factors (i.e., history of gestational diabetes, known impaired glucose metabolism, or obesity [body mass index of 30 or more]). If early screening results are negative, screening should be repeated at 24 to 28 weeks' gestation. The screening approach widely used in the United States involves an initial venous glucose measurement one hour after administration of 50 g of oral glucose solution. Women who meet or exceed the screening threshold in the initial test then undergo a 100-g, three-hour oral glucose tolerance test.

Although there are insufficient data to recommend for or against cesarean delivery in cases of suspected macrosomia to reduce birth trauma, macrosomia is more common with gestational diabetes, and shoulder dystocia is more common in larger newborns whose mothers have gestational diabetes. Therefore, it is reasonable to discuss the option of cesarean delivery if gestational diabetes is diagnosed and the fetal weight is estimated at 4,500 g (9 lb, 15 oz) or more.

Consensus and Expert Opinion

Screening thresholds for the one-hour glucose challenge have ranged from 130 mg per dL (7.2 mmol per L) to 140 mg per dL (7.8 mmol per L), showing varying sensitivities and specificities. Because there is no clear evidence to determine the best threshold, physicians should select either 135 mg per dL (7.5 mmol per L) or 140 mg per dL as a single consistent cutoff for their practice. Factors such as community prevalence of gestational diabetes should be considered in the decision. Similarly, no one set of diagnostic criteria can be recommended for the three-hour oral glucose tolerance test. Physicians should choose a single set of diagnostic criteria to use consistently in their practice: plasma or serum glucose levels designated by the Carpenter and Coustan criteria, or the plasma levels established by the National Diabetes Data Group.

After gestational diabetes is diagnosed and nutrition therapy begins, blood glucose should be monitored to establish whether glucose levels are sufficiently controlled. Although there is insufficient evidence to determine the optimal frequency of glucose

Source: Adapted from Am Fam Physician. 2014;96(5):416-417.

monitoring, the general recommendation is four times daily (fasting and one or two hours after each meal). Monitoring can be adjusted after glucose levels are well controlled by diet. Women with gestational diabetes who have good glycemic control and no other complications can be treated expectantly. Most women with good glycemic control on medical therapy do not require delivery before 39 weeks' gestation.

All women with gestational diabetes should be screened six to 12 weeks postpartum for diabetes, impaired fasting glucose, or impaired glucose tolerance. Women with positive screening results should be referred for preventive therapy, and women with negative screening results should receive follow-up testing every three years. A fasting plasma glucose test or a 75-g, two-hour oral glucose tolerance test is appropriate for postpartum screening.

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Photo Quiz

BALD PATCH IN THE BEARD

A 44-year-old man presented with a focal patch of hair loss in his beard that had been present for about two months. It was not itchy or painful. His history findings were unremarkable.

Physical examination revealed a well-circumscribed, hairless patch on the right jawline (Figures 1 and 2). The patch was 1 × 1 cm and smooth. There was no surrounding erythema or scale, and no cervical lymphadenopathy. There were no other lesions.

Question

Based on the patient's history and physical examination findings, which one of the following is the most likely diagnosis?

A. Alopecia areata.

B. Cicatricial alopecia.

C. Tinea barbae.

D. Traction alopecia.

E. Trichotillomania.

Figure 1.

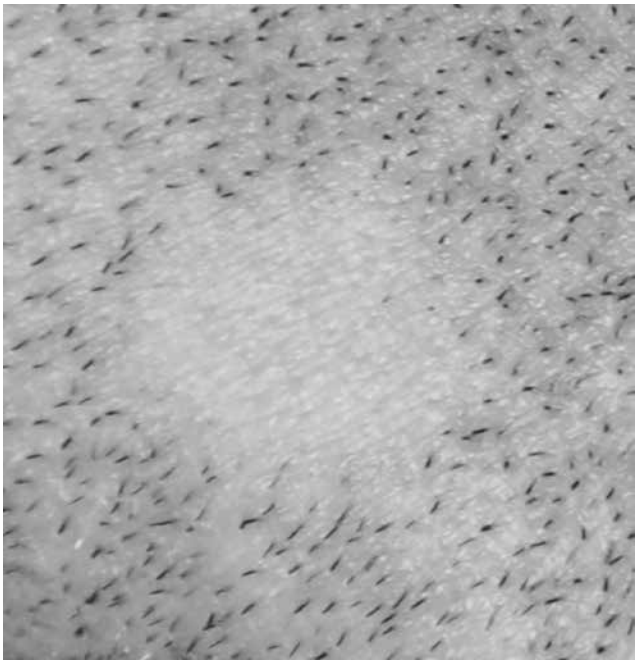

Figure 2.

SEE THE FOLLOWING PAGE FOR DISCUSSION.

Source: Adapted from Am Fam Physician. 2014;89(7):583-584.

Discussion

The answer is A: alopecia areata. This T cell–mediated autoimmune disease has a lifetime prevalence of about 2%.[1] It is characterized by a localized area of complete hair loss with normal skin pattern. Alopecia areata has a sudden onset and may involve the entire scalp (alopecia totalis) or the entire body (alopecia universalis).[2] Alopecia areata increases the risk of other autoimmune disorders.[3]

The diagnosis is usually made clinically; however, a skin biopsy may be performed if the diagnosis is unclear.[1,4,5] Spontaneous remission is common and usually occurs within six to 12 months.[1,2] Topical, intralesional injection and, occasionally, systemic glucocorticoids are used for treatment.[1,2,5] Immunomodulating agents (e.g., irritant dithranol, diphenylcyclopropenone) and topical minoxidil have been used with variable results.[1,4,5]

Cicatricial alopecia is permanent hair loss caused by destruction of the hair follicles by inflammatory or autoimmune diseases, commonly discoid lupus erythematosus.[2,5] The condition causes folliculitis and eventually leads to scarring and skin atrophy.

Tinea barbae is an uncommon fungal infection that most often occurs in farm workers.[6] It usually causes pruritic, erythematous, and scaling patches with fragile, broken hairs.[2,5] Pulling infected hairs is usually painless.[6]

Traction alopecia is unintentional hair loss due to high-tension grooming style.[2,5] Although it can occur in the beard, it is more common on the scalp. In rare cases, chronic traction alopecia results in folliculitis and scar formation.[5]

Trichotillomania is a compulsive disorder that involves repetitive hair pulling.[2,5] The most common location is the scalp.[2] Scar formation occurs in rare cases.[2,5]

Summary Table

Condition	Characteristics
Alopecia areata	Sudden onset; localized hair loss with normal skin pattern
Cicatricial alopecia	Folliculitis; scarring and skin atrophy
Tinea barbae	Pruritic, erythematous, and scaling patches with fragile, broken hairs
Traction alopecia	Patchy; related to high-tension grooming style; more common on the scalp; occasional folliculitis and scar formation
Trichotillomania	Patchy; chronic course; incomplete thinning; occasional scarring; associated with psychological conditions

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To Deduce Optimal Fentanyl Infusion Dose for Effective Analgesia with Minimal Side Effects and Maximum Hemodynamic Stability

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ABSTRACT

Objective: To deduce optimal fentanyl infusion dose for effective analgesia with minimal side effects and maximum hemodynamic stability. **Material and methods:** In our prospective study, comparing the three groups (of 30 patients each) namely group 2, 3, 4 receiving three different doses of fentanyl (20 μg, 30 μg, 40 μg), respectively along with control group (Group 1) receiving conventional analgesics through intramuscular or intravenous route. Effective analgesia rated on linear visual analog scale (VAS) with minimum side effects and most stable hemodynamic parameters. **Results:** The VAS scores, at rest, were significantly lower for epidural fentanyl groups as compared to control group. Mean blood pressure and pulse rate in all groups were comparable at all times. The incidence of side effects was similar in the three groups as compared to control group. **Conclusion:** Fentanyl dose of 40 μg is thus the optimal epidural dose of background infusion along with patient on demand analgesia in terms of maximum analgesic efficacy, maximum hemodynamic stability and minimum side effects in patients undergoing unilateral total knee replacement.

Keywords: Fentanyl infusion, analgesia, optimal dose, unilateral total knee replacement

"The greatest evil is physical pain" —Saint Augustine

Adequate relief of postoperative pain is the cornerstone of any acute pain management service in the modern era. Introduction of new pain management standards by the Joint Commission on Accreditation of Healthcare Organizations (JCAHO) and recognition of the untoward consequences of uncontrolled postoperative pain have led to a greater appreciation for the importance of acute postoperative pain control. Inadequate control of postoperative pain may result in a higher incidence of chronic postsurgical pain, increased postoperative morbidities and worsened patient-oriented outcomes such as quality-of-life.

In the past postoperative pain experienced by patients was treated conventionally with boluses of intramuscular or intravenous analgesics either on demand or at fixed intervals, which provided inadequate analgesia for inappropriate length of time. These two routes are least desirable because while intramuscular route is painful, both routes produce unpredictable blood levels due to erratic absorption. Patient dissatisfaction is common because of delays in drug administration and incorrect dosing. Cycles of sedation, analgesia and inadequate analgesia are common.

After knee surgery, poorly managed pain may inhibit the early ability to mobilize the knee joint. This, in turn, may result in adhesions, capsular contracture and muscle atrophy, all of which may delay or permanently impair the ultimate functional outcome, increased complications and diminished patient oriented outcomes such as quality-of-life and satisfaction. Early mobilization results in shorter hospital stay and cost containment and better resource utilization.

Postoperative epidural analgesia has been used in orthopedic surgeries and reported to expedite the achievements in postoperative rehabilitative milestones, reduce postoperative morbidity and decrease the length of hospital stay, compared with general anesthesia.

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Since, there is lack of availability of sufficient data on "dose response" studies done with epidural fentanyl and a lack of consensus on its efficacy as compared to the traditional analgesic modalities, we planned this study to compare the analgesic effects of various doses of epidural fentanyl (background infusion) along with "on demand" boluses to determine the "optimal dose" postoperatively in patients undergoing unilateral total knee replacement.

MATERIAL AND METHODS

After obtaining informed consent from each and every patient, 120 (American Society of Anesthesiologists [ASA] physical status I or II) patients of either sex, scheduled for elective unilateral knee replacement were enrolled in the study. Their age ranged from 20 to 70 years.

Adult patients who were to undergo unilateral total knee replacement under spinal anesthesia were divided randomly into four groups of 30 patients each for the purpose of this study. Patients were randomly assigned to one of the four groups to receive either none (Group 1 receiving traditional intravenous or intramuscular analgesics referred to as "control" group) or 20 μg/hr (Group 2), 30 μg/hr (Group 3), 40 μg/hr (Group 4) dose of background epidural fentanyl infusion along with "on demand" dose of 20 μg fentanyl.

Combined spinal epidural set: The combined spinal epidural set consisted of

- Sponge holding forceps
- Sterile gauze pieces
- Sterile towel
- Glass syringe (10 and 20 mL)
- Epidural Kit
- Spinal needle 26G
- Sterile dressing.

Visual Analog Scale

The linear visual analog scale (VAS) was used to assess the pain and pain relief of the patients. It consists of a straight line with 0.5 cm segments. One end having a mark 'O' represented "no pain" and the other having mark '10' represented "worst imaginable pain".

Interpretation of the VAS was explained to each and every patient during pre-anesthetic check-up and was explained for the second time after surgery in the recovery room before starting the background infusion of fentanyl. It was thus ascertained that every patient is able to aptly correlate his pain and accurately report it when asked about the same. The surgery was performed under spinal anesthesia. In the postoperative recovery room, before starting the individual background infusion, return of active toe movements was confirmed.

Any "breakthrough pain" before the return of active toe movements was treated likewise with epidural bolus dose of 20 μg but the background infusion was started only after the return of active toe movements and on confirmation of catheter position. Patients experiencing severe breakthrough pain and requiring analgesia even after loading epidural dose of 20 μg fentanyl, before return of active toe movements were excluded from the study. All patients were monitored before starting infusion (0 hour) and for up to 36 hours at 4 hours, 8 hours, 12 hours, 24 hours and 36 hours (Table 2), respectively after starting epidural fentanyl infusion.

In the following parameters: Blood pressure, pulse rate, respiratory rate, SpO_2, pain (as per sedation score), nausea/vomiting (as per nausea, vomiting score), adverse effects (e.g., pruritus, skin allergy, urinary retention respiratory depression)- noted and treated with naloxone/ondansetron. The Duncan's mean test was used to compare the four groups of patents for demographic variables, hemodynamic parameters, VAS scores, analgesia quality, received demand doses and quantifying side effects each time of the study i.e., at 0, 4, 8, 12, 24, 36 hours, respectively. The data were compiled and analyzed to compare the analgesic efficacy of various doses of epidural fentanyl and to determine the optimal dose in terms of effective pain control, minimal number of additional demands made by patient, minimum sedation, maximum hemodynamic stability and minimum side effects.

OBSERVATION AND RESULTS

Hemodynamic parameters were in normal range during entire perioperative period and there was no serious concern.

The mean VAS in Group 1 was 3.62 ± 0.39, in Group 2 was 2.48 ± 0.34, in Group 3 was 1.42 ± 0.31 and in Group 4 was 0.97 ± 0.27. The difference of mean VAS was statistically significant in Group 1 vs. 2, Group 1 vs. 3, Group 1 vs. 4 (Table 1).

The analgesic efficacy in the four groups of patients at 0, 4, 8, 12, 24, 36 hours has been defined as (i) Excellent if mean VAS was between 0 to 3; (ii) Good if mean VAS between 4 to 6 and (iii) poor if mean VAS was between 7 to 10. This shows that there was significant reduction in pain score (VAS) as the background infusion dose of fentanyl increased from 20 μg/hr in Group 2 to 40 μg/hr in Group 4 (Table 2).

Table 1. VAS Score in the Groups 1 to 4

G-1 (n = 30)		G-2 (n = 30)		G-3 (n = 30)		G-4 (n = 30)		Significant pairs	F value
Mean	SD	Mean	SD	Mean	SD	Mean	SD		370.80
3.62	0.39	2.48	0.34	1.42	0.31	0.97	0.27	Gr2 vs. Gr1 Gr3 vs. Gr1 Gr4 vs. Gr1 Gr3 vs. Gr2 Gr4 vs. Gr2 Gr4 vs. Gr3	

Table 2. Analgesic Efficacy in the Four Groups of Patients at 0, 4, 8, 12, 24, 36 Hours

VAS Group	G-1 (n = 30)		G-2 (n = 30)		G-3 (n = 30)		G-4 (n = 30)		Significant pairs	F value
	Mean	SD	Mean	SD	Mean	SD	Mean	SD		
VAS0	2.10	0.60	1.83	0.38	1.80	0.61	1.86	0.62	-	1.73
VAS4	4.43	1.04	3.03	0.85	1.33	0.60	0.97	0.61	G4 vs. G1 G4 vs. G1 G3 vs. G2 G3 vs. G1 G2 vs. G1	121.08
VAS8	4.13	1.19	2.73	0.64	1.37	0.61	0.97	0.56	G4 vs. G2 G4 vs. G1 G3 vs. G2 G3 vs. G1 G2 vs. G1	98.12
VAS12	4.23	0.81	2.80	0.76	1.46	0.73	0.80	0.66	G4 vs. G3 G4 vs. G2 G4 vs. G1 G3 vs. G2 G3 vs. G1	124.75
VAS24	3.60	0.72	2.33	0.54	1.37	0.67	0.60	0.56	G4 vs. G3 G4 vs. G2 G4 vs. G1 G3 vs. G2 G3 vs. G1 G2 vs. G1	126.74
VAS36	3.23	0.81	2.17	0.46	1.20	0.96	0.63	0.67	G4 vs. G3 G4 vs. G2 G4 vs. G1 G3 vs. G2 G3 vs. G1 G2 vs. G1	69.45

DISCUSSION

Postoperative pain is the most common form of pain encountered by the anesthesiologist. The associated morbidity and severity requires adequate management of postoperative pain. Besides the humanitarian cause, the effective management of postoperative pain is mandatory also for prevention of complications like nausea and vomiting, negative nitrogen balance, deep vein thrombosis, lung atelectasis and other respiratory complications. Ureteral and bladder hypomobility, which may delay recovery and prolong hospitalization.

When an opioid is administered to the chief site of action, the substantia gelatinosa of the dorsal horn, it produces a highly selective depressing action on nociceptive pathway in the rexed laminae of the dorsal horn without effecting motor sympathetic or proprioceptive pathways thus allowing pain relief without sympathetic or motor blockade.

The cardiovascular and hemodynamic effects of fentanyl have usually been relatively small and limited to minimal depression in the heart rate, blood pressure and right ventricular work with a compensatory increase in stroke volume.

The mean VAS in Group 1 was 3.62 ± 0.39, in Group 2 was 2.48 ± 0.34. There was no statistically significant difference in the mean VAS scores in the four groups at 0 hours. The mean VAS scores at 4, 8, 12, 24 and 36 hours post-fentanyl infusion along with on demand rescue analgesia were least in Group 4 followed by Group 3, 2 and 1. This shows the analgesic efficacy of 40 μg/hr fentanyl infusion dose in Group 4. Thus, in terms of analgesic efficacy 40 μg/hr epidural fentanyl dose is the 'optimal dose' along with 'on demand' 20 μg bolus dose of fentanyl. The analgesic efficacy of fentanyl can be attributed to supraspinal and spinal mechanisms.

The results support a segmental spinal effect of epidural fentanyl bolus administration and a nonsegmental dual spinal and supraspinal effect of epidural fentanyl infusion. They also provide evidence of clinical benefits from its predominant spinal action, notably improved analgesia, with a reduction in central side effects. The study thus provides support for a spinal mechanism of action of bolus administration of epidural fentanyl.

CONCLUSION

We thus conclude that epidural fentanyl dose of 40 μg/hr (Group 4) as "background infusion" is the most efficacious dose in terms of pain relief (analgesic efficacy) followed by 30 μg/hr (Group 3) and 20 μg/hr (Group 2), respectively along with patient's "on demand" rescue analgesia bolus dose of 20 μg in patients undergoing unilateral total knee replacement. Epidural fentanyl dose of 40 μg/hr is the "optimal dose" of background infusion along with patient control analgesia in terms of maximum analgesic efficacy, maximum hemodynamic stability and minimum side effects, in patients undergoing unilateral total knee replacement.

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Postural 2:1 Heart Block in a Elderly Male: A Case Report

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ABSTRACT

Syncope or dizziness is defined as a transient, self-limited loss of consciousness with an inability to maintain postural tone that is followed by spontaneous recovery. Syncopal episodes are typically triggered by a sudden, temporary drop in blood flow to the brain, which leads to loss of consciousness and muscle control. Commonest cause is reflex (vasovagal syncope); this is neurally-mediated during emotional stress, orthostatic stress, situational or carotid sinus hypersensitivity. Syncope due to cardiac causes increases with age and is found in 2-3% population over the age of 80 years. Cardiac causes like sick sinus, AV block, PSVT, VT, long QT syndrome, malfunctioning pacemakers or ICD, drugs may lead to syncope/dizziness. But AV block occurring due to change in posture from supine to sitting/erect posture without any of the above-mentioned cause is very rare; we encountered such a case in an elderly male and hence this case report.

Keywords: Syncope, vasovagal, posture, cardiac causes, atrioventricular block

Dizziness or syncope may occur in any human being due to inadequate perfusion of brain due to various reasons, commonest among it is reflex (vasovagal syncope). This is neurally-mediated during emotional stress, orthostatic stress, situational or carotid sinus hypersensitivity. Other causes are numerous and approximately 40% population is affected once during lifetime (more common in young female), but only few need medical intervention. Syncope/dizziness due to cardiac causes increases with age and is found in 2-3% population over age of 80 years.[1]

A careful history about posture, situation, recent medication or history of comorbidity may help in arriving at diagnosis and further management. Cardiac causes like sick sinus, atrioventricular (AV) block, PSVT, VT, long QT syndrome, malfunctioning pacemakers or implantable cardioverter defibrillator (ICD), drugs may lead to syncope/dizziness. But AV block with change in posture from supine to sitting/erect posture without any of the above-mentioned cause is very uncommon;[2] we encountered such a case in an elderly male and hence this case report.

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CASE REPORT

An elderly male aged about 60 years suddenly felt dizziness and sense of palpitation (missing heart beats) during normal activity. Patient had no history of any comorbid conditions like diabetes, hypertension, coronary artery disease (CAD), drug intake or any other major illness in recent past but had a history of occasional episodes of palpitation for few seconds for past 30 years and repeated.

Holter monitoring had shown only few ventricular premature contraction in 2-3 reports, which was insignificant. Due to giddiness and unable to do normal activity, was taken to tertiary care hospital for needful. On examination, in supine posture heart rate was 78/min regular, blood pressure was 140/86 mmHg, respiratory rate 18/min was kept for observation in cardiac care unit.

All other investigations like complete blood count (CBC), liver function tests (LFT), renal function tests (RFT), chest X-ray, blood sugar level, electrolyte, troponin test and cardiac markers were within normal limits. ECG was normal in supine position but whenever patient assumed sitting position felt giddiness and irregular heart beat. So, ECG was recorded on 3 (Three) occasions at time intervals in supine as well as sitting posture, which showed 2:1 heart block (Figs. 1 and 2); on each occasion with assuming sitting posture. As the patient was symptomatic on assuming sitting posture, a permanent pacemaker device was implanted, that solved the problem.

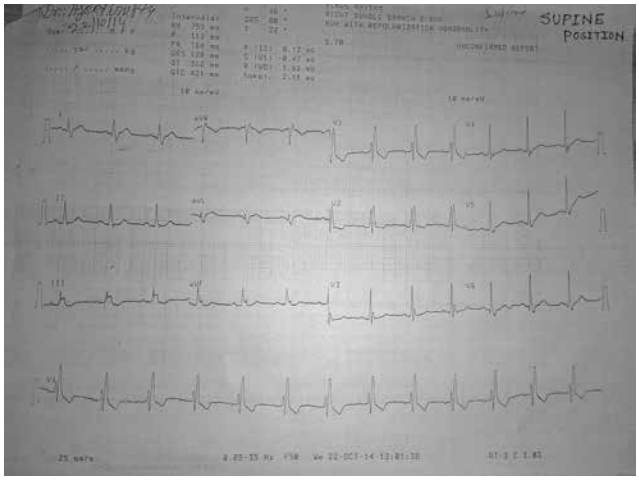

Figure 1. ECG in supine position.

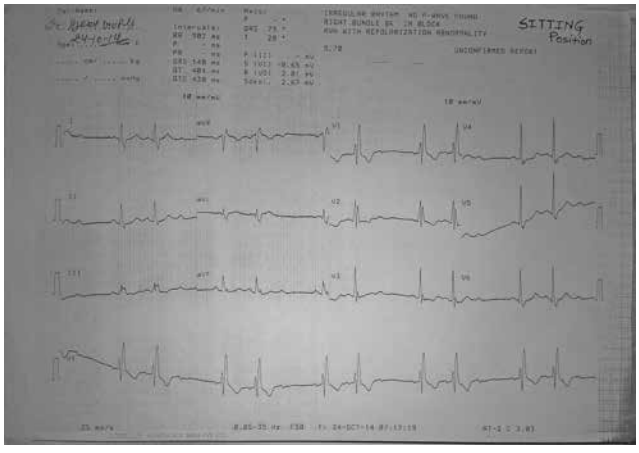

Figure 2. ECG in sitting position showing 2:1 heart block.

DISCUSSION

Transient loss of consciousness or dizziness is a common symptom in human due to transient fall in cerebral perfusion. Hypotension i.e., a fall in blood pressure of 20 mmHg systolic and 10 mmHg diastolic is acceptable with change in posture from supine to upright position but any fall more than that may be due to medications or failure of autonomic reflex with resulting pooling of blood in dependent part.

Most of the syncope is reflex mediated (depressor reflex) arising in heart, first described by Bezold, is compensated through activation of autonomic nervous system by vasoconstriction and increase in heart rate. Studies suggests that cardiac *C*-fibers are responsible for slowing heart rate and vasodilatation leading to pooling of blood in dependent part, carotid sinus hyperactivity, parasympathetic activation, organic heart disorders, rhythm abnormality are other leading cause of syncope.[3]

Paroxysmal heart block by act of sitting up in bed or assuming upright posture with severe symptoms like syncope and fainting without change in blood pressure has been reported by Klein et al in two of their cases, relieved by permanent pacemaker implant.[4] In a similar case report, Kartikeyan et al[5] reported reflex syncope in a 52 years lady with normal AV conduction in supine position but advanced AV block in upright posture, necessitating permanent pacemaker implant.

Such cases are encountered infrequently and literature reports only few cases of heart block with change of posture, as with this case. Because of rare occurrence we are reporting this case.

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Systemic Amyloidosis Presented as Carpal Tunnel Syndrome: An Unusual Presentation

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ABSTRACT

Systemic amyloidoses are multisystem disorders caused by abnormal proliferation and deposition of insoluble amyloid proteins in various body organs and tissues, eventually leading to organ dysfunction and death. The organs most commonly affected are the kidney, heart and liver. Patients usually present with nonspecific symptoms like fatigue, weight loss and pedal edema followed by symptoms and signs related to specific organ involvement. We report a patient of systemic amyloidosis presented with sign and symptoms consistent with carpal tunnel syndrome, with no systemic features that is an unusual presentation.

Keywords: Systemic amyloidosis, carpal tunnel syndrome, amyloid protein

Amyloidoses are a heterogenous group of disorders caused by extracellular deposition of insoluble fibrillar proteins arranged in a β-pleated sheet conformation throughout the body.[1] Term "amyloid" was given by Rudolph Virchow in 1854 to describe tissue deposits that stained like cellulose when exposed to iodine. Amyloid deposits, after staining with Congo red stain, appear red under normal light microscopy and have apple-green birefringence under polarized light.[2]

Traditionally, amyloidosis was classified as localized and systemic, familial and nonfamilial form. However, nowadays amyloidosis can be classified chemically depending on chemical nature of amyloid protein. Capital letter A is designated for amyloid followed by an abbreviation for the type of fibril protein. In previously so called primary amyloidosis and myeloma-associated amyloidosis, the fibril protein is an immunoglobulin light chain or light chain fragment (abbreviated L), therefore this type of amyloidosis is now know as light chain amyloidosis (AL). Common clinical forms of systemic amyloidosis are AL, AA, ATTR and Aβ2M types.[3]

CASE REPORT

A 59-year-old male presented with history of tingling sensation, paresthesia of thumb, index and middle fingers of both hands for last 3 years, predominantly during night time, difficulty in gripping objects and difficulty in doing fine motor activities for last 2 years. There was no history of numbness over the hands as patient could perceive hot and cold sensation.

He also had complaints of rash over face, neck and upper chest for last 1½ years, initially erythematous then papulonodular followed by hyperpigmentation over face and patches of waxy discoloration (hypopigmentation) below eyes for last 5-6 months, interspersed with punctate bleeding points. He took homeopathic treatment for 1 year but had no relief. Dermatologist diagnosed it as a case of seborrheic dermatitis with pyoderma and started oral steroids for 6-7 months without improvement. He also had significant weight loss of around 10 kg in the last 1 year without decreased appetite, low backache for 3-4 months and swelling of tongue and ulcerations over tongue for last 15-20 days. There was no history of diabetes and hypothyroidism.

General physical examination revealed coarse facies, pallor, waxy papules over face and chest, purpuric lesions to almost confluent ecchymotic patches,

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macroglossia (Fig. 1). On per abdominal examination, there was no organomegaly. Central nervous system (CNS) examination revealed weakness of small muscles of hand in median nerve distribution. Tinel's and Phalen's sign were positive, ankle jerk was decreased on right side and absent on left side. Straight leg raise (SLR) was positive bilaterally (left-50°, right-60°). Autonomic function tests were normal. Peripheral nerves were not palpable.

A functional diagnosis of bilateral (B/L) carpal tunnel syndrome with B/L L5-S1 radiculopathy with papulonodular and purpuric rashes with macroglossia and significant weight loss was made. Possibility of a multisystem disease involving peripheral nerves, nerve roots, skin and soft tissue, small vessels and tongue was kept. Differentials considered were connective tissue disorders, systemic amyloidosis, sarcoidosis and paraneoplastic disorders.

Routine investigations revealed: Fasting blood sugar (FBS) - 86 mg/dL, blood urea - 58 mg/dL, serum creatinine - 1.6 mg/dL, serum uric acid - 3.6 mg/dL, serum calcium - 9.7 mg/dL, phosphate - 2.7 mg/dL, sodium - 142 mEq/L, potassium - 4.0 mEq/L, total bilirubin - 0.8 mg/dL, serum glutamic oxaloacetic transaminase (SGOT) - 24 IU/L, serum glutamic pyruvic transaminase (SGPT) - 51 IU/L, alkaline phosphatase - 106 IU/L, lactate dehydrogenase (LDH) - 433 U/L, creatine phosphokinase (CPK) - 99 U/L, thyroid-stimulating hormone (TSH) - 3.31 mIU/L, serum vitamin B_{12} - 483 pg/mL, hemoglobin - 7.7 g/dL, total leukocyte count (TLC) - 5,460/mm^3, erythrocyte sedimentation rate (ESR) - 80 mm/hr, rheumatoid factor - negative, C-reactive protein (CRP) - positive. Peripheral blood smear - normocytic normochromic, no abnormal cells, urine-protein-trace, RBC - 10-12/hpf. Total protein - 6.8 mg/dL, albumin - 3.5 mg/dL, A:G ratio = 1:1, human immunodeficiency virus (HIV) - nonreactive, serum cortisol - 9.63 μg/dL (5-25). ECG and chest radiographs were normal. Nerve conduction study showed sensorimotor axonal and demyelinating neuropathy affecting both median nerves suggestive of B/L carpal tunnel syndrome. Sympathetic skin response was negative. Ultrasonography of abdomen and pelvis showed B/L early medical renal disease. Magnetic resonance imaging (MRI) LS spine showed disc bulge at L4-5 and L5-S1 levels with ligamentum flavum hypertrophy causing B/L lateral recess stenosis and compression of exiting nerve roots. Dermatology consultation confirmed waxy papules and pinch purpura over face and chest, but skin biopsy was negative for amyloid stain. Rectal biopsy showed evidence of chronic inflammation but negative for amyloid stain on Congo red. CT thorax and abdomen was negative for any hilar lymph nodes but hepatomegaly was present. Skull radiograph did not show any lytic lesion and urine for Bence-Jones protein was negative. Serum protein electrophoresis was positive for M-band (γ-globulin fraction - 32.8%) with A/G ratio reversal (0.73).

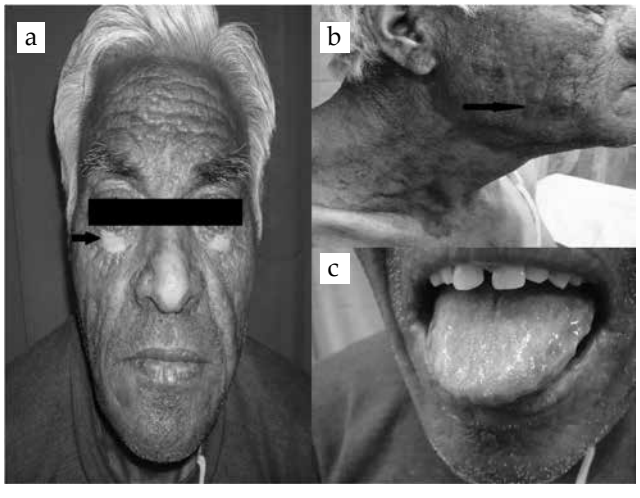

Figure 1. Hypopigmented patches below eyes **(a)**, ecchymotic patches on face **(b)** and macroglossia **(c)**.

At this point, hemato-oncologist opinion was taken and bone marrow aspiration and biopsy was done. Bone marrow smear showed normoblastic erythroid hyperplasia with increased no. of plasma cells (12%). Bone marrow biopsy was hypercellular with M:E ratio of 4:1 with 35% plasma cells suggestive of plasma cell myeloma. Tongue biopsy revealed submucosal deposits of pink acellular hyaline material with apple-green birefringence on polarizing microscopy suggestive of amyloidosis (Fig. 2). 2D Echo study was negative for any cardiac deposits.

So, a final diagnosis of AL amyloidosis secondary to plasma cell myeloma was considered with multiple organ system involvement in the form of neuropathy,

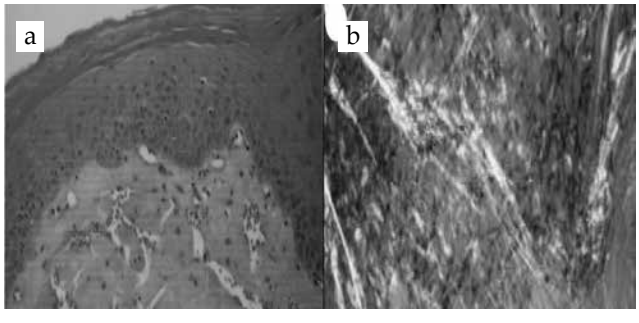

Figure 2. Tongue biopsy revealed submucosal deposits of pink acellular hyaline material on H&E stain **(a)** and apple-green birefringence on polarizing microscopy **(b)**.

radiculopathy, skin, subcutaneous tissue and small blood vessels involvement, macroglossia, hepatomegaly, nephropathy and bone marrow plasmacytosis.

Patient was started on a chemotherapy regimen which included induction with bortezomib, lenalidomide and dexamethasone once a week for 24 weeks followed by maintenance with lenalidomide and plan for bone marrow transplantation after complete remission. After 6 months of chemotherapy, skin lesions showed healing with serum electrophoresis showing γ-globulin fraction of 15.4% with A/G ratio of 1.47 and bone marrow plasma cells reduced from 35% to 8% suggestive of partial to near complete remission of myeloma.

DISCUSSION

AL amyloidosis is usually associated with plasma cell dyscrasias. Insidious onset, diverse clinical manifestations and initial presentation with vague symptoms make diagnosis more difficult. Multiple organ systems are involved, kidney and heart being most commonly affected. Liver involvement is seen in 15-25% of patient and cardiac involvement in up to 50%.[4]

Approximately 90% patients present with profound fatigue, weight loss and edema. Edema may have multiple causes including hypoalbuminemia (from kidney, bowel or liver involvement) and right-heart failure.[5]

Our patient presented with tingling sensation, paresthesia of thumb, index and middle finger with weakness of both hand in the median nerve distribution suggestive of carpal tunnel syndrome. While systemic amyloidosis presenting as a carpal tunnel syndrome is very rare, this syndrome results from progressive infiltration of flexor retinaculum and synovial tissue with amyloid fibrils causing compression of the medium nerve.

Peripheral nerve involvement in amyloidosis occurs very late in the disease course. The typical pattern of amyloid neuropathy is diffuse, symmetrical, length-dependent, lower-limb predominant, primarily axonal with prominent involvement of small (pain and autonomic features) fibers.[6] Nerve conduction studies show changes of axonal neuropathy with low amplitude or absent sensory nerve action potentials (SNAPs) and low amplitude compound muscle action potentials (CMAPs) but preserved motor conduction velocities. Distal median motor latencies are prolonged in patients with carpal tunnel syndrome.

Skin involvement in the form of petechiae, purpura and ecchymoses occur due to infiltration of blood vessel walls by amyloid deposits.[7] Similar cutaneous lesions were also seen in our patient in the form of erythematous papulonodular rash and ecchymotic patches over face, neck and upper chest. Vascular infiltrates result in easy bruising typically seen around the eyes producing "raccoon-eyed" appearance.

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Insulin Pumps: Novel Techniques in the Management of Diabetes Mellitus

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ABSTRACT

Diabetes mellitus is rapidly evolving as a major health epidemic globally that threatens human health devastatingly. A significant number of diabetic patients are using insulin injections to achieve normoglycemic control. Glycemic fluctuation and frequent hypoglycemic events by conventional injection methods has led to invention and increasing demand of insulin pumps. Different types of insulin pumps are developed to mimic the release pattern of insulin from pancreas. Besides that, invention of insulin pumps is also aimed to ease patients in their diabetes management and improve patients' quality-of-life by freeing the patients from the constraints of injections. In this review, we will be discussing the features of different types of insulin pumps; CSII pump including durable pump, patch insulin pump and the artificial pancreas system which provides insulin continuously for 24 hours daily which needs to be replace every 3 days. It is also able to deliver bolus insulin to cover carbohydrates in the meal. CIPII is another type of insulin pump that delivers insulin through intraperitoneal route with the added advantage that its insulin kinetics are more physiological. Better glycemic control can be achieve with CIPII but this comes with a very steep price. There is a new patch pump with the latest technology, the JewelPUMP™ (JP), which can overcome catheter occlusion which is a common problem with the insulin pumps.

Keywords: Insulin device, insulin pumps, diabetic management, novel techniques

Diabetes mellitus is rapidly evolving as a major health epidemic globally that threatens human health devastatingly. In Malaysia, from year 1996 till 2011, the rate of growth of diabetes patients has stayed high at 80%. It is predicted that if this rate remains unabated by the year 2020, more than a third of adults over age 30 would have developed this debilitating disease.[1]

Diabetes mellitus is a cluster of metabolic disorders of carbohydrate, protein and fat metabolism characterized by raised plasma glucose or hyperglycemia due to defect in insulin secretion, insulin action or both.[2] There are two major types of diabetes mellitus namely type 1 and type 2 diabetes mellitus (T1DM and T2DM). T1DM is also known as juvenile diabetes. As the name implies, majority of patients with T1DM are diagnosed at an early age either around 4 to 5 years or in their teens and early adulthood.[3] This is the result of cellular-mediated autoimmune destruction of pancreatic β cells, which often leads to absolute insulin deficiency.[4] The presence of antiglutamic acid decarboxylase, islet cell or insulin antibodies clearly indicates the autoimmune process that occurred. Ultimately, insulin therapy has to be initiated in all T1DM patients to maintain normal blood glucose levels. Thus, T1DM is also known as insulin-dependent diabetes.[4] T2DM accounts for 80-90% of all diabetes mellitus cases. Under normal physiological conditions, a well-regulated and dynamic interaction between insulin secretion and insulin sensitivity maintains plasma glucose concentration at optimum levels.[3] However, this mechanism breaks down in cases of T2DM due to occurrence of insulin resistance and relative insulin deficiency.[2,3] Liver, muscle and adipose tissues are among the principal tissues influenced by insulin resistance.[5] For patients with T2DM, insulin treatment is not indicated at least initially and often throughout their entire lifetime.[2]

In terms of treatment, there is no doubt that T1DM patients should be started with insulin therapy. For

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T2DM patients, pharmacological therapy involves the use of oral hypoglycemic agents (OHA) that include biguanides, sulfonylureas, meglitinides, α-glucosidase inhibitors, thiazolidinediones, dipeptidyl peptidase-4 (DPP-4) inhibitors and sodium-glucose cotransporter 2 (SGLT2) inhibitors. Injectable agents include glucagon-like peptide-1 (GLP-1) receptor agonists and insulin.[1] OHA can be used as monotherapy or as combined therapy with other class of OHA and/or injectable agents. Metformin and thiazolidinediones are known to improve fasting hyperglycemia, while others mainly reduce postprandial hyperglycemia.[1] Metformin which belongs to class of biguanides should always be the first-line therapy as supported by evidence for its great safety profile without hypoglycemia risk.[5] If monotherapy fails, combination therapy should be initiated and if glycemic targets are not achieved, treatment intensification should be done every 3 months. Minimal dose of OHA is recommended initially and titrated gradually up to an optimum dose.[1] When glycemic control cannot be achieved using the maximum-tolerated dose of metformin (or another OAD), insulin therapy should be initiated. The traditional view of insulin as a last resort should not be accepted, because most medical endocrinology societies, recommend that insulin therapy be started sooner rather than later. Many patients with type 2 diabetes eventually require and benefit from insulin therapy.[6,7]

Common mode of delivering insulin is subcutaneous (SC) injections and insulin pens. SC insulin preparations, which are more commonly used, include rapid-, intermediate- and long-acting insulin, which are used in different combinations (1-4 times or more daily). Disadvantages of current approved insulin regimens relate to the injectable mode of its administration, need for multiple injections, lack of dose precision and risk of developing hypoglycemic events.[8] Insulin pens combine the insulin container and the syringe into a single modular unit. Insulin pens eliminate the inconvenience of carrying insulin vials and syringes and are more accurate and less painful. Insulin pens are user-friendly, with decreased discomfort of injection, ease of cartridge replacement, insulin-dose setting dial use and prominence of audible clicks, which results in dose accuracy. Patient satisfaction and preference is higher with pen use compared to syringes and needles.[8]

Now, insulin pumps are sought after mainly due to constant raised glycated hemoglobin (HbAlc) level despite intensive single or multiple dose insulin injection therapy, repeated hypoglycemia and pronounced glycemic fluctuations.[9] In the past 20 years, technological advancement has transformed the diabetes therapeutic landscape. Today's insulin pumps are the outcome of decades of design and bioengineering efforts towards development of reliable and convenient modern pumps.[9] Besides being small and light, these pumps have been advanced to the level of precisely mimicking physiological demands. The integrated software have also been developed so as to keep track of insulin delivered and enable blood glucose measurements, permit bolus dose calculations and link-up with other compatible systems.[10,11] In this review, our focus will mainly about durable insulin pump, patch insulin pump, artificial pancreas device system and implantable pump.

TYPES OF INSULIN PUMP

Continuous Subcutaneous Insulin Infusion

Durable Pump (Fig. 1)[10]

Durable insulin pump is historically how insulin pump was designed.[11] It's about the size of a deck of cards and various types and colors are available in the market. This pump is made of a hard plastic case with a front screen, buttons, a battery compartment with a screw on top, and a space for the reservoir that is filled with insulin. The outer surface of the pump is attached with a clip which allows the pump to be attached to the belt or waistband of the user. The sticker on the pump provides useful information such as the serial number, model and type, company phone numbers and other general information. At the base of the reservoir shaft is a computer-controlled mechanical plunger that can deliver incredibly small amounts of insulin. The plunger is connected to tubing which runs from a reservoir (in the pump) filled with insulin to an infusion set, which is secured to the body of the patient. The infusion

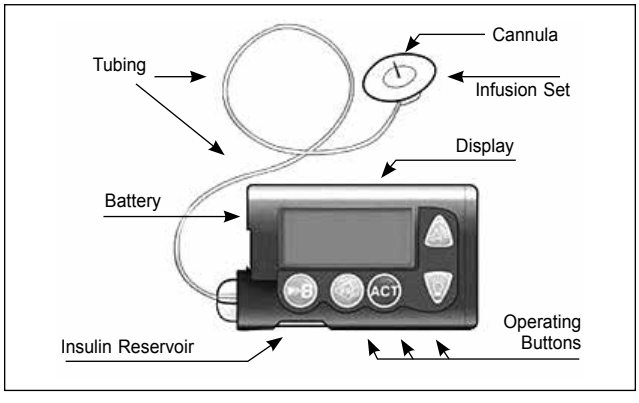

Figure 1. Durable pump.[10]

set is a soft plastic cannula which is about 6-9 mm (<0.5 inch) that is inserted beneath the skin, which can be removed later. The cannula can also be a very small steel needle which is easily inserted under the skin. Besides that, the pump also has a display screen and buttons to program insulin delivery. The pump controls a motor which dispenses insulin in the desired amounts. When the insulin is dispensed, it flows from the reservoir into the tubing and then through the cannula into the tissue under the skin.[12]

Patch Insulin Pump (Fig. 2)[12]

Another type of insulin pump is patch insulin pump. Patch pump neither have an infusion set nor tubing as it is directly attached to the body. The pod compartment (the patch) of the pump and the controller of the pump is separate. The display screen is on the controller and not the patch. The patch contains a reservoir which needs to be filled with insulin before placing it on the skin. It also has a needle that places a small cannula under the skin for insulin delivery. Other than that, the separate controller of the patch pump can integrate with the motor in the patch to control insulin delivery. All commands are transmitted wirelessly through the controller to the patch pump.[12]

Artificial Pancreas Device System (Close Loop System) (Fig. 3)[13]

The artificial pancreas device system which is also referred to as a close-loop system is a device that functions like a healthy pancreas in regulating glucose level.[13] The first artificial pancreas was been approved by the US Food and Drug Administration (FDA) on 28th September 2016.[13] It is intended to automatically monitor glucose and provide appropriate basal insulin doses in people aged 14 years and older with type 1 diabetes.[13] Medtronic® is the only brand available in Malaysia which provides insulin pump with continuous glucose monitoring (CGM).[14]

The artificial pancreas device systems consist of a CGM system and an insulin infusion pump. A computer-controlled algorithm connects the CGM and insulin infusion pump to allow continuous communication between the two devices. The system monitors glucose levels in the body and automatically adjusts the delivery of insulin to reduce high blood glucose levels (hyperglycemia). It also reduces the incidence of low blood glucose (hypoglycemia) with little or no input from the patient.[13]

The CGM system provides information regarding user's blood glucose levels. A sensor which is placed SC under the user's skin measures the glucose in the interstitial fluid around the cells, which is associated with blood glucose levels. The information is sent to a receiver by a small transmitter. Hence, CGM continuously displays both an estimate of blood glucose levels and the direction and rate of change of these estimates. However, the users need to calibrate the CGM system regularly using the blood glucose measurement from a blood glucose device to ensure that the CGM provides the most accurate estimation of blood glucose level. The control algorithm is a software embedded in the controller that receives information from the CGM to carry out mathematical calculation of the proper insulin dosing for the user. The dosing instruction is then sent to the infusion pump from the

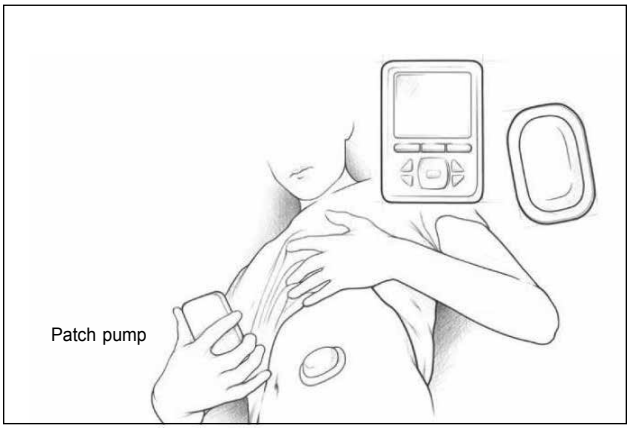

Figure 2. Patch insulin pump.[12]

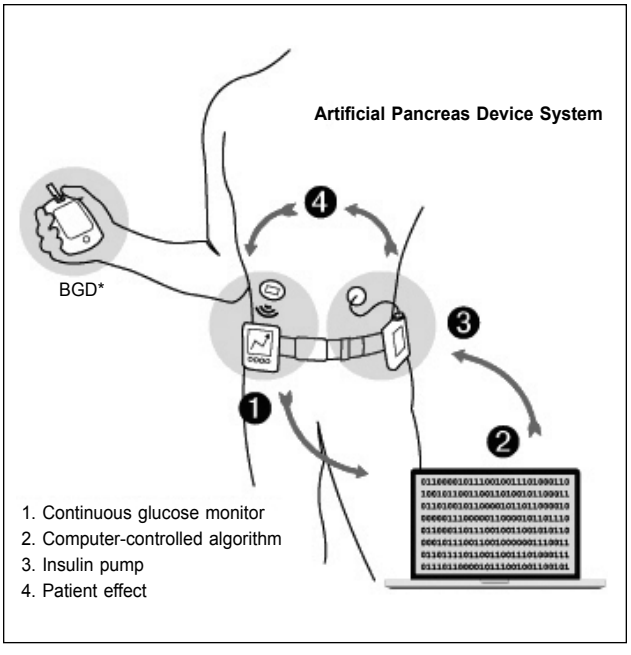

Figure 3. Artificial pancreas device system.[13]

controller. The control algorithm can be run on any number of devices such as an insulin pump, smartphone or computer. The infusion pump contains a reservoir that is filled with insulin. The pump adjusts the insulin delivery according to the dosing instructions sent by the controller and insulin is then delivered through the tubing.[13]

Mechanism of Continuous Subcutaneous Insulin Infusion Pump[15]

Insulin pump delivers insulin by continuous infusion through a single SC site, which needs to be replaced every 3 days on an average. The insulin pump only delivers short-acting insulin. The pump delivers basal insulin dose continuously for 24 hours a day, which is tailored to the patient's 24-hour glucose profile. Insulin requirement can be influenced by different factors such as individual's physiology, the type and duration of daily activity, work schedule, exercise, illness, concomitant medications, etc. Hence, most insulin pumps are capable to program basal rates that are modifiable every hour as the glucose level may vary throughout the day. Moreover, insulin pumps are also able to deliver bolus insulin, which infuses over a few minutes to a few hours. The bolus insulin is to cover the carbohydrate in each meal and reduce the high glucose level. Carbohydrate content in food and the blood glucose level are needed for the pump to calculate the accurate bolus dose for the patient. Correction dose can also be delivered if necessary when the patient has sudden spike in glucose level.

Continuous Intraperitoneal Insulin Infusion

Implantable Pump[16]

Implantable pump is a treatment option for patients with T1DM. An implantable insulin pump has a titanium case which contains different compartments including an insulin reservoir, a pump and valves, a motor and a battery for power supply, a clock, a computer and a radio transmitter and receiver. The titanium case comprises a connecting outlet for catheter attachment. There is also an external programmer to modulate insulin delivery according to patient needs.[17] The insulin pump is usually implanted in the subcutaneous pocket in the lower abdominal quadrant (Fig. 4). The peritoneum is opened from the SC pocket and the tip of the catheter is carefully inserted and directed towards the liver. General anesthesia is needed for implantation. After implantation, the pump reservoir needed to be refilled transcutaneously at least every 3 months, depending on the individual insulin requirement.[18]

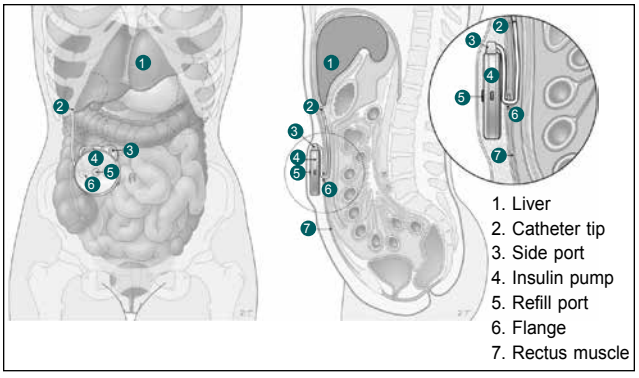

Figure 4. Implantable pump.[16]

Mechanism of Continuous Intraperitoneal Insulin Infusion Pump[16-18]

A new human recombinant insulin (400 IU/mL; human insulin of *Escherichia coli* origin, trade name: Insuman Implantable, Sanofi-Aventis, Frankfurt/Main, Germany) is used for implantable insulin pump.[16] The pump strokes of the insulin pump are programmed by the external programmer to order pump cycles according to desired insulin delivery.[17] It enables programming of multiple basal rates throughout the day.[17] Besides that, maximum limit of insulin dose that can be programmed per hour can be set to prevent excessive insulin delivery due to erroneous order.[17] If there is suspected electronic or mechanic malfunction of the device, the insulin delivery will be stopped and a corresponding warning sign will be shown on the programmer screen.[17]

Implantable insulin pump deliver insulin in the intraperitoneal space allows insulin to infuse directly into the intraperitoneal space, where it is absorbed via the capillaries of the visceral peritoneum into the portal vein.[16] This leads to a more physiologic mode of insulin distribution with high hepatic uptake compared to SC insulin administration.[16] Hence, insulin is able to enter to the liver and take up more glucose from bloodstream. Other than that, the blood glucose values are able to return to baseline values rapidly resulting in a more predictable insulin profile due to fast insulin absorption (approximately 15 minutes to peak).[16,18]

As insulin is absorbed into the portal system, there is a higher hepatic uptake of insulin, with first-pass liver insulin extraction occurring directly after absorption.[16] Therefore, the concentration of peripheral insulin will be alleviated and this improves glucagon secretion and hepatic glucose production in response to hypoglycemia.[18]

Continuous CSII versus CIPII, Implanted Insulin Pumps[11,16,19-20]

The use of implanted insulin pumps began enthusiastically because it freed the patient from the constraints of injections. Studies in animals have shown the benefits of the intraperitoneal route, which has pharmacokinetics that are closer to physiological than the SC route. After delivery into the peritoneal cavity, insulin is primarily resorbed in the portal vein. There is an approximately 50% degradation during the first hepatic passage, thereby recreating a physiological insulin gradient between the portal vein and systemic circulation. Compared with the SC route, the intraperitoneal route induces lower peripheral insulinemia while allowing resorption and a faster return to baseline plasma levels. These insulin kinetics are more physiological, maintaining reproducibility of insulin profiles in the long-term and resulting in an improved glucagon response to hypoglycemia.[19]

Observational clinical studies conducted by EVADIAC have clearly demonstrated the feasibility, metabolic efficacy and safety of the implanted pump in type 1 diabetic patients. The metabolic benefits consist of a reduction in HbA1c as well as in the frequency of severe hypoglycemias and glycemic variability. These benefits are maintained in the long-term even in type 1 diabetics who remain far from the HbA1c target of 7% or have large blood glucose fluctuations including severe recurrent hypoglycemia.[19] The most recent study demonstrated significant improvement in glycemic control, expressed as a 0.8% decrease in HbA1c over a period of 6 months when using implanted insulin pumps compared with SC insulin treatment in 24 poorly controlled diabetic patients. On the other hand, when compared with the implanted insulin pumps, the absorption of insulin with SC insulin delivery is slow, variable and has the risk of inducing secondary hyperinsulinemia.

Other than that, portal insulin concentrations can inhibit production of hepatic glycoprotein sex hormone-binding globulin (SHBG). Lassmann-Vague et al tested the hypothesis that CIPII therapy decreases SHBG concentrations in T1DM patients who switched from SCII therapy to CIPII therapy.[19] In the presence of higher SHBG- and normal total testosterone concentrations, lower concentrations of free testosterone are present among T1DM men using SC insulin therapy; a switch to CIPII therapy is therefore beneficial.

Although CIPII therapy is beneficial, it is associated with complications such as catheter-related complications, aggregation at pump level, pump failure, pump-pocket events and surgical events other than initial implantation. Insulin aggregation may happen at pump level and catheter which then causes back-flow of insulin, flow slow-down and blocked pumps. This can lead to catheter-related complications. Most of these cases can be solved by rinsing the procedures of catheter and if it irresolvable by rinsing, surgical intervention is required to replace the catheter or pump and remove the blockage in the catheter or pump. Other disadvantages of CIPII are pump-pocket events such as infection and skin ulcerations and pump failure due to battery failure can occur. If there is battery failure, surgical procedure is ideally needs to be done every 7 years to change the depleted battery.[20]

An increased production of anti-insulin antibodies among CIPII-treated patients has been reported previously. Although the exact cause remains unknown, it has been suggested that it may be due to insulin aggregates which are known to be antigenic or may be due to insulin modifications occurring during storage in the implantable pump.[16] Increased production of anti-insulin antibodies do not seem to correlate with the absence or presence of other subclinical and clinical autoimmune diseases.[16] Even though the anti-insulin antibodies associate with insulin and have been hypothesized to increase the risk of delayed hypoglycemia and increase the postprandial blood glucose concentrations, they do not induce changes in insulin requirements, metabolic consequences or the number of hypoglycemic episodes.[16]

The most important issue of CIPII therapy is the expense involved, but many health insurance plans will cover most of the cost. In 2010, direct pump and-related costs for CIPII were estimated to be € 31 000 in the first year and € 7500 in each of the following 6 years. The annual costs of CIPII are estimated to be € 6000 higher on average than CSII.[20]

Accuracy of a New Patch Pump Based on a Micro-electromechanical System versus Other Commercially Available Insulin Pumps[21]

The JewelPUMP™ (JP) is a new patch pump based on a microelectromechanical system (MEMS) that operates without any plunger. MiniMed® Paradigm® 712 (MP), Accu-Chek® Combo (AC), OmniPod® (OP), Animas® Vibe™ (AN) are the commercially available

pumps meeting the ISO standard were compared to the JP. In a study, pump accuracy was measured over 24 hours using a continuous microweighing method. The JP showed reduced absolute median error rate over a 15-minute observation window compared to other pumps but there was no difference over 24 hours. This accuracy over short times is due to the MEMS technology used for insulin delivery, which allows accurate infusion control of 0.02 insulin units per delivery step.

On the other hand, JP shows a more significant response time between a full occlusion and the alarm. Because of the rigidity of the system (silica chip, membrane), the JP showed a quick response to a full occlusion (after 3 or 4 strokes) compared to other pumps made of more readily deformable materials (plunger, plastic reservoir, catheter). JP is able to detect occlusion before glycemia rises, which may lead to a decrease in unexplained hyperglycemia potentially due to partial or complete catheter occlusion. Furthermore, the rapid occlusion detection of the JP may avoid insulin accumulation with rapid and uncontrolled release in the event of a temporary obstruction. This would be of great value, especially in subjects with a low basal rate. Overall, JP was found to be easier to wear than conventional pumps, more precise over a short time period, more sensitive to catheter occlusion and well-accepted by patients.

Dose Accuracy of Durable Pumps versus Patch Insulin Infusion Pumps[22]

As all major insulin pump manufacturers comply with the international infusion pump standards, there may be a general assumption that all pumps are equal in insulin-delivery accuracy. A research investigated single-dose and averaged-dose accuracy of incremental basal deliveries for patch model (OmniPod) and three durable models of insulin pumps (OneTouch Ping, Accu-Chek Combo and Paradigm Revel/Veo). It was observed that the single-dose and averaged-dose accuracy was statistically significantly different between patch and durable pumps ($p < 0.0001$). Among the durable pumps, the OneTouch Ping demonstrated better accuracy on a single-dose basis when compared with the Accu-Chek Combo and Paradigm Revel/Veo. There was no statistically significant difference in accuracy between the Accu-Chek Combo and Paradigm Revel/Veo pumps on a single-dose basis. However, the Accu-Chek Combo was more accurate than the Paradigm Revel/Veo when averaged-dose accuracy was compared.

Overnight Closed-loop Therapy versus Sensor-augmented Pump Therapy during Pregnancy in Women with Type 1 Diabetes[23]

As compared with sensor-augmented pump therapy, overnight closed-loop therapy resulted in a significant increase (by 15 percentage points) in the percentage of time that glucose levels were in the target range for pregnancy over a 24-hour period, as well as in a lower mean glucose level. These improvements were achieved without an increased incidence of hypoglycemia or an increase in the total insulin dose but with more variable insulin delivery to minimize hyperglycemic excursions. The closed-loop system maintained maternal glycemic control in study participants throughout pregnancy, delivery and associated challenges without any changes in programming to the system and without any episodes of severe hypoglycemia requiring third-party assistance.

Findings from recent trials show that a closed-loop system, as compared with sensor-augmented pump therapy, improved glycemic control, without increases in hypoglycemic episodes or the insulin dose. The glucose control achieved during control phase was similar to that achieved with closed-loop interventions among patients who were not pregnant. This observation probably reflects the strong motivation to maintain glucose control during pregnancy and tighter glycemic targets. Despite impressive glycemic control with sensor-augmented pump therapy, closed-loop therapy still generated substantial improvements when used overnight.

In conclusion, the crossover trial showed that overnight closed-loop therapy, as compared with sensor-augmented pump therapy, resulted in improved glucose control during pregnancy in women with type 1 diabetes. In the continuation phase, women receiving day-and-night closed-loop therapy maintained glycemic control during a high percentage of the time in a period that encompassed antenatal hospital admission, labor and delivery.

GLOBAL SCENARIOS OF INSULIN PATCH

Latest technological advancement has resulted in the development of "insulin patch pumps" that is intended to improve the patient's quality-of-life and prevent the common side effects arising from the use of conventional insulin pens. The term "patch", however, may be misleading. Although these new pumps are smaller in size and tubeless, they usually have SC cannula through which insulin is injected. The patch

pump is nevertheless a proud milestone in the field of insulin delivery. Many companies either start-ups or established form has already initiated the development of the patch pump. At present, a few of these pumps have been approved for marketing in the US FDA, while a wide range of other devices are also reported to be currently under development.[24]

US is the first country to have a FDA approved insulin patch pump which is OmniPod® that was developed by Ypsomed, a renowned specialist of diabetes care products with over 30 years' experience. Currently, there are 4,00,000 diabetics on insulin pump and the growth rate of insulin pump usage among them is 8% per annum. Continuous SC insulin infusion pumps currently are used by 20% of 25% of patients with type 1 diabetes in the United States.[25] Only the OmniPod® is currently available for use, and has been sold in the US for several years. The device will soon be available in France. Ypsomed expects to introduce the OmniPod® System to Switzerland, the Netherlands, Belgium, the Nordic countries and Australia in the second-half of 2010 and in China in the first-half of 2011. However, the current situation in Australia is, that it has been approved for sale by the TGA but the Federal Government's Prostheses legislation and NDSS has not approved equal reimbursement for new diabetes technologies like OmniPod®. Therefore, OmniPod® is currently not yet available for sale in Australia.[25]

In 2010, the US FDA cleared Valeritas's V-Go, designed for adults with type 2 diabetes who require insulin. It has been marketed in the United States since 2012. The V-Go is a disposable insulin delivery device that delivers a continuous, SC infusion of rapid-acting insulin. It sticks directly to the skin with a strong adhesive, allowing it to stay for 24 hours even when wet.[26] Valeritas announced that it has received CE mark approval for its V-Go disposable insulin delivery device. CE mark indicates that V-Go had been assessed to meet high safety, health and environmental protection requirements to be sold in the European Economic Area (EEA).[27]

The SOLO MicroPump® Insulin Delivery System is a patch pump originally made by Medingo and purchased by Roche in 2010. It has also gained approval from FDA since 2009, but has not yet entered the market. Solo MicroPump® was planned for a limited launch in the Netherlands in 2011 and worldwide release in 2012. The system also still needs clearance in Europe, so the company is preparing a filing for CE mark to get an approval to market their product in UK. This device has two parts: The MicroPump itself and a remote device that programs and directs the MicroPump. The MicroPump is small and slim, consisting of a 2 mL insulin reservoir, a cannula cradle infusion set and a pump base. The pump base includes a reusable 90-day unit that holds the electronics, memory, pump motor and bolus buttons. Boluses are delivered via the remote device or directly from the pump.[26]

The Cellnovo® system (Cellnovo, London, United Kingdom) also takes a "semi-disposable" approach. The current version of the Cellnovo system is patented and has obtained CE marking; furthermore, it complies with existing reimbursement schemes governing insulin pumps and their consumables. Cellnovo® already launched the marketing of its insulin patch pump system in the United Kingdom and France in 2014 via a direct sales force. Its commercialization is now being extended to other countries through a network of key distributors. As a first step in its international expansion strategy, Cellnovo® has signed an agreement for distribution in some European countries with Air Liquide Healthcare.[28]

CONCLUSION

Glycemic fluctuations and frequent hypoglycemic events by conventional injection methods has led to invention and increasing demand of insulin pumps. Different types of insulin pumps are being introduced in the market now with mechanisms of action that aim to bring pharmacokinetics of insulin administration more closely to physiological form of pancreas. Besides that, invention of insulin pumps is also aimed to help patients make their diabetes management easy and improve patients' quality-of-life by enabling patients to themselves free from the constraints of injections.

CSII pumps including durable pump, patch insulin pump and artificial pancreas system are some of the insulin pumps available in the market with the benefit that insulin needs to be replaced every 3 days on average when given continuously for 24 hours daily. Moreover, they are also able to deliver bolus insulin to cover carbohydrate in each meal that cause sudden spurt in blood glucose level. However, the downside of these type of insulin pumps is that insulin requirement is influenced by different factors like individual's physiology, daily activities, illness and medication.

When comparing CSII with CIPII, CIPII is another type of insulin pump delivering insulin through intraperitoneal route in which the insulin kinetics are more physiological. Therefore, a significant

improvement in glycemic control and less frequent of hypoglycemic events were observed with CIPII therapy. Although CIPII is beneficial, it is associated with complications like catheter-related complications, aggregation at pump level, pump failures, pump-pocket events and surgical events, and most importantly, it is very expensive.

Furthermore, different brands also have their unique type of technology that improve dosing accuracy and reduce dosing error. Besides that, another common problem of every insulin pump is the catheter occlusion during insulin delivery which has been overcome by the new patch pump with new technology, JewelPUMP™ (JP), which can detect occlusion rapidly to avoid insulin accumulation with rapid and uncontrolled release in the event of a temporary obstruction.

Different target populations are also important in the selection of insulin pump. In pregnancy with type 1 diabetes patients, overnight closed-loop therapy is preferred over sensor-augmented pump therapy due to the improvement of glycemic control by 15% with overnight closed-loop therapy.

There is still a lot of space for improvement in technology of insulin pump. There are still a lot of weaknesses that present in insulin pump system, which need further innovation and modification in order to produce the 'perfect' insulin pump in the future. Although it is impossible for insulin pump to completely replace and mimic the function of human pancreas in today's technology, we believe that diabetes patient with perfect 24-hour control of blood glucose can be achieved by insulin pump in near future.

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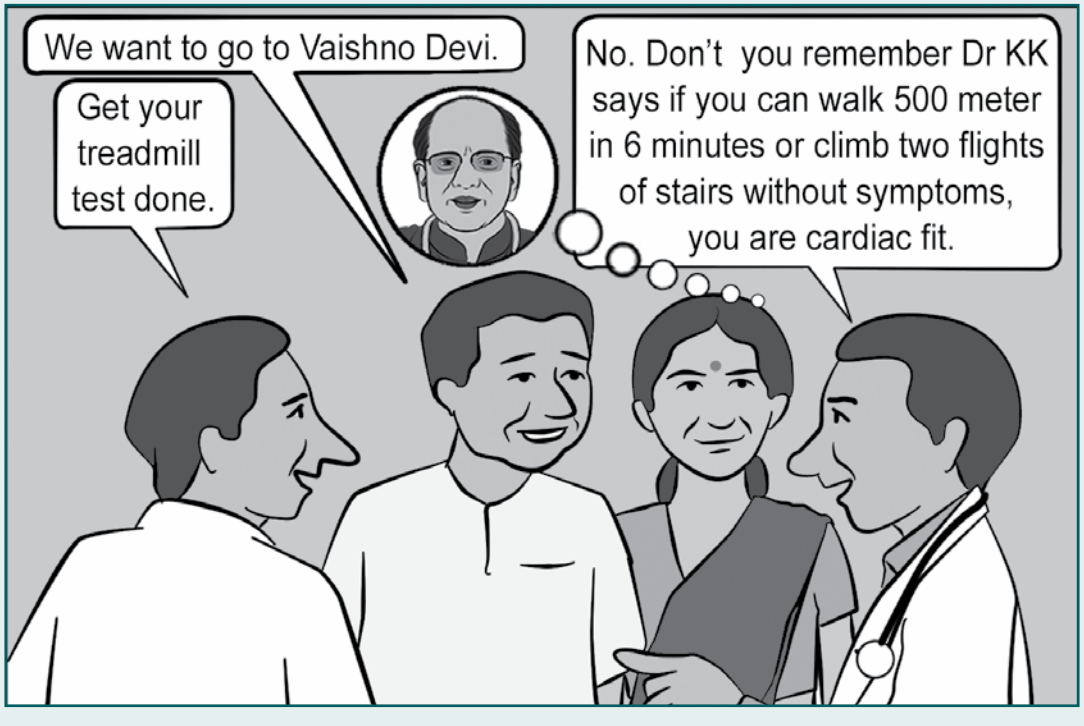

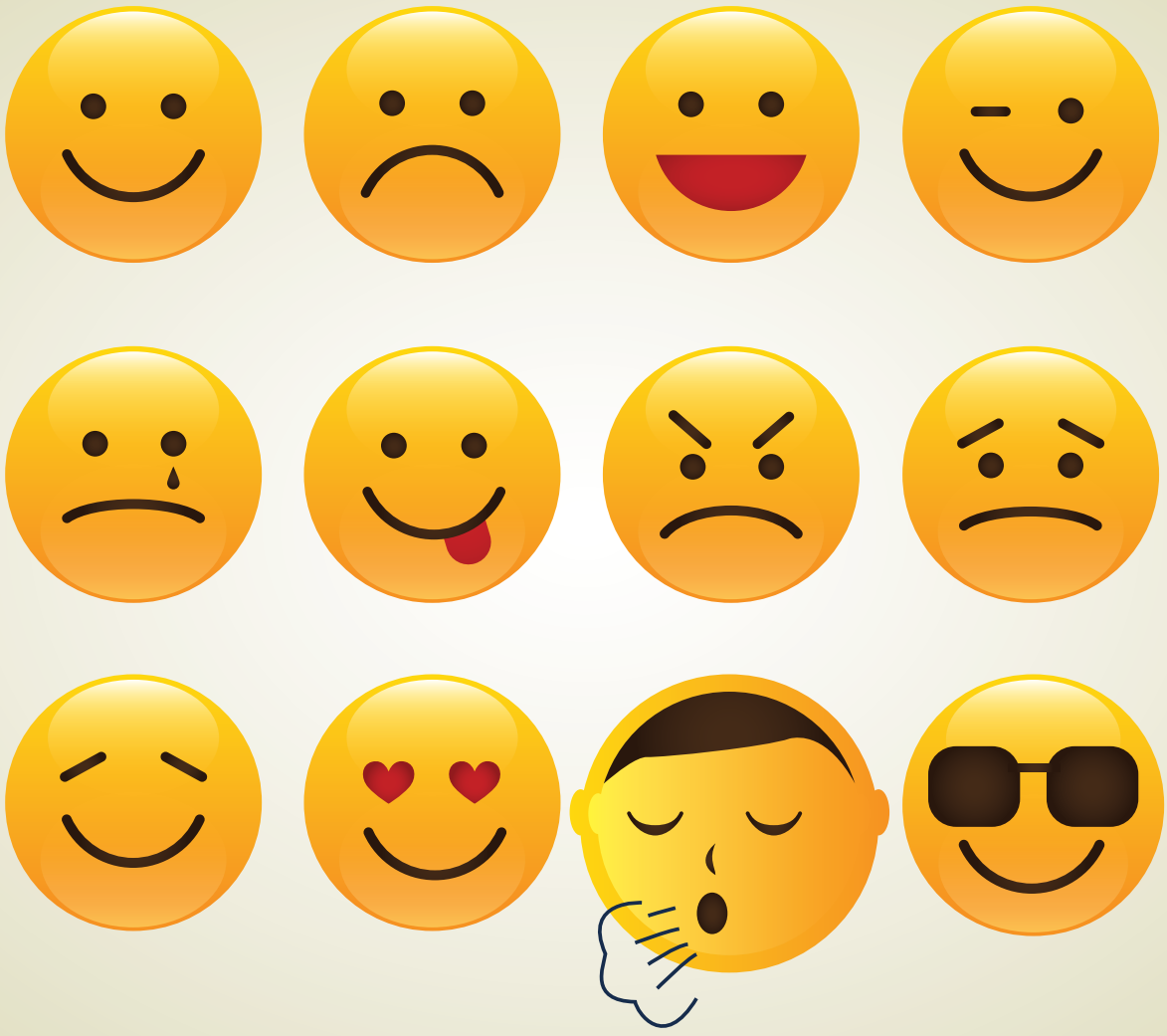

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Intralesional Sclerotherapy Cures Unusual Presentation of Hemangioma in a Child

BIMAL KUMAR MANDAL*, RINA DAS†, JAYANTA BAIN‡

ABSTRACT

Hemangiomas are benign tumors made up of blood vessels. They usually regress spontaneously within 9 years of age. Hemangioma of retropharyngeal space is a rare entity. History, digital palpation, computed tomography (CT) and fine-needle aspiration cytology (FNAC) clinches the diagnosis. We want to report a case of retropharyngeal hemangioma in a 33-month-old female child who presented with respiratory distress. She was diagnosed and treated successfully in our department.

Keywords: Retropharyngeal hemangioma, CT scan, aspiration, sclerotherapy

CASE REPORT

NK, a 33-month-old Muslim female child from Jharkhand presented in early August 2010 to the local doctor with fever, cough and cold who treated her symptomatically (Fig. 1).

She used to have frequent episodes of upper respiratory tract infection (URTI) until last week of January 2011, when she got first attack of breathing difficulty during sleep. Her parents took her to Dept. of ENT, Ranchi Medical College, where she was admitted and stayed for 2 days. X-ray and computed tomography (CT) scan of nasopharynx revealed a retropharyngeal space occupying lesion (SOL) (Fig. 2) and they referred the case to a higher center.

Subsequently, they came to Dept. of ENT, Calcutta National Medical College and Hospital (CNMCH), Kolkata. Her parents complained of sleepless nights for a fortnight because of the breathing difficulty she felt each time she desired to sleep. Only in prone position she got some relief of the distress, but unknowingly during sleep her posture change to supine and again she felt the distress. On examination, her general condition was poor, her cry sounded a bit hoarse and she was very much apprehensive.

She was admitted on 22nd February 2011 and planned for examination of the SOL under general anesthesia.

Figure 1. Photography shows a 33-month-old girl admitted in our female ward.

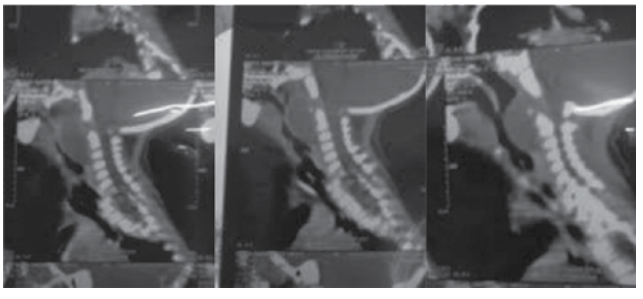

Figure 2. Shows retropharyngeal space occupying lesion.

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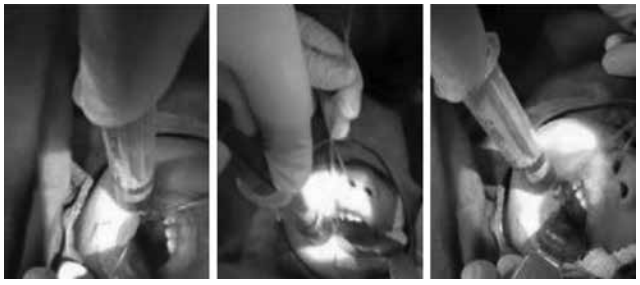

Figure 3. Shows aspiration of altered blood from retropharyngeal mass.

In operation theater (OT), digital palpation was done under general anesthesia. A cystic retropharyngeal mass was diagnosed. About 15 mL of altered blood from the cystic mass was aspirated (Fig. 3).

Cytologic examination of that fluid showed RBC-5.5 million/dL, WBC-6,400/dL, platelets-1,50,000/mL and no pus cells.

She was kept under observation for 5-6 days and was discharged. In late March 2011, she was readmitted in our department with the same complaints. Digital palpation and aspiration was done under general anesthesia. At this time, 10 mL of fluid was aspirated followed by injection of sclerosing agent sodium tetradecyl sulfate (2 mL of the sclerosing agent was mixed with 4 mL of distilled water). She was asked to come for follow-up 2-3 weeks later. For approximately 3 months she did well. On 6th June 2011, again she got admitted but there was mild breathing problem and examination under general anesthesia was done. This time no fluid came out of the aspiration but 2 mL of the same diluted sclerosing agent was injected into the site. Follow-up CT scan of neck was found normal. The patient is under regular follow-up and leading a normal life.

DISCUSSION

The retropharyngeal space lies between the buccopharyngeal fascia covering posterior pharyngeal wall anteriorly and cervical vertebra with prevertebral muscles covered by prevertebral fascia posteriorly. This space is divided into two compartments (right and left) by its attachment with the median raphe. Types of retropharyngeal SOL: 1) Congenital (brachial cleft cyst, ectopic thyroid); 2) inflammatory (retropharyngeal abscess and retropharyngeal cellulitis); 3) neoplastic (cystic hygroma, neurofibroma, neuroblastoma, hemangioma); 4) traumatic (foreign body, hematoma) and 5) metabolic (hypothyroidism). Of them, the hemangioma is a rare cystic mass in this space, a benign tumor that grows within the blood vessels. Hemangiomas are the most common childhood tumor. A hemangioma (comes from the Latin words *hemangio* meaning blood vessel and *oma* meaning tumor with active cell dividing activity) is a benign self-involuting tumor of endothelial cells. This tumor is most often found on the head or neck. However, they may occur anywhere on the skin or internal organs. It is usually found at 2-4 months of age. In most cases, hemangioma appears during the first days or weeks of life and resolve at the latest by age 10. Hemangiomas never develop in an adult. There is no reason in this day to accept that the only option available is to 'leave it alone' and wait for the hemangioma to 'go away' or allow to attaining mega size. Secondly, the most appropriate treatment plan needs to be individualized for each patient and each lesion. Therefore, similar lesions in different patients may be treated differently.[1,2]

Sclerotherapy is a procedure used to treat blood vessels or blood vessel malformations (vascular malformations) and also those of the lymphatic system. A medicine is injected into the vessels, which makes them shrink. It is used for children and young adults with vascular or lymphatic malformations.

In adults, sclerotherapy is often used to treat varicose veins and hemorrhoids. Sclerosant is diluted with blood as it diffuses away from the site of injection, thus if a strong sclerosant is injected there will be three zones of action. In zone 1, vascular endothelium is irreversibly injured: The vessel will be fully sclerosed and eventually will be completely replaced by a fibrous tissue. In zone 2, vascular endothelium is injured, and the vessel will be partially or completely thrombosed but will eventually recanalize. In zone 3, the sclerosant will be diluted below its injurious concentration, and there will be no endothelial injury. Sclerosants are polidocanol, 5% phenol, absolute alcohol, hot water, hypertonic saline and sodium teradecyl sulfate.[3] In our case, we unanimously thought that sclerothrapy would be the best treatment option and accordingly we did it. We used sodium teradecyl sulfate as sclerosant.

Being a detergent-based chemical, its action is on the lipid molecules in the cells of the vein wall, causing destruction of the internal lining of the vein and causing them to shed, leading to thrombosis, fibrosis and obliteration (sclerosis). It is used in concentrations ranging from 0.1% to 3% for this purpose. Until now, the patient is relieved of the distress with this treatment (1 and half years follow-up) and we expect no recurrence in future. There are various types of treatment protocol like sclerotherapy, laser, interferon α_2, intralesional corticosteroid therapy[3-6] but we used sclerotherapy with successful result without any complication.

CONCLUSION

Hemangioma of retropharyngeal space is a rare entity. CT scan followed by digital palpation and fine-needle aspiration cytology (FNAC) can clinch the diagnosis in case of retropharyngeal hemangioma presented with respiratory distress. Repeated aspiration of collected fluid and sclerotherapy in hemangioma is a preferable treatment option.

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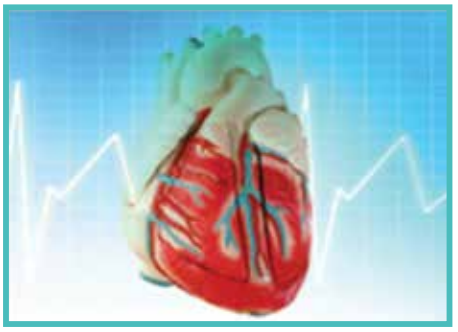

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Drowned in Fluids: A Rare Case of Polyserositis Due to Non-Hodgkin's Lymphoma

MOHAMED ILIYAS*, RAJASEKARAN†

ABSTRACT

Polyserositis is defined as general inflammation of serous membranes associated with simultaneous effusions in various cavities. This rare syndrome has some unusual etiologies some of which are end-stage diseases. Tuberculosis, rheumatism, systemic lupus erythematous are the usual causes, while hematological malignancies are on the other end of the spectrum. We came across one such case of polyserositis masquerading as tuberculosis, which turned out to be non-Hodgkin's lymphoma. We present it here because of its rarity and the associated high mortality.

Keywords: Polyserositis, hypothyroidism, non-Hodgkin's lymphoma, adenosine deaminase, Concato's disease, angioimmunoblastic T-cell lymphoma

CASE REPORT

A 30-year-old female presented with weight loss of 7 kg over 4 months, high-grade intermittent fever with chills and rigor for 15 days with night sweats. Since 1 week, she became breathless progressing from Grade II to IV and is orthopneic. She has diffuse, dull and non-colicky abdominal pain since 4 days along with nausea and loss of appetite since 4 months. She was apparently normal 4 months back. She is not under treatment for any chronic illness. She is amenorrheic since 4 months.

On examination, she was conscious and febrile (104^0F) with pulse rate - 112/min, blood pressure (BP) - 110/70 mmHg, respiratory rate - 21/min, SpO_2 - 95% with oxygen. She was thin built and pale. She had bilateral cervical lymphadenopathy with matting of right supraclavicular lymph nodes. The largest node was of 2 × 2 cm size, immobile with overlying normal skin. There was no sinus or scar. She had a palpable left axillary lymph node in the central group of size 4 × 4 cm, hard and mobile. Her cardiovascular and CNS examination was normal. Abdomen was diffusely tender to palpation. She had features of bilateral pleural effusion on clinical examination. We suspected tuberculosis and proceeded with further investigations.

CBC: WBC-5,800; DC- $N_{75\%}$, $L_{22.7\%}$, $E_{3\%}$; RBC-2.49 lakhs	**Peripheral smear:** Severe microcytic hypochromic anemia
Hb-5.9 g/dL	**TFT:**
PLT-5.85 lakhs	Total T3-57 ng/dL (N:60-100)
HCT-19.5%	Total T4-12 ng/dL (N:4.5-12)
MCV-78.3fl; MCH-23.7 pg; MCHC-30.3 g/dL	TSH-16.8 mcU/mL **(**N:0.3-5.5)
ESR-110 mm/hr	**Pleural fluid analysis: Glucose-20 mg/dL;** Protein-3.7 g/dL; **LDH-1,085 U/L 50 cells/mm^3**
RFT: Sugar-131 mg/dL; Urea-18 mg/dL; Creatine-0.8 mg/dL; Na^+-138 mEq/L; K^+-3.2 mEq/L: Ca^{2+}-8.2 mg/dL	Predominantly lymphocytes with reactive mesothelial cells. **Lymphocytic effusion.**
LFT: Bilirubin(T)-0.6 mg/dL SGOT-22 U/L; SGPT-89 U/L	Smear negative for AFB. No growth in culture.
ALP-181 U/L: Protein-6.9 g/dL; Albumin-3.8 g/dL	**Adenosine deaminase: (pleural fluid) 196.50 U/L**
LDH-740 U/L	**Sputum:** AFB negative. No growth in culture.
HIV 1&2-Nonreactive; HbsAg-Negative; Anti-HCV-Negative	CRP-Negative; ANA-Negative; Widal-Negative; Dengue-Negative; MSAT-Negative; Blood culture-No growth; Urine culture-No growth; UPT-Negative

CBC = Complete blood count; WBC = White blood cell; DC = Differential count; RBC = Red blood cell; Hb = Hemoglobin; PLT = Platelets; HCT = Hematocrit; MCV = Mean corpuscular volume; MCH = Mean corpuscular hemoglobin, MCHC = Mean corpuscular hemoglobin concentration; ESR = Erythrocyte sedimentation rate; RFT = Renal function test; Na^+ = Sodium ions; K+ = Potassium ions; Ca^{2+} = Calcium ions; LFT = Liver function test; SGOT = Serum glutamic oxaloacetic transaminase; SGPT = Serum glutamic pyruvic transaminase; ALP = Alkaline phosphatase; LDH = Lactate dehydrogenase; HBsAg = Hepatitis B surface antigen; HCV = Hepatitis C virus; TFT = Thyroid function test; T3 = Triiodothyronine; T4 = Thyroxine; TSH = Thyroid-stimulating hormone; AFB = Acid-fast bacillus; CRP = C-reactive protein; ANA = Antinuclear antibodies; MSAT = Macroscopic slide agglutination test.

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Chest X-ray revealed bilateral pleural effusion, left more than right with mediastinal widening (Fig. 1). From the blood investigations, anemia with reactive thrombocytosis and hypothyroidism was made out. Liver function was deranged but not suggestive of hemolysis. Peripheral smear revealed no more than anemia.

Other blood investigations for fever and weight loss were negative. Pregnancy and human immunodeficiency virus (HIV) were ruled out. Pleural fluid analysis showed an exudative lymphocytic effusion with very high adenosine deaminase (ADA) levels. Matted cervical lymphadenopathy with the hematological and pleural fluid analysis lead us to make a provisional diagnosis of extrapulmonary tuberculosis.

Before starting antitubercular treatment, we did an ultrasonogram of the abdomen, which showed ascites with bilateral pleural effusion. Therapeutic thoracentesis was done and 800 mL of hemorrhagic pleural fluid was drained. Oxygen therapy, diuretics, broad-spectrum antibiotics and antipyretics were given. But the patient worsened so we did an echocardiogram, which revealed mild pericardial effusion. We revised our diagnosis to polyserositis and did further work-up. Contrast-enhanced computed tomography (CECT) abdomen revealed left para-aortic lymphadenopathy, ascites and bilateral pleural effusion. Since, the patient became very dyspneic, CT chest couldn't be done. Fine needle aspiration cytology (FNAC) of the cervical lymph node was proceeded and it showed monotonous population of lymphocytes and few atypical lymphocytes in a background of red blood cells (RBCs) and fibrinous material. It suggested lymphoproliferative disorder of non-Hodgkin's lymphoma (NHL) type.

Excision biopsy of the right supraclavicular lymph node (Fig. 2) showed small- to intermediate-sized lymphoid cells infiltrating the adjoining perinodal fat, with predominant areas of lymph node showing infarction. Immunohistochemistry of the biopsy material showed CD20-negative and CD3 strong positivity in 90% of lymphoid cells suggestive of NHL of T-cell lineage. By this time, the patient's vital organs started to drown in her own fluids.

A final diagnosis of polyserositis due to NHL of T-cell type was made. Further typing of the T-cell variant couldn't be done because of her unwillingness. Knowing the worse prognosis of her condition, her husband took her home and the next day she had expired.

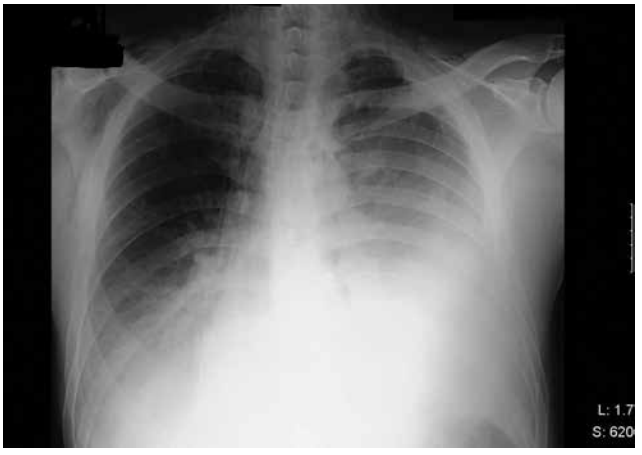

Figure 1. Chest X-ray: Bilateral pleural effusion left more than right with mediastinal widening.

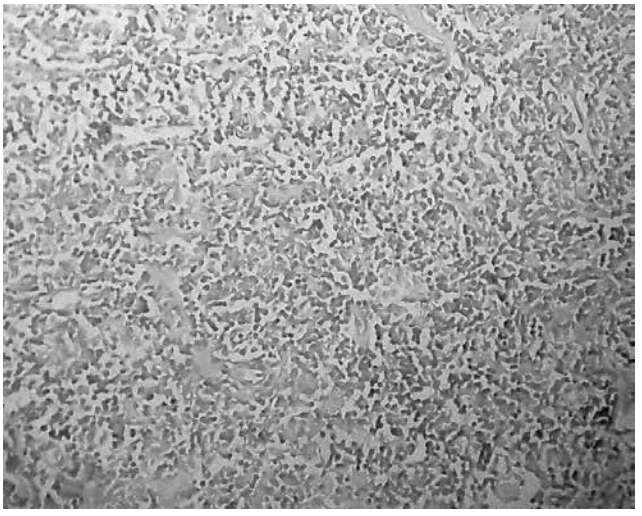

Figure 2. HPE of the right supraclavicular lymph node. Distorted architecture. Small- to intermediate-sized lymphocytes.

DISCUSSION

Concato's disease is defined as progressive malignant polyserositis with large effusions of pericardium, pleura and peritoneum.[1] Six to 50% of NHL present as pleural effusion of which 20% are chylothoraces, while 7-21% of Hodgkin's lymphoma present with pleural effusion and 3% of are chylothoraces. In NHL, 20-70% have evidence of mediastinal disease and 90% have disease elsewhere. Pleural effusion is frequently associated with large cell NHL compared to small cell variants.[2] Nodular sclerosis is the predominant Hodgkin's variant in this setting. In NHL, patient's survival is not adversely affected by the presence of pleural effusion as a presenting feature.[3] Around 40% of angioimmunoblastic T-cell lymphomas (AITLs) have pleural effusion. It extensively infiltrates the lymph nodes with atypical lymphocytes, there is

proliferation of arborizing small vessels and amorphous acidophilic material deposits.[4] Atypical lymphocytes are also present. Most of AILD cases have monoclonal T-cell population and 95% have Epstein-Barr virus (EBV) infected cells. AILD presents with generalized lymphadenopathy, hepatosplenomegaly, rash, effusions and polyarthritis. Most of them have elevated erythrocyte sedimentation rate (ESR) and lactate dehydrogenase (LDH), hypergammaglobulinemia and anemia, thrombocytopenia and lymphopenia. It is generally an aggressive disease. Most of the treatment regimens include a combination of an alkylating agent and an anthracycline.

Causes of polyserositis

Infectious

Whipple's disease

Picchini's polyserositis (Trypanosome)

Hereditary

Familial Mediterranean fever

Autoimmune

Systemic lupus erythematous (SLE)

Drug-induced SLE

Mixed connective tissue disorder

Adults Still's disease

Juvenile rheumatoid arthritis

Retroperitoneal fibrosis

Tuberculous effusions are unilateral usually and have glucose more than 60 mg/dL. Our patient had bilateral effusion with a 20 mg/dL of glucose. ADA levels are raised in tuberculosis, infectious mononucleosis, viral hepatitis and malignancy. While values higher than 70 U/L are highly sensitive and specific for pleural tuberculosis, values more than 100 U/L highly suggest malignancy. Our patient had a pleural fluid ADA of 196.50 U/L and lead to suspect a malignancy. In SLE, the effusion is bilateral in 50% with a glucose of more than 50 mg/dL, LDH of <500 U/L, ANA >1:160. Pleural fluid ANA: Serum ANA >1 strongly suggestive of lupus pleuritis. Our patient had a pleural fluid LDH 1,085 U/L. Her ANA was negative. Familial Mediterranean fever (FMF) is an autosomal recessive disorder due to FMF gene mutation. It presents with recurrent attacks of fever and serositis. Ninety-five percent of cases present with peritoneal inflammation rather than pleural inflammation as in our case. Variable involvement of pleura, pericardium, synovium and skin are reported. Acute phase reactants are elevated during the attacks. But generalized lymphadenopathy like in our case is uncommon.

Malignant etiology was proved in our case. Primary effusion lymphomas, also known as body cavity lymphomas are seen primarily in HIV patients and are associated with HHV-8 and EBV DNA. They don't express surface markers for B or T cells and are thought to represent a preplasmacytic differentiation. Our patient had strong positivity for T-cell lineage (CD3) and was negative for B-cell lineage (CD20). Kikuchi-Fujimoto disease is a rare benign condition of unknown cause primarily affecting young women. It is characterized by fever, weight loss, SLE like rash and cervical lymphadenopathy. Usually, it mimics malignancy but biopsy of lymph nodes show necrosis and follicular hyperplasia. It closely mimics Hodgkin lymphoma and SLE lymphadenitis. It is CD4 and CD8 positive. Our patient is CD3 positive.

Hypothyroidism can cause pleural and pericardial effusion but lymphadenopathy and weight loss is contrary to its weight gain. Early suspicion of polyserositis and a thorough knowledge of its various etiologies can diagnose this rare syndrome earlier and can prevent death. Although we couldn't save this patient, we gained knowledge and experience in handling such cases in future. This brought us forward to publish this case.

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Rare Cause of Bilateral Facial Nerve Palsy

SHUBHA SUBRAMANIAN*, CHANDRAMOULEESWARAN V†, LAKSHMINARASIMHAN R‡, KANNAN V#, PRATHEEP KUMAR S*

ABSTRACT

Melkersson-Rosenthal syndrome is a rare neurological condition which is often underdiagnosed especially in case of oligosymptomatic and monosymptomatic forms. It is characterized by the triad of lip swelling, fissured tongue and lower motor neuron (LMN) type of facial paralysis. Steroids are used in the treatment of this condition. In this case report, we have described a 23-year-old male patient who presented to our OPD with 2 years history of bilateral LMN type facial palsy with facial and lip swelling.

Keywords: Melkersson-Rosenthal syndrome, fissured tongue, LMN facial palsy, cheilitis granulomatosa

Melkersson-Rosenthal syndrome is characterized by a triad of recurrent orofacial swelling, relapsing facial paralysis and fissured tongue.[1] The classic triad is not seen all the time with fissured tongue being the least common manifestation.[2,3] Facial paralysis is lower motor neuron (LMN) type. Orofacial swelling is characterized by edema of face or nonpruritic swollen lips. Histopathology of lips reveals noncaseating granuloma.[4] It is a rare disorder and there is dearth of medical literature on the true incidence and etiology of the disease though there are case reports from all over the world.

CASE REPORT

A 23-year-old male patient presented to our outpatient department (OPD) with 2 years history of inability to close both eyes associated with watering of eyes preceded by swelling of face and lower eye lids. It initially started in left eye then was followed by right eye, gradual in onset, progressive in nature. He was treated with steroids which gave him partial improvement. After a period of 3 months, he developed painless swelling of his upper lips. There is a history of native medicine intake for the same.

On examination, he had hyperpigmentation over the right half of the face, bilateral LMN type of facial palsy without hyperacusis and intact taste sensation with swollen upper lip (Fig. 1 a and b). He was worked up for all the causes of bilateral LMN type of facial palsy.

His basic blood investigations were normal. Magnetic resonance imaging (MRI) brain was normal, angiotensin-converting enzyme (ACE) inhibitor levels with computed tomography (CT) chest was done, which was found to be normal. His audiometry also turned out to be negative. Opinion was sought from skin department and Hansen's disease was ruled out after SSS of both ear lobes turned out to be negative. Hence, lip biopsy was done which revealed hyperkeratosis and acanthosis of epidermis, edema with dilated lymphatics and mononuclear inflammatory infiltrate in dermis and

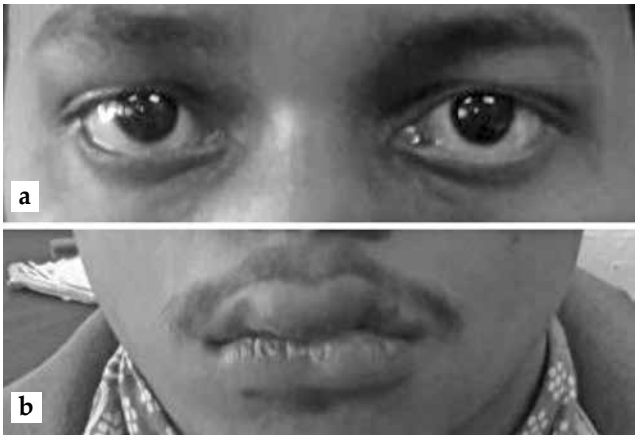

Figure 1. Ectropion of lower eyelids with tearing noted bilaterally **(a)** edema of lips **(b).**

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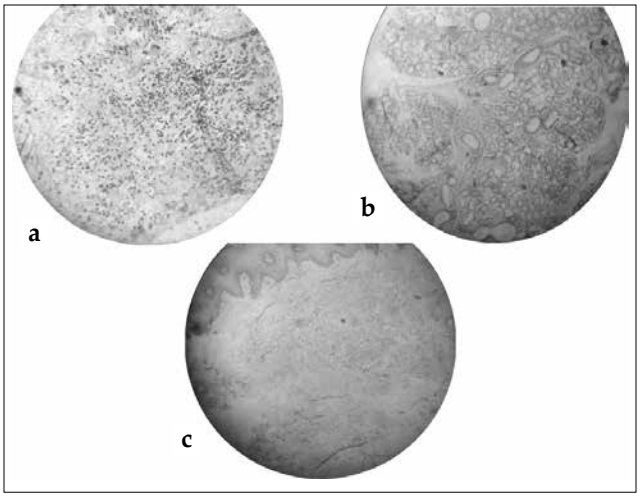

Figure 2. Inflammatory infiltrate in dermis and glandular tissue containing lymphocytes, histiocytes and plasma cells **(a and b),** dermo-epidermal junction showing hyperkeratosis and acanthosis **(c)**.

glandular tissue containing lymphocytes, histiocytes and plasma cells (Fig. 2 a-c).

With the clinical features and biopsy findings, a diagnosis of Melkersson-Rosenthal syndrome was made though he had only 2 features out of the triad. He was given treatment in the form of facial exercises, lubricant eye drops for dry eyes, patching of both eyes during sleep. After dermatology review, intralesional steroid injection into his upper lip was given.[5]

DISCUSSION

Melkersson-Rosenthal syndrome is a rare neuro-mucocutaneous disorder with incidence of 0.08% of general population. It has a recurrent and progressive course, characterized by the triad of lip swelling (cheilitis granulomatosa or Miescher cheilitis), fissured tongue (lingua plicata or scrotal tongue) and facial paralysis.[6] The disease can occur in people of any age it years is most common in the age group of 25-40 years and there is no gender predilection.[7] The diagnostic delay may exceed several decades especially in case of the oligosymptomatic and monosymptomatic forms, which are the most common clinical presentations of the disease. Etiology is unknown though genetic predisposition, infection (herpes simplex virus, adenoid and tonsillar infection, odontogenic infection, Streptococcus *Mycobacterium tuberculosis*, leprosy, candidiasis), allergy, angioedema and autoimmune causes have been implicated.[1,6]

The presence of orofacial edema is one of the dominant signs. The edema is painless, nonpitting, lasts from hours to weeks and can also recur. It commonly involves upper lip, cheek, lower lip, nose, eyelids, upper alveolar processes. Recurrent unilateral or bilateral lip swelling is the most common monosymptomatic presentation. Scrotal tongue is characterized by deep fissures on the dorsal and lateral surfaces of the tongue. Facial palsy is commonly LMN type, unilateral/bilateral, partial or complete and may occur months to years before or after the onset of facial edema. The facial palsy can become permanent with repeated attacks.[8] Other clinical features associated with the disease are ocular palsies, keratitis, epiphora, blepharospasm, migraine, trigeminal neuralgia, otosclerosis, salivary and sweat gland dysfunction, hyperplastic gingivitis, buccal and palatal enlargement, Raynaud's phenomenon.

Melkersson-Rosenthal syndrome is essentially a clinical diagnosis. Complete blood count, renal function test, C-reactive protein, immunological screens, C1-esterase, serum ACE levels, audiogram, chest X-ray will help to identify other differential diagnoses. Histopathology is confirmatory and the characteristic features are lymphoedema, noncaseating epitheloid cell granulomas, presence of multinucleated Langerhans type giant cells, presence of perivascular mononuclear inflammatory cell infiltration and presence of perivascular fibrosis.[1,9]

Therapeutic options are limited and produce only short-term benefits. Some of the treatment options are systemic/intralesional steroids, immunosuppressants (azathioprine, cyclosporine A), antibiotics (penicillin, tetracycline, erythromycin, metronidazole), danazol, clofazimine, hydroxychloroquine, antihistamines.[10]

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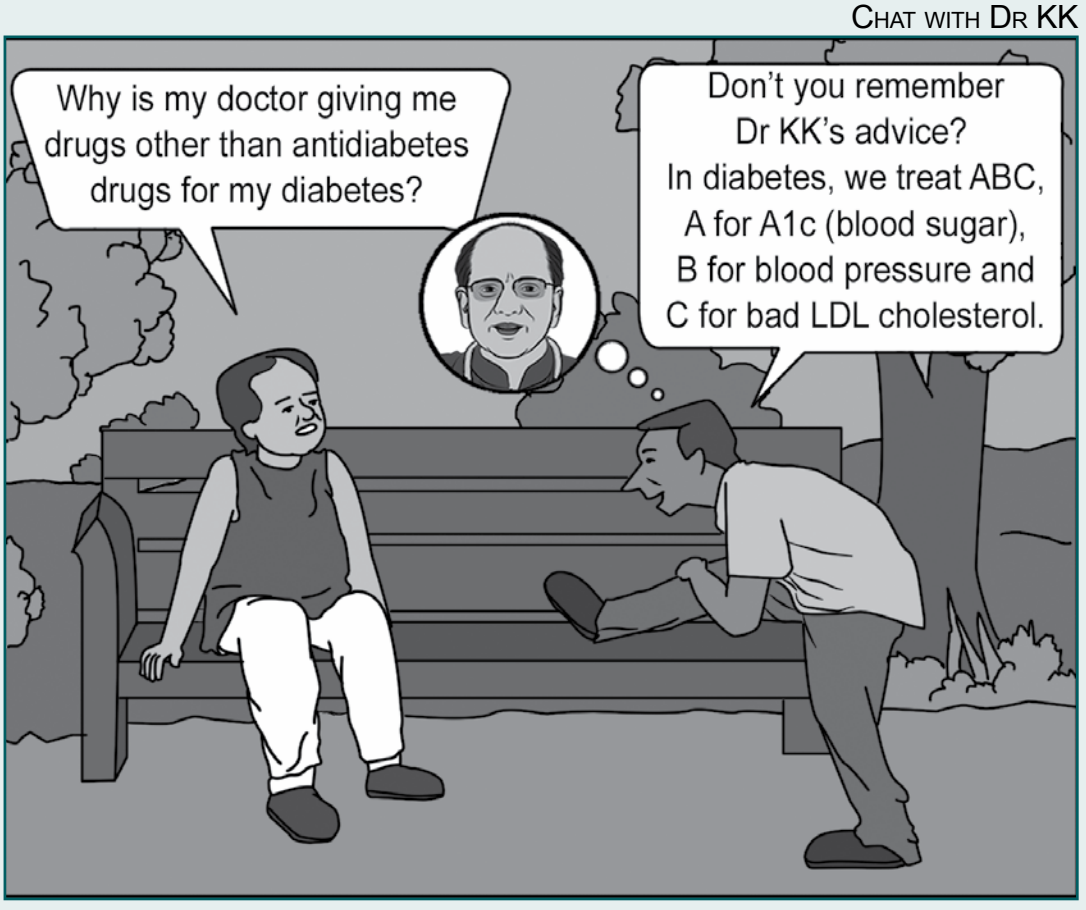

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Role of Aspirin in Prevention of Pregnancy-induced Hypertension and Intrauterine Growth Restriction in Primigravida Women with Abnormal First and Early Second Trimester Uterine Artery Doppler

PAYEL ROY[*], PALLAB KUMAR MISTRI[†], BANDANA BISWAS[‡], AVISHEK BHADRA[#], CHATALI DATTA ROY[†], SUDIP MUKHOPADHAYAY[¥]

ABSTRACT

Aim of our study was to see whether low-dose aspirin started early in pregnancy was efficacious in preventing pre-eclampsia and IUGR in high risk primigravida patients. The present study was conducted in the Dept. of Obstetrics and Gynecology in association with the Dept. of Radiodiagnosis in the IPGME&R over a period of 1 year. A total of 124 primigravida patients were recruited in whom uterine artery Doppler at 11-14 weeks gestation showed diastolic notch and/or PI ≥1.7. Patients with abnormal bleeding per vagina, having any contraindications to aspirin, chronic liver disease/chronic hypertension/renal disease/ overt diabetes mellitus and any other comorbid condition predisposing to vasculopathy, heart disease, documented fetal malformation and uterine malformation were excluded from the study. They were divided into two groups each comprising of 62 patients - test and control. Each woman of test group received tablet aspirin 75 mg o.d. from 16 to 34 weeks of gestation unless early termination became necessary. Women of control group did not receive aspirin. All these 124 women were followed till delivery at an interval of 1-4 weeks according to gestational age to see whether they were developing PIH and/or IUGR. After delivery, their babies were also examined to assess the perinatal outcome. SBP at 20 and 24 weeks gestation between different groups was comparable but it was decreased in aspirin-treated group at 28, 32, 34 and 36 weeks gestation and at term. Difference in the DBP at 20, 24, 28 and 36 weeks gestation and at term between different groups was not significant but it was significant at 32 and 34 weeks gestation. Hemoglobin and platelet values were comparable between the two groups. Urea and creatinine levels were also comparable between the two groups but uric acid levels decreased significantly in aspirin-treated group. LDH level was comparable between the two groups. Proteinuria decreased significantly in aspirin-treated group at 28, 32 and 34 weeks gestation but not so at 36 weeks gestation and at term. It was seen that aspirin reduces the incidence of pre-eclampsia significantly in this high-risk population. Among the several parameters, NICU admission rate was significantly decreased in aspirin-treated group, respectively but other parameters like Apgar score at birth, birth weight, NICU stay could not be influenced significantly by aspirin. However, incidence of IUGR was significantly less in the patients treated with aspirin. Incidence of postpartum hemorrhage was comparable between the two groups.

Keywords: Pregnancy-induced hypertension, aspirin, uterine artery Doppler, proteinuria

Hypertensive disorders complicate 5-10% of all pregnancies and together they form one member of the deadly triad, along with hemorrhage and infection, that contribute greatly to maternal and perinatal morbidity and mortality.[1] The huge subset of this entity is pregnancy-induced hypertension (PIH) which is defined as hypertension (blood pressure [BP] >140/90 mmHg measured 2 times at least 6 hours apart when the patient is at rest) that develops as a direct effect of the gravid state. It has many subsets-gestational hypertension, pre-eclampsia, eclampsia and pre-eclampsia or eclampsia superimposed on chronic hypertension. It may have various detrimental effects on the mother or fetus e.g., convulsions, intracranial hemorrhage, liver failure, renal failure, disseminated intravascular coagulation (DIC), placental abruption, intrauterine growth restriction (IUGR) and even intrauterine fetal death (IUFD).

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IUGR is often associated with PIH, but it can also occur without any maternal hypertension or proteinuria. Recent pathophysiological studies have focused on pre-eclampsia, which is increasingly recognized to be an early disease of the trophoblast characterized by maladaptation of spiral arteries, endothelial injury and secondary thrombosis. Although the exact etiology of pre-eclampsia is not certain, biochemical studies have suggested that it may be related to an imbalance between vasodilator and vasoconstrictor substances,[2] the most relevant substances being prostacyclin I2 (PGI2) and thromboxane A2 (TXA2). Based on this assumption, a number of studies have demonstrated that low-dose aspirin can rectify the intravascular imbalance between PGI2 and TXA2, thus preventing or retarding the pathogenesis of the disease.[3-5]

IUGR is associated with high risk for perinatal morbidity and mortality. The risk rises with the severity of restriction. The definition of IUGR has been suggested by the American College of Obstetricians and Gynecologists (ACOG) describing it as "a fetus that fails to reach his potential growth".[6] It is suspected when fetal growth velocity is reduced, demonstrated by serial ultrasonographic scans, which determine an estimated fetal weight, which is below the 10th percentile or below two standard deviations of the mean for the gestational age. It has many short- and long-term problems e.g., respiratory distress, jaundice, necrotizing enterocolitis, growth failure, infection, intraventricular hemorrhage, periventricular leukomalacia, hydrocephalus, cerebral palsy, retinopathy, pulmonary hypertension. Currently a link has been established between IUGR and development of cardiovascular disease, type 2 diabetes mellitus and hyperlipidemia in adulthood.

IUGR and its concomitant fetal and neonatal morbidity and mortality continue to represent a formidable challenge in terms of both diagnosis and treatment. Intrauterine growth depends on the genetically determined growth potential, but various growth promoting and inhibiting factors also play a crucial role. Therefore, attempts at prenatal treatment have focused on improving uteroplacental perfusion and on improving substrate and energy supply.

Histologically, IUGR shows same defective placentation as pre-eclampsia.[7] Consequently, if low-dose aspirin prophylaxis against pre-eclampsia is effective as shown in some trials, it might prevent not only that disorder but also some cases of IUGR by shifting the balance towards inhibition of TXA2 synthesis and thereby improving uteroplacental blood flow.

So, it is necessary to determine whether aspirin is really effective in prevention or amelioration of IUGR also, as has already been shown with PIH in many studies.

On the other hand, faulty trophoblastic invasion of spiral arteries results in diminished placental perfusion and upstream increased uterine artery resistance, which results in abnormal waveform represented by diastolic notch. So, increased uterine artery resistance or diastolic notch determined by Doppler ultrasound in first or early second trimester serves as a predictor of subsequent pre-eclampsia and IUGR. In this study, bilateral uterine artery notch and/or bilateral uterine artery PI >1.7[2] has been used to select the "high-risk" pregnancies.

The aim of our study was to determine the effectiveness of prophylactic low-dose aspirin in patients who are at high risk for developing pre-eclampsia and IUGR.

The objectives of our study was to note correlation between early uterine artery abnormality and future development of PIH and/or IUGR.

- To see how aspirin affects onset of PIH in patients who present with early uterine artery abnormality.
- To see how aspirin affects fetal growth in patients who present with early uterine artery abnormality.
- To see the perinatal outcome of giving aspirin to pregnant women who present with early uterine artery abnormality.

MATERIAL AND METHODS

The present study was a prospective, randomized, open-ended, controlled, interventional, unicentric study conducted in the Dept. of Obstetrics and Gynecology and Dept. of Radiology, Institute of Postgraduate Medical Education and Research and Seth Sukhlal Karnani Memorial (IPGMER and SSKM) Hospital for 1 year (June 2013 to May 2014). Data were collected from outdoor and indoor primigravida pregnant mothers of IPGMER and SSKM Hospital. We included primigravid mothers with singleton pregnancy, gestational age <16 weeks and bilateral uterine artery notch and/or bilateral uterine artery PI >1.7 revealed in Doppler ultrasound scan at 11-14 weeks gestation. Mothers having abnormal bleeding per vagina, any contraindications to aspirin e.g., allergy to aspirin, bleeding disorder, peptic ulcer, concomitant use of other nonsteroidal anti-inflammatory drugs (NSAIDs) or anticoagulants or antiplatelet drugs, chronic liver disease/chronic hypertension/renal disease/overt diabetes mellitus and any other comorbid condition predisposing to vasculopathy, heart

disease, documented fetal malformation or uterine malformation were excluded from our study. One hundred twenty-four mothers were selected according to inclusion criterias by random sampling technique, subjects- 62 subjects in each group.

The following parameters were noted for data collections:

- Identification of abnormal uterine artery Doppler - PI >1.7 and/or presence of diastolic notch.
- For PIH - Regular BP monitoring.
- For IUGR - Clinical palpation of fundal height (a lag of 4 weeks is suggestive of IUGR), estimated fetal weight - if <10th percentile for the average for gestational age is considered as IUGR in USG, head circumference (HC) and abdominal circumference (AC) ratios - if >1.0 even after 34 weeks suggests IUGR.
- Regular BP monitoring of the selected patients.
- Baby: Physical features at birth (Apgar score at birth, weight- <2,500 g at term is suggestive of IUGR, HC and AC), number of days of stay in NICU, resultant morbidity/mortality of newborn.

Study tools used in our study were sphygmomanometer, USG for uterine artery Doppler velocimetry, fetal profile and amniotic fluid index, measuring tape, neonatal weighing machine. Antenatal mothers meeting inclusion and exclusion criteria were subjected to uterine artery Doppler at 11-14 weeks gestation.

The study protocol was submitted to Institutional Ethics Committee and clearance was obtained before the commencement of the study. One hundred twenty-four primigravida women were selected according to inclusion and exclusion criteria. The women included in the study were told in detail about the potential significance of the test and its benefit in detail in their own language and an informed consent was obtained from them after explaining that the details obtained from them would be used only for study purposes.

Each subject was enquired of present pregnancy, duration of amenorrhea, detailed obstetric history, family and personal history. Detailed general physical examination was done along with routine hematological investigations, blood sugar level, ABO-Rh grouping, renal function test (RFT), liver functon test (LFT), urine for albumin. All patients included in the study were subjected to congenital anomaly scan to rule out anomalies and routine sonological tests. They were advised regular antenatal check-up and follow-up which enabled us to properly evaluate the fetomaternal outcomes.

These 124 women were randomly divided into two groups according to computer-generated randomization table - test and control containing 62 women in each group. Each woman of test group received tablet aspirin 75 mg o.d. from 16 weeks up to 34 weeks of gestation unless early termination became necessary. Women of control group did not receive aspirin. All of these 124 women were followed up till delivery at an interval of 1-4 weeks according to gestational age to see whether they were developing PIH and/or IUGR. After delivery, their babies were also examined to see the perinatal outcome.

Analysis of Data

Data were summarized by routine descriptive parameters like mean, median, standard deviation (SD) and quartiles for numerical variables and counts and percentages for categorical variables.

Data were analyzed using statistical version 6 (Tulsa, Oklahoma: StatSoft Inc., 2001) to see whether aspirin had significant role in prevention of PIH and/or IUGR in high risk mothers.

RESULTS AND ANALYSIS

Numerical variables are normally distributed by Kolmogorov-Smirnoff goodness-of-fit test other than age, thyroid-stimulating hormone (TSH), creatinine, uric acid, lactate dehydrogenase (LDH), Apgar at birth, birth weight, HC_AC and NICU stay. Age distribution is comparable (p value by Mann-Whitney *U*-test = 0.844 insignificant) between control (mean ± SD**:** 23.82 ± 3.628) and study groups (mean **±** SD**:** 23.81 ± 3.492).

Table 1 shows systolic BP (SBP) and diastolic BP (DBP) range with mean ± SD at 20, 24, 28, 32, 34 and 36 weeks and at term gestation in control and test groups. P value in the last column is for intergroup comparison by Student's unpaired *t*-test. From the Table 1, it is seen that difference in the SBP at 20 and 24 weeks gestation between groups is not significant (p value 0.950 and 0.263, respectively) but at 28, 32, 34, 36 weeks gestation and at term is significant (p value 0.001, 0.000, 0.001, 0.001 and 0.031, respectively). Difference in the DBP at 20, 24, 28 and 36 weeks gestation and at term between groups is not significant (p value 0.064, 0.116, 0,514, 0.093 and 0.183) but it is significant at 32 and 34 weeks gestation (p value 0.002 and 0.002, respectively).

Table 2 shows hemoglobin level (g/dL), platelet count, urea, creatinine, uric acid and LDH (IU/L) in different groups. From the table, it is seen that difference in the hemoglobin level between groups is not significant

(p value 0.060) and the difference in the platelet level between groups is not significant (p value 0.269). It is also seen that difference in the urea and creatinine level between groups is not significant (p value 0.166 and 0.732, respectively), but uric acid level is significantly decreased in aspirin-treated group (p value 0.011).

From the Table 3, it is seen that proteinuria at 28, 32 and 34 weeks aspirin-treated group is reduced significantly (p value 0.006, 0.031, 0.016, respectively) and proteinuria at 36 weeks and term pregnancy between groups is not significant (p value 0.142 and 0.737, respectively).

Table 1. Systolic Blood Pressure and Diastolic Blood Pressure Changes at Different Gestational Weeks

	20 weeks	24 weeks	28 weeks	32 weeks	34 weeks	36 weeks	Term
SBP in mmHg (Range) control	100-136	110-136	112-166	116-190	112-170	114-178	112-196
SBP in mmHg (Range) test	110-134	112-132	112-136	112-150	114-160	112-180	114-176
SBP in mmHg (mean ± SD) control	120.71 ± 6.232	122.87 ± 6.654	128.55 ± 10.578	134.29 ± 13.051	141.08 ± 13.965	147.11 ± 14.366	147.30 ± 16.919
SBP in mmHg (mean ± SD) test	120.77 ± 5.202	121.77 ± 3.834	123.58 ± 5.458	127.29 ± 7.674	132.87 ± 11.410	138.16 ± 15.020	140.39 ± 15.078
P value	*0.950*	*0.263*	*0.001*	*0.000*	*0.001*	*0.001*	*0.031*
DBP in mmHg (Range) control	70-84	66-90	68-100	72-120	70-110	70-120	76-120
DBP in mmHg (Range) test	70-82	70-84	60-86	70-96	70-100	70-120	70-112
DBP in mmHg (mean ± SD) control	78.52 ± 3.176	80.42 ± 4.115	80.26 ± 8.977	84.55 ± 7.107	88.95 ± 8.411	91.50 ± 8.716	91.22 ± 10.553
DBP in mmHg (mean ± SD) test	77.39 ± 3.541	79.48 ± 2.171	79.45 ± 3.660	81.23 ± 4.366	84.56 ± 6.786	88.52 ± 10.249	88.60 ± 9.281
P value	*0.064*	*0.116*	*0.514*	*0.002*	*0.002*	*0.093*	*0.183*

Table 2. Hemoglobin Level (g/dL), Platelet Count, Urea, Creatinine, Uric Acid and LDH Levels in Different Groups

Parameters		Control group	Test group	P value (Student's unpaired *t*-test)
Hemoglobin level (g/dL)	Range	9-13.6	8.6-14	0.060
	Mean ± SD	11.63 ± 1.172	12.03 ± 1.148	
Platelet count	Range	1,11,000-5,12,000	1,26,000-5,22,000	0.269
	Mean ± SD	3,26,419.35 ± 1,00,495.91	3,06,661.29 ± 97,520.73	
Urea	Range	10-62	16-56	0.166
	Mean ± SD	29.5 ± 9.735	31.66 ± 7.384	
Creatinine	Range	0.1-2.1	0.2-1.9	0.732
	Mean ± SD	0.6 ± 0.261	0.62 ± 0.219	
Uric acid	Range	1.2-8.2	1.30-5.20	0.011
	Mean ± SD	4.15 ± 1.749	3.28 ± 1.002	
LDH (IU/L)	Range	124-610	110-600	0.596
	Mean ± SD	255.87 ± 110.709	240.32 ± 93.458	

Table 3. Proteinuria at 28, 32 and 36 Weeks in Different Groups

Proteinuria at weeks of gestational age (GA/Grade)	Control (62)	Test (62)	P value
(28/nil)	54	62	0.006 (Fisher's exact test 2-tailed)
(28/+)	8	0	
(32/nil)	45	57	Chi-square test (Yate's corrected) p value 0.031
(32/+)	3	2	
(32/++)	13	3	
(32/++++)	1	0	
(34/nil)	37	52	0.016 (Chi-square test (Yate's corrected)
(34/++)	19	10	
(34/+++)	4	0	
(34/++++)	1	0	
(36/nil)	19	30	0.142 (Chi-square test (Yate's corrected)
(36/++)	30	28	
(36/+++)	3	0	
(36/++++)	5	4	
(Term/nil)	23	19	0.737 (Chi-square test (Yate's corrected)
(Term/++)	17	23	
(Term/+++)	8	8	
(Term/++++)	7	8	

From the Table 4, it is obvious that reduction in the occurrence of pre-eclampsia, IUGR and NICU admission in aspirin-treated group are significant (p value 0.014, 0.019 and 0.011, respectively) but the difference in birth weight, the Apgar score at birth, NICU stay and occurrence of postpartum hemorrhage (PPH) between groups is not significant (p value 0.339, 0.128, 0.082 and 1.000, respectively). There was no incidence of hypertension without proteinuria in any of the patients. Eclampsia also did not develop in any of the study groups.

There was no occurrence of altered sugar, thyroid profile, disturbed LFT, coagulation profile and antepartum hemorrhage (APH) in any of the study groups.

Table 4. Occurrence of Pre-eclampsia, IUGR, PPH, Birth Weight, Apgar Score at Birth, NICU Admission and Stay in Different Groups

Parameters	Control (n = 62)	Test (n = 62)	P value
Pre-eclampsia	7	19	0.014 (Fisher's exact test 2-tailed p value)
IUGR	17	6	0.019 (Fisher's exact test 2-tailed p value)
PPH	2	1	1.00 (Fisher's exact test 2-tailed p value)
Birth weight in kg (mean ± SD)	2432.26 ± 458.624	2599.68 ± 262.285	0.339 (Mann-Whitney *U*-test)
Apgar score (mean ± SD)	8.19 ± 1.084	8.63 ± 0.550	0.128 (Mann-Whitney *U*-test)
NICU admission	15	4	0.011 (Fisher's exact test 2-tailed p value)
NICU stay (mean ± SD)	3.37 ± 7.382	0.66 ± 2.997	0.082 (Mann-Whitney U-test)

In this study, number needed-to-treat (NNT) for pre-eclampsia avoidance is 5.17 i.e., 5.17 subjects need to be on aspirin rather than on control treatment to avoid 1 additional case of pre-eclampsia.

NNT for IUGR avoidance is 5.64 i.e., 5.64 subjects need to be on aspirin rather than on control treatment to avoid 1 additional case of IUGR.

DISCUSSION

Gestational hypertension and pre-eclampsia syndrome remains one of the most intriguing topics even in modern day obstetrics. Even though complications associated with PIH have been observed from ancient times and various treatment modalities have been suggested, till now appropriate preventive measures have not been devised.

In this context, we studied the effectiveness of low-dose aspirin started at 16 weeks gestation in prevention of pre-eclampsia and IUGR in high risk primigravida. High risk group was defined by diastolic notch and/or PI ≥1.7 in uterine artery Doppler at 11-14 weeks gestation. One hundred twenty-four antenatal women carrying singleton pregnancy, fulfilling all inclusion and exclusion criteria were included in our prospective interventional study. All relevant patient data and investigations were analyzed statistically using Statistical version 6 (Tulsa, Oklahoma: StatSoft Inc., 2001).

We can see that the age distribution between the different groups is not statistically significant. Mean age in control and test group is 23.82 and 23.81 years, respectively.

Table 1 shows that SBP at 20 and 24 weeks gestation between different groups is comparable but it is significantly decreased in aspirin-treated group at 28, 32, 34 and 36 weeks gestation and at term (p value 0.001, 0.000, 0.001, 0.001 and 0.031, respectively). Table 1 also shows that difference in the DBP at 20, 24, 28 and 36 weeks gestation and at term between different groups is not significant but it is significant at 32 and 34 weeks gestation (p value 0.002 and 0.002, respectively).

As we all know that severe pre-eclampsia is characterized by vasoconstriction and a 'leaky' microcirculation, resulting in fluid moving into the extracellular interstitial space and relative hypovolemia. The red cell volume in pre-eclampsia is no different than in normal pregnancy. Thus, the hemoglobin concentration or hematocrit is a reasonable surrogate measure of plasma volume in pre-eclampsia. Abnormally high hemoglobin levels correlate with adverse perinatal outcome.[1-6] On the other hand, thrombocytopenia is the most frequent hemostatic abnormality in established pre-eclampsia[7,8] and one of the components of the dreaded complication of pre-eclampsia-HELLP syndrome. From Table 4 and 5; however, we can see that in our study hemoglobin and platelet values are comparable between the two groups i.e., aspirin does not appear to have any effect on hemoglobin and platelet levels. It is noteworthy that in our study population hemoglobin level seems to be quite improved in comparison to the general population (mean value 11.63 and 12.03, respectively for control and test groups), which may be due to good antenatal care and/or hemoconcentration as a result of the leaky microcirculation of the pre-eclampsia syndrome.

Table 2 shows that urea, creatinine levels are comparable between the two groups but uric acid level has decreased significantly in aspirin-treated group (p value is 0.011). Uric acid levels are usually found to be significantly elevated in patients with pre-eclampsia[6] - our study corroborates well with this finding - as incidence of pre-eclampsia is significantly higher in the control group - uric acid level is also significantly elevated in that group.

Serum LDH is most often measured to evaluate tissue damage in pre-eclampsia. Elevated LDH level indicates microangiopathic hemolytic anemia, which is the result of vascular endothelial damage.[9] LDH level >800 IU/L is most often associated with adverse maternal and fetal outcome. Increased LDH, thus indicates the severity of the pre-eclampsia syndrome.[10] However in this study, it is seen that LDH level is comparable between the two groups.

In Table 3, we can see that proteinuria has decreased significantly in aspirin-treated group at 28, 32 and 34 weeks gestation (p value 0.006, 0.031 and 0.016, respectively) but not so at 36 weeks gestation and at term.

From Table 4, it is evident that aspirin reduces the incidence of pre-eclampsia significantly in this high-risk population (p value 0.014).

The Perinatal Antiplatelet Review of International Studies (PARIS) Collaborative Group[10] performed a meta-analysis of the effectiveness and safety of low-dose aspirin for the prevention of pre-eclampsia and concluded that low-dose aspirin has small-to-moderate benefits when used for prevention of pre-eclampsia and is also safe. Results from a meta-analysis[11] suggested that low-dose aspirin improves pregnancy outcome in women with persistent increases in uterine Doppler resistance index at both 18 and 24 weeks' gestation. Findings of our study corroborates well with the findings of these studies. However, in other studies with abnormal Doppler measurements of uterine arteries at 22-24 weeks gestation, low-dose aspirin after 23 weeks gestation did not prevent pre-eclampsia.

Table 4 represent the perinatal outcome. Among the several parameters of perinatal outcome, NICU admission rate are significantly decreased in aspirin-treated group (p value 0.011), but other parameters like Apgar score at birth, birth weight and NICU stay were not influenced significantly by aspirin. However, incidence of IUGR was significantly less in the patients treated with aspirin (p value 0.019).

Table 4 also shows that incidence of PPH is comparable between the two groups. It is noteworthy that APH did not occur in any of the study groups.

There was no incidence of hypertension without proteinuria in any of the patients. Eclampsia also did not develop in any of the study groups. There was no alteration of glycemic, thyroid, liver or coagulation status in either group.

In this study, NNT for pre-eclampsia avoidance is 5.17 i.e., 5.17 subjects need to be on aspirin rather than on control treatment to avoid 1 additional case of pre-eclampsia.

NNT for IUGR avoidance is 5.64 i.e., 5.64 subjects need to be on aspirin rather than on control treatment to avoid additional case of IUGR.

LIMITATIONS

- Small sample size (less time).
- Absence of blinding.
- Measurement of proteinuria by dipstick method.
- Absence of follow-up of patients up to 12 weeks postpartum.
- Absence of follow-up of babies after discharge.

CONCLUSIONS

Pre-eclampsia, one of the most discussed enigmatic diseases in obstetrics, affects 2-8% of all pregnancies. Abruptio placentae, renal failure, cerebral hemorrhage, DIC, pulmonary edema, circulatory collapse, IUGR and IUD are the problems associated with pre-eclampsia.

There has been an explosion of research activities worldwide for early prediction and prevention of pre-eclampsia but till date it remains an uphill task for all obstetricians and researchers. Various methods have been tried but none is full proof. Some studies have shown that low-dose aspirin started early in pregnancy in high risk group may be quite efficacious in preventing pre-eclampsia and IUGR.

In our study, we came to the conclusion that treatment with low-dose aspirin starting early in pregnancy in high risk group (defined by diastolic notch and/or PI ≥1.7 in uterine artery Doppler done at 11-14 weeks gestation) is efficacious in preventing pre-eclampsia and IUGR. Perinatal outcome is also improved in aspirin-treated group.

However, further studies with large number of patients are needed to establish the definite role of low-dose aspirin in this context.

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Pancytopenia in Indian Children: A Clinico-hematological Analysis

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ABSTRACT

Objective: To determine the etiological profile of pancytopenia in pediatric patients in India. **Material and methods:** Medical records review of a 5-year period between 1st September 1997 and 31st August 2002. Clinical and hematological data of all patients with pancytopenia (hemoglobin [Hb] ≤10 g/dL, TLC ≤4 × 10^9/L, platelet count ≤150 × 10^9/L) at presentation were analyzed. Patients on cytotoxic chemotherapy, those developing pancytopenia during hospital stay, patients referred from other centers with hematological malignancies and neonates were excluded. **Results:** Forty-two children (mean age 8.26 years, range 8.5 months to 13 years, M:F : 1:0.8) were included. Megaloblastic anemia, aplastic anemia and infections were commonest causes, being responsible for 25%, 19.6% and 32.1% of the cases, respectively. Bone-marrow aspiration (BMA) was helpful in reaching a definitive diagnosis in 92.8% of those in whom sufficient marrow tissue was retrieved for analysis. Aplastic anemia was the commonest reason for failure of BMA in providing a diagnosis. **Conclusions:** Majority (almost 60%) of the causes of pancytopenia among pediatric patients in this region are easily treatable. There is a need to be aware of such conditions and appropriate investigative modalities should be undertaken for the same.

Keywords: Megaloblastic anemia, aplastic anemia, bone-marrow aspiration

Pancytopenia is the simultaneous presence of anemia (hemoglobin [Hb] less than the normal for age), leukopenia (total leukocyte count [TLC] <4,000 × 10^9/L) and thrombocytopenia (platelet count <150 × 10^9/L). It is a common clinical problem with an extensive differential diagnosis, but there is relatively little discussion of this abnormality in major pediatric and hematology textbooks.[1,2] Although a few authors have discussed it as a separate entity,[3] most of the discussion is centered on aplastic anemia, which is a relatively uncommon cause of pancytopenia in children. The lack of an optimal investigative approach to pancytopenia (especially the role of bone-marrow examination) has also been previously highlighted.[1] A wide variety of disorders can lead to pancytopenia but their relative frequency differs considerably between different age groups and different geographical areas.[1] Also, there have been very few systematic studies of pancytopenia.[1,4] Quite a few studies from India have been published on this topic, but none has addressed this issue in the pediatric age group.[5-8] We, therefore, retrospectively reviewed the medical records of 42 pediatric patients presenting with pancytopenia over a 5-year period, to determine the clinico-hematological characteristics of pancytopenia among pediatric patients in India.

MATERIAL AND METHODS

Pancytopenia was defined as Hb ≤10 g/dL, TLC ≤4,000 × 10^9/L and platelet count ≤150 × 10^9/L. The case-records of all the patients admitted in the Dept. of Pediatrics with an admitting diagnosis of pancytopenia over a 5-year period between 1st September 1997 and 31st August 2002 were reviewed. The records of the Hematology Division, Dept. of Pathology for the same period were also reviewed to identify all cases in which a diagnosis of pancytopenia was made at the time of admission. The details of clinical profile, hematological parameters (Hb, TLC and differential leukocyte count [DLC], platelet count, reticulocyte count, peripheral smear), and BMA and/or biopsy examination results were recorded in a structured proforma. In the Hematology Division, blood

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counts are performed on an automated counter and abnormal findings confirmed by a hematopathologist. All peripheral blood films, bone marrow aspirates (BMA) and/or trephine biopsies were processed as per standard techniques. Other investigations done (cultures of blood, body fluids and bone marrow; splenic aspiration, radiological examination, Mantoux testing, serological tests, etc.) were also recorded.

Children receiving cytotoxic chemotherapy and those developing pancytopenia during the hospital stay were not included. If a patient was admitted more than once, only the first admission record was included for analysis, although the final etiological diagnosis made was recorded. Records of the Neonatal Unit were not included. A total of 47 cases of pancytopenia were thus identified. Full blood counts at admission were available for all of them but counts at discharge and BMA/biopsy results were available for 45 and 42 cases, respectively (as they obtained discharge against advice or absconded prior to BMA).

RESULTS

Complete records of 42 children were analyzed. The mean age of the children was 8.26 years (range, 8.5 months to 13 years; median age, 9 years; mode, 7 years; M:F : 1:0.8). The underlying causes for pancytopenia in these children are tabulated in Table 1.

On statistical analysis, no significant difference was found between the major diagnostic categories (megaloblastic anemia, aplastic anemia and acute lymphoblastic leukemia [ALL]) with regards to sex, age at presentation, presenting complaints and initial hematological values. Megaloblastic anemia was the commonest cause of pancytopenia and responsible for one-fourth of the cases. It was due to folate deficiency in two cases, and vitamin B_{12} deficiency in one case. One patient with megaloblastic anemia passed *Ascaris* worms in stool during hospital stay. All patients with disseminated tuberculosis were over 8 years of age and all patients of kala-azar were residents of endemic areas.

Table 1. Underlying Causes in 42 Children Presenting with Pancytopenia

Diagnosis	Number of patients (%)
Megaloblastic anemia	10 (23.8)
Aplastic anemia	8 (19)
Acute lymphoblastic leukemia	6 (14.3)
Enteric fever	7 (16.6)
Kala-azar	4 (9.5)
Disseminated tuberculosis	4 (9.5)
Others	3*

*One case of non-Hodgkin's lymphoma, one cases of disseminated tuberculosis with associated enteric fever. One case was not diagnosed.

Aplastic anemia was responsible for 20% of the cases but no etiologic factors could be implicated in any of these children except three with probable heavy metal poisoning. Two of these were distant cousins working in a battery-manufacturing unit although they presented to the hospital 8-month apart. Another had received indigenous medicines (Unani medicine) for atopic dermatitis with sudden appearance of pallor and petechiae within a month of these medications. No other clinical evidence of heavy metal poisoning was noted in these three children.

BMA had been done in all 42 patients and was inconclusive in 6 patients only. Three of these had aplastic anemia (proved on bone-marrow biopsy) and one had kala-azar (proved on splenic puncture and serology, and responded to sodium antimony gluconate). The remaining two had evidence of disseminated tuberculosis elsewhere in the body but no supportive bone marrow findings; although, one had associated enteric fever. One responded to antitubercular therapy alone, and the other to antitubercular therapy in combination with antibiotics, respectively. Bone marrow biopsy was helpful in making the diagnosis in only 3 patients out of the 6 in whom it was conducted. However, it ruled out underlying aplastic anemia/ aleukemic leukemia in the other 3 patients.

Six patients with aplastic anemia and 5 patients with ALL were referred to higher centers for management and 3 patients were lost to follow-up.

DISCUSSION

The results of this study show that pancytopenia can be the presenting feature of a wide variety of illnesses in the pediatric population of our country. Similar to the studies of pancytopenia in adults from India, majority of the patients had megaloblastic anemia, aplastic anemia and hematological malignancies. Although, kala-azar has previously also been reported to present with pancytopenia, disseminated tuberculosis and enteric fever were found to be responsible for a significant number of case (9.5% and 16.6%, respectively).

Megaloblastic anemia was the commonest cause of pancytopenia (23.8%) in this study similar to African reports and adults studies in our country.[1,5,6]

The proportion reported from the West has been much lower (7.5% in adults).[4] Savage et al[1] have reported megaloblastic anemia to be responsible for 35.8% of their 134 hospitalized African pancytopenic patients (age range, 1-73 years; median, 40 years). Among studies in adults in India also megaloblastic anemia is responsible for a significant proportion of pancytopenic patients that varies from 22.3% to 39%.[5-10] Tilak and Jain have however reported a very high proportion of 68% in adult pancytopenic patients.[8]

The cause of megaloblastic anemia could only be determined in 3 of our patients due to the nonavailability of facilities for estimating folic acid and B_{12} at our center. Most studies from India have suffered from this drawback.[5-9] Folic acid and B_{12} are reported to be responsible for similar proportion of pediatric patients with megaloblastic anemia in this region and treatment with a combined preparation of B_{12} and folic acid is an acceptable option.[9]

Although megaloblastic anemia was found to be the commonest cause of pancytopenia among children, a diagnosis of megaloblastic anemia should not be based on the presence of macrocytes on the peripheral smear alone, as this finding is not infrequently found in those with aplastic anemia and also acute leukemia. Similarly, Kumar et al found megaloblastic marrow in 5 patients with falciparum malaria and in 1 patient with enteric fever, who presented with pancytopenia.[5]

Aplastic anemia was the next most common cause (19%) of pancytopenia in this study. Savage et al also reported it to be the second most common cause (26.1%) of pancytopenia in their study. It was responsible for pancytopenica in 62.9% of patients aged below 21 years.[1] Kumar et al; however, found it to be the commonest cause (29.5%) of pancytopenia among adults at a hematology center, which may have been due to high proportion of referred cases at their center.[5] No etiologic factor could be implicated in majority of our cases with aplastic anemia.

Acute leukemia was seen in 6 cases, all of which had ALL. One patient had non-Hodgkin's lymphoma. During the period under review, 4 other patients with pancytopenia and leukemia were seen by us (3 ALL, 1 acute myeloid leukemia [AML]) but were not included for analysis. Eight percent of patients in a Zimbabwean study of adults and children had acute leukemia and these cases were often children.[1]

Hematological findings in kala-azar can include any or all of the findings of anemia, thrombocytopenia, neutropenia and pancytopenia.[10,11] Pancytopenia is caused by hypersplenism, hemolysis, plasma volume expansion, ineffective erythropoiesis and reticuloendothelial hyperplasia. Hemophagocytic syndrome and trilineage myelodysplasia have also been reported as a complication of this illness.[10,12] All the patients with kala-azar in this study came from endemic areas, had history of prolonged fever with a massive splenomegaly, and the diagnosis was clinically suspected prior to bone marrow examination. One patient did not demonstrate Leishman-Donovan (LD) bodies on BMA and had to undergo splenic puncture. Kumar et al reported kala-azar in 4% of their patients; this low frequency could again have been due to the referral nature of their patients.[5]

The two unusual findings observed in this study were the previously unreported high proportion of pancytopenia due to enteric fever and tuberculosis (16.6% and 9.5% of the cases). In patients with tuberculosis, various hematological abnormalities including anemia, lymphocytopenia, thrombocytopenia, leukopenia, pancytopenia, etc. have been described. The commonest of these among Indian patients with disseminated tuberculosis has been reported to be anemia (present in 84%).[13]

In the same study, pancytopenia was found in 19% of the patients with disseminated or miliary tuberculosis. The various postulated mechanisms for pancytopenia include splenic sequestration, immune-mediated bone marrow depression and malnutrition.[13] The presence of a granuloma on bone marrow had no relationship with the occurrence of pancytopenia in previous studies.[13,14] Contrary to these reports; we found granulomas in 3 of the 4 patients with disseminated tuberculosis and pancytopenia. One other case of disseminated tuberculosis had associated enteric fever, thus pancytopenia could not be ascribed to any single condition. There was no granuloma on BMA but the child improved with antitubercular therapy in combination with specific therapy. The suggested conclusive proof of tuberculosis-induced pancytopenia is the resolution of both tuberculosis and pancytopenia with antitubercular therapy.[14]

Another patient had pulmonary tuberculosis with absence of any diagnostic finding on BMA. He was discharged on request prior to bone marrow biopsy and was lost to follow-up. Merely the presence of pulmonary tuberculosis in this child did not justify labeling it as the cause of pancytopenia. In a previous series also, none of the patients with pulmonary tuberculosis had pancytopenia.[10]

As tuberculosis is quite common in our country, it may be coincidentally present in quite a few patients of pancytopenia. Presence of pancytopenia and disseminated tuberculosis in a pediatric patient does not therefore imply causation, and BMA or biopsy should demonstrate granuloma to definitively ascribe pancytopenia to be because of the tubercular infection. Kumar et al reported only 1 patient with disseminated tuberculosis out of 166 adult patients with pancytopenia and diagnosis was made only on a post-mortem liver biopsy.[5]

Isolated cytopenias, bicytopenias and pancytopenia in enteric fever are well-documented in literature.[15,16] Multidrug-resistant *Salmonella typhi* (MDRST) are reported to be more commonly associated with hematological findings. Around 84% of the pediatric patients with enteric fever at our center are found to be suffering from MDRST. Bone marrow histiocytic hemophagocytosis has been reported to be a cause for pancytopenia in enteric fever,[16] but was not found in any of our cases. Bone marrow hypocellularity was observed in 3 (43%) of the 7 patients with pancytopenia associated with enteric fever. In others, probably a peripheral mechanism for pancytopenia was operating. None of the children had been receiving chloramphenicol or any other bone marrow depressant. Studies in adults have also reported similar findings.[15]

BMA was extremely helpful in reaching a definitive diagnosis in a majority (92.3%) of those where sufficient marrow tissue was retrieved for analysis. It was inconclusive in only 6 (14.3%) cases; in 3 of which, sufficient marrow tissue was not available by aspiration (all aplastic anemia) and in three others, no diagnostic information could be provided after the examination.

In these 3 also, a primary marrow involvement was ruled out after the marrow examination. Bone marrow biopsy was most helpful in cases of aplastic anemia, where it was diagnostic in all the 4 cases in which it was done (after aspiration was inconclusive). Although BMA has been reported to be inconclusive in up to 38% of adult patients in one series, and simultaneous aspiration and biopsy have been recommended to overcome this problem,[5] we find ourselves unable to concur with this for pediatric patients. Bone marrow biopsy is definitely a more painful procedure than BMA, and subjecting every child with pancytopenia to it does not seem justified in the light of results from this study.

On the other hand, certain authors are of the opinion that BMA is not even needed in certain pancytopenic patients e.g., those with hypersegmented neutrophils on peripheral smear and, those with mild pancytopenia, splenomegaly, an unremarkable blood film and a known cause of portal hypertension.[1] In our opinion, the recommendations of Savage et al[1] seem more appropriate for pediatric patients in our country especially in the setting, where BMA is not feasible. However, at centers where facilities are available, BMA remains a simple test, which not only clears the diagnostic confusion but also rules out the more serious primary marrow involvement like malignancies and aplastic anemia.

This study shows that megaloblastic anemia and infections (kala-azar, enteric fever and tuberculosis), both of which are eminently treatable, cause nearly 60% of the pediatric cases presenting with pancytopenia in this region. This is contrary to the widespread perception of acute leukemia and aplastic anemia as the most common etiologic factors, with their associated poor prognostic implications. It is important to be aware of these conditions as a frequent cause of pancytopenia, so that prompt and appropriate investigative and therapeutic measures can be instituted and a uniformly poor prognosis is not communicated to the relatives.

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Do not Ignore Complications

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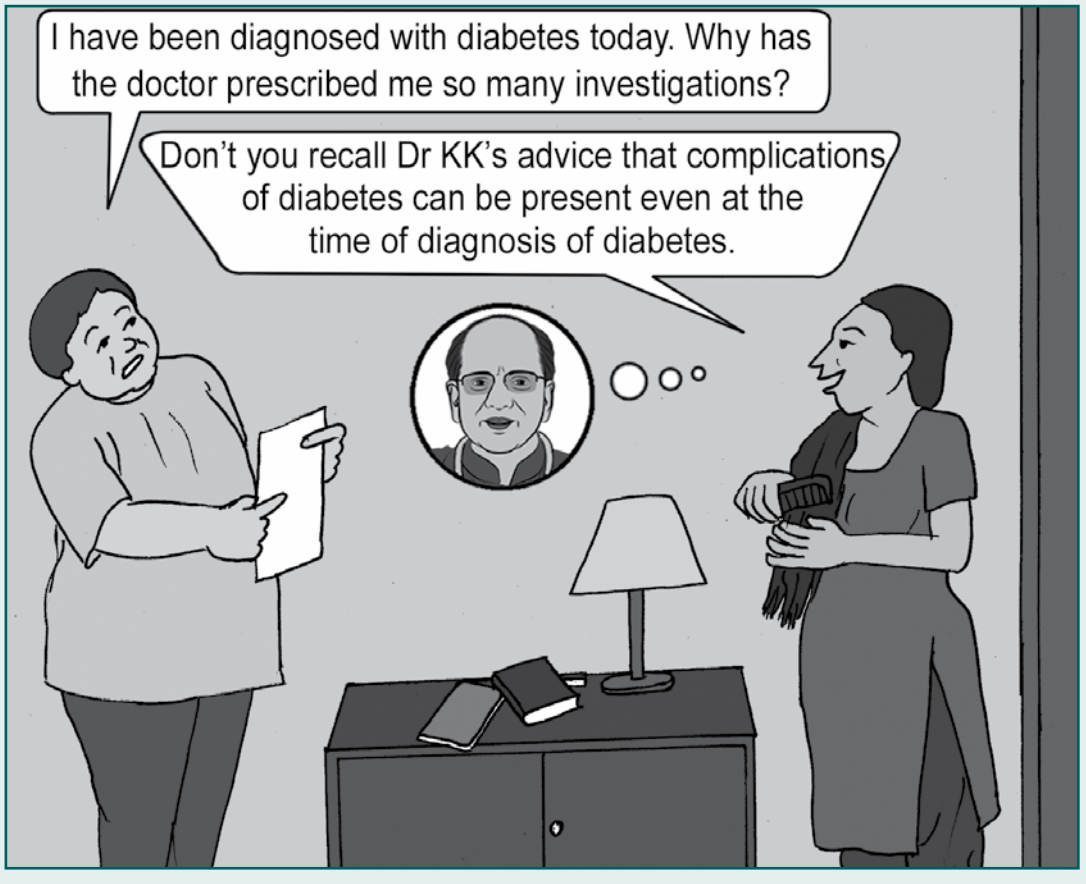

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About Sameer Malik Heart Care Foundation Fund

"Sameer Malik Heart Care Foundation Fund" it is an initiative of the Heart Care Foundation of India created with an objective to cater to the heart care needs of people.

Objectives

- Assist heart patients belonging to economically weaker sections of the society in getting affordable and quality treatment.
- Raise awareness about the fundamental right of individuals to medical treatment irrespective of their religion or economical background.
- Sensitize the central and state government about the need for a National Cardiovascular Disease Control Program.
- Encourage and involve key stakeholders such as other NGOs, private institutions and individual to help reduce the number of deaths due to heart disease in the country.
- To promote heart care research in India.
- To promote and train hands-only CPR.

Activities of the Fund

Financial Assistance

Financial assistance is given to eligible non emergent heart patients. Apart from its own resources, the fund raises money through donations, aid from individuals, organizations, professional bodies, associations and other philanthropic organizations, etc.

After the sanction of grant, the fund members facilitate the patient in getting his/her heart intervention done at state of art heart hospitals in Delhi NCR like Medanta – The Medicity, National Heart Institute, All India Institute of Medical Sciences (AIIMS), RML Hospital, GB Pant Hospital, Jaipur Golden Hospital, etc. The money is transferred directly to the concerned hospital where surgery is to be done.

Drug Subsidy

The HCFI Fund has tied up with Helpline Pharmacy in Delhi to facilitate patients with medicines at highly discounted rates (up to 50%) post surgery.

The HCFI Fund has also tied up for providing up to 50% discount on imaging (CT, MR, CT angiography, etc.)

Who is Eligible?

All heart patients who need pacemakers, valve replacement, bypass surgery, surgery for congenital heart diseases, etc. are eligible to apply for assistance from the Fund. The Application form can be downloaded from the website of the Fund. http://heartcarefoundationfund.heartcarefoundation.org and submitted in the HCFI Fund office.

Important Notes

- The patient must be a citizen of India with valid Voter ID Card/ Aadhaar Card/Driving License.
- The patient must be needy and underprivileged, to be assessed by Fund Committee.
- The HCFI Fund reserves the right to accept/reject any application for financial assistance without assigning any reasons thereof.
- The review of applications may take 4-6 weeks.
- All applications are judged on merit by a Medical Advisory Board who meet every Tuesday and decide on the acceptance/rejection of applications.
- The HCFI Fund is not responsible for failure of treatment/death of patient during or after the treatment has been rendered to the patient at designated hospitals.
- The HCFI Fund reserves the right to advise/direct the beneficiary to the designated hospital for the treatment.
- The financial assistance granted will be given directly to the treating hospital/medical center.
- The HCFI Fund has the right to print/publish/webcast/web post details of the patient including photos, and other details. (Under taking needs to be given to the HCFI Fund to publish the medical details so that more people can be benefitted).
- The HCFI Fund does not provide assistance for any emergent heart interventions.

Check List of Documents to be Submitted with Application Form

- Passport size photo of the patient and the family
- A copy of medical records
- Identity proof with proof of residence
- Income proof (preferably given by SDM)
- BPL Card (If Card holder)
- Details of financial assistance taken/applied from other sources (Prime Minister's Relief Fund, National Illness Assistance Fund Ministry of Health Govt of India, Rotary Relief Fund, Delhi Arogya Kosh, Delhi Arogya Nidhi), etc., if anyone.

Free Diagnostic Facility

The Fund has installed the latest State-of-the-Art 3 D Color Doppler EPIQ 7C Philips at E – 219, Greater Kailash, Part 1, New Delhi.
This machine is used to screen children and adult patients for any heart disease.

Free Education and Employment Facility

HCFI has tied up with a leading educational institution and an export house in Delhi NCR to adopt and to provide free education and employment opportunities to needy heart patients post surgery. Girls and women will be preferred.

Laboratory Subsidy

HCFI has also tied up with leading laboratories in Delhi to give up to 50% discounts on all pathological lab tests.

Help Us to Save Lives

The Foundation seeks support, donations and contributions from individuals, organizations and establishments both private and governmental in its endeavor to reduce the number of deaths due to heart disease in the country. All donations made towards the Heart Care Foundation Fund are exempted from tax under Section 80 G of the IT Act (1961) within India. The Fund is also eligible for overseas donations under FCRA Registration (Reg. No 231650979). The objectives and activities of the trust are charitable within the meaning of 2 (15) of the IT Act 1961.

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About Heart Care Foundation of India

Heart Care Foundation of India was founded in 1986 as a National Charitable Trust with the basic objective of creating awareness about all aspects of health for people from all walks of life incorporating all pathies using low-cost infotainment modules under one roof.

HCFI is the only NGO in the country on whose community-based health awareness events, the Government of India has released two commemorative national stamps (Rs 1 in 1991 on Run For The Heart and Rs 6.50 in 1993 on Heart Care Festival- First Perfect Health Mela). In February 2012, Government of Rajasthan also released one Cancellation stamp for organizing the first mega health camp at Ajmer.

Objectives

- Preventive Health Care Education
- Perfect Health Mela
- Providing Financial Support for Heart Care Interventions
- Reversal of Sudden Cardiac Death Through CPR-10 Training Workshops
- Research in Heart Care

Heart Care Foundation Blood Donation Camps

The Heart Care Foundation organizes regular blood donation camps. The blood collected is used for patients undergoing heart surgeries in various institutions across Delhi.

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Entrepreneur

President

Dr KK Aggarwal

Padma Shri, Dr BC Roy National & DST National Science Communication Awardee

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This Fund is dedicated to the memory of **Sameer Malik** who was an unfortunate victim of sudden cardiac death at a young age.

- HCFI has associated with Shree Cement Ltd. for newspaper and outdoor publicity campaign
- HCFI also provides Free ambulance services for adopted heart patients
- HCFI has also tied up with Manav Ashray to provide free/highly subsidized accommodation to heart patients & their families visiting Delhi for treatment.

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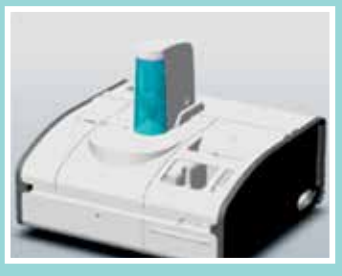

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Judgement of High Court of Bombay on the Mentally Challenged Person cannot Donate his Organs Even to his Brother

In the matter titled as "**Ganpatrao & Others versus State of Maharashtra & Others, Writ Petition No. 13918 of 2017, the Hon'ble High Court of Bombay, Bench at Aurangabad** dealt with the issue whether a person who is mentally challenged and represented by natural guardians father and mother can be a donor for removal of his organs or tissues within the meaning of Section 2(f) of the Transplantation of Human Organs and Tissues Act, 1994 and whether he can be permitted to donate human organ for transplantation in favour of his real brother inspite of bar provided under Section 9(1-C) of the Transplantation of Human Organs and Tissues Act, 1994.

The provisions of Section 2(f) of the Transplantation of Human Organs and Tissues Act, 1994 are as follows:

> "***Section 2(f) of the Act*** *defines donor as any person, not less than eighteen years of age, who voluntarily authorises the removal of any of his [human organs or tissues or both] for therapeutic purposes under subsection (1) or subsection (2) of section 3."*

The provisions of Section 9(1C) of the Transplantation of Human Organs and Tissues Act, 1994 are reproduced hereunder:

> ***"9. Restrictions on removal and transplantation of [human organs or tissues or both]***
>
> *(1C) No human organs or tissues or both shall be removed from the body of a mentally challenged person before his death for the purpose of transplantation.*
>
> *Explanation For the purpose of this subsection,*
>
> *(i) the expression "mentally challenged person" includes a person with mental illness or mental retardation, as the case may be;*
>
> *(ii) the expression "mental illness" includes dementia, schizophrenia and such other mental condition that makes a person intellectually disabled;*
>
> *(iii) the expression "mental retardation" shall have the same meaning as assigned to it in clause(r) of section 2 of the Persons with Disabilities (Equal Opportunities, Protection of Rights and Full Participation) Act, 1995 (1 of 1996)]*

In the present case, the Hon'ble High Court of Bombay held that as per the provision of Section 2(f) of the Act, the donor has to be a person who is not less than eighteen years of age and who voluntarily authorises removal of his organ or tissues. Further, the provisions of Section 9(1C) of the Act puts bar on removal of human organ or tissues or both from body of a mentally challenged person. Thus, the person who is suffering from mental retardation and who is not capable of making a decision for himself, is a person who not in a position to voluntarily authorise removal of his organ or tissues as per Section 2(f) of the Act and also in view of the bar of Section 9(1C) of the Act, the organ or tissues of such person cannot be removed and donated.

The relevant paragraphs of the judgement passed by the Hon'ble High Court of Bombay is reproduced hereunder:

> *"15. As has been recorded above, the principles in Common Law jurisdiction based upon "best interest test" cannot be made applicable in view of specific provisions in Transplantation of Human Organs and Tissues Act, 1994. Section 2(f) of the Act defines donor as the person not less than eighteen years of age, who voluntarily authorises removal of his organ or tissues. In the instant matter, petitioner no. 3 is not an individual who is in a position to voluntarily authorise removal of his organ or tissues. Apart from this, section 9(1C) puts bar on removal of human organ or tissues or both from body of a mentally challenged person. In the instant matter, petitioner no. 3 is adjudged as suffering from mental retardation and he is reported to be a person not capable of making decision for himself. We, with a view to find out whether petitioner no. 3 has a minimum level of understanding, interviewed him by calling him in chamber in presence of the counsel of both the sides. We have noticed that petitioner no. 3 even was not in a position to understand the questions put to him and is incapable of understanding the consequences of his act.*

His decision making power is severely impaired and we do not doubt the opinion of the Consultant Psychiatrist.

16. The restriction on removal and transplantation of human organs or tissues or both contained in subsection (1C) of section 9 of the Act in respect of mentally challenged person is an absolute prohibition. The Statutory provision is couched in negative language and as such shall have to be construed mandatory."

Therefore, the person who is mentally challenged and represented by natural guardians' father and mother cannot be a donor for removal of his organs or tissues within the meaning of Section 2(f) of the Transplantation of Human Organs and Tissues Act, 1994.

Also, he cannot be permitted to donate human organ for transplantation in favour of his real brother in view of the bar provided under Section 9(1-C) of the Transplantation of Human Organs and Tissues Act, 1994.

Thanks and regards

Dr KK Aggarwal **Ira Gupta**
Advocate

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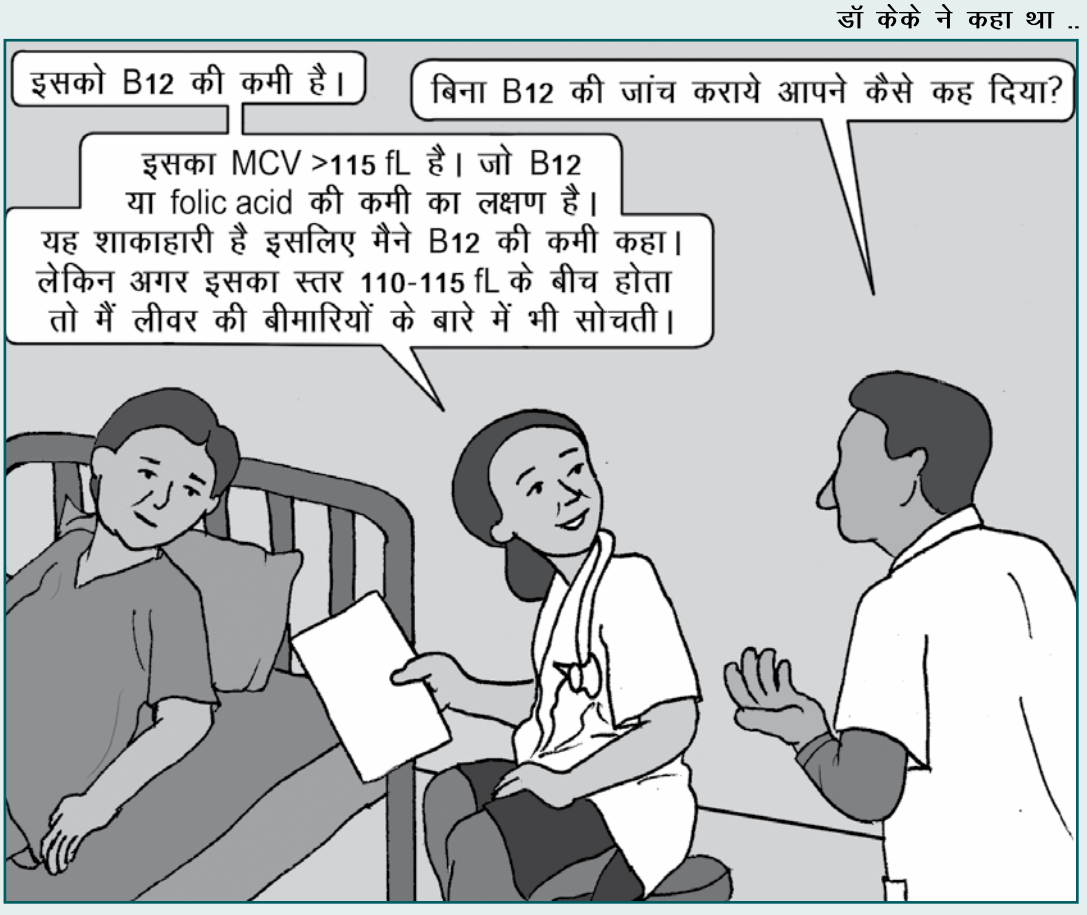
Vitamin B12 Deficiency in Vegetarians



Medical Update 2017

- **Elvitegravir-cobicistat use during pregnancy:** For HIV-infected women who become pregnant while on an elvitegravir-cobicistat-containing regimen switch to a different regimen.[1,2]
- **Acetylcysteine IV or oral does not prevent contrast nephropathy**.[3]
- **Frequency for dosing of oral iron for** individuals with iron deficiency should be every other day rather than every day.[4]
- Patients ≥60 years of age with new onset dyspepsia should undergo an upper endoscopy.[5]
- Patients <60 years with new onset dyspepsia upper GI endoscopy is reserved for those with clinically significant weight loss, overt gastrointestinal bleeding, more than one alarm feature or rapidly progressive alarm features. These patients should be tested and treated for *Helicobacter pylori* infection.[5]
- For patients with suspected multiple myeloma do cross-sectional imaging (low-dose CT, PET/CT, or MRI scan), rather than a skeletal survey, as the imaging modality to detect bone involvement.[6]
- For patients age ≤60 years with an embolic-appearing cryptogenic ischemic stroke who have a patent foramen ovale (PFO) with a right-to-left shunt detected by saline contrast bubble study go for percutaneous PFO closure in addition to antiplatelet therapy, rather than antiplatelet therapy alone.[7-9]
- For patients with RAS/BRAF wild-type (wt) metastatic colorectal cancer (mCRC) and a left-sided primary tumor, treat with an antibody targeting the epidermal growth factor receptor (EGFR), rather than bevacizumab, when a biologic agent is chosen as a component of first-line therapy.[10]
- For most patients with RAS/BRAF wt mCRC and a right-sided primary tumor treat with bevacizumab rather than an anti-EGFR antibody in conjunction with first-line chemotherapy.[10]
- In mild-to-moderate treatment resistant major depression augment the initial antidepressant with a second drug and/or psychotherapy, rather than other strategies such as switching antidepressants or switching from pharmacotherapy to psychotherapy.[11]
- For patients with chronic HCV genotype 1 infection who have not been previously treated with sofosbuvir or an NS5A inhibitor give ledipasvir-sofosbuvir, sofosbuvir-velpatasvir or glecaprevir-pibrentasvir.[12-16]
- For patients with advanced systemic mastocytosis give midostaurin for initial systemic therapy rather than imatinib or other cytoreductive therapies.[17,18]
- In patients with a presumptive diagnosis of acquired TTP administer rituximab as a component of initial therapy.[19]
- For patients with cutaneous melanoma and a positive sentinel lymph node biopsy go for clinical observation and ultrasound surveillance of the positive nodal basin rather than immediate completion lymph node dissection.[20]
- For patients with newly diagnosed ALK-positive NSCLC go for **alectinib as first-line treatment.** For those without access to alectinib, appropriate alternatives include crizotinib or ceritinib. For patients with advanced anaplastic lymphoma kinase (ALK)-positive non-small cell lung cancer (NSCLC), crizotinib has been administered as frontline therapy. However, newer agents have shown promising efficacy in advanced ALK-positive NSCLC.[22,23]
- For patients with an asymptomatic solid or subsolid (pure ground glass or part-solid) solitary pulmonary nodule (SPN) <6 mm, no routine follow-up is required. For patients with solid SPNs that have been stable on serial CT over a 2-year period, or with subsolid SPNs that have been stable over a 5-year period, we suggest no further diagnostic testing.[24]
- For women with postpartum hemorrhage diagnosed within three hours of delivery administer tranexamic acid as a component of overall treatment.[25]
- For patients with ALS who have a disease duration of two years or less, are living independently, and have an FVC ≥80% treat with edaravone and edaravone for patients with more advanced ALS.[26,27]
- For adults with acquired severe aplastic anemia who are not candidates for allogeneic hematopoietic

cell transplantation treat with eltrombopag *plus* standard immunosuppressive therapy (IST) rather than IST alone.[28]

- For patients with primary progressive multiple sclerosis treat with ocrelizumab.[29]
- **Scalp hypothermia can prevent chemotherapy-induced alopecia in** women with breast cancer.[30,31]
- **Do not give** venom immunotherapy (VIT) to patients with reactions to stinging insects limited to cutaneous systemic symptoms and not involving other organ systems. However, VIT is effective in reducing the severity of future reactions and may still be offered in selected situations.[32]
- For most patients with chronic HBV infection who initiate therapy with tenofovir give tenofovir alafenamide rather than tenofovir disoproxil fumarate (tenofovir DF). Those initially started on tenofovir DF switch to tenofovir alafenamide.[33-35]

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69th Annual Conference of Cardiological Society of India (CSI 2017)

WHEN SHOULD I ASK FOR ABPM IN MY HYPERTENSIVE PATIENT WHO IS ALREADY ON TREATMENT?

Dr Anjan Lal Dutta, Kolkata

Ambulatory BP monitoring is done for: White-coat HT; masked HT; early morning surge of BP; suspected episode of HT; patients with high risk CV events, even if clinical BP is normal.

It can also be used to diagnose postural hypotension and syncope. Cost remains an important constraint prohibiting its clinical use where indicated. Discomfort from automatic cuff inflation occasionally causes disturbance to the patient resulting in BP variability.

CLINICAL DILEMMAS IN LIPID MANAGEMENT

Dr Prakash Deedwania, USA

Diabetes is a vascular disease and most patients with diabetes die from CV complications. Diabetes is associated with 2- to 4-fold increase in the risk of MI, stroke, CHD and HF. Most of the macro- and microvascular complications of diabetes can be prevented by comprehensive management of risk factors including lifestyle changes, BP, dyslipidemia and hyperglycemia.

Of all the risk factors, management of dyslipidemia, especially with high intensity statins provides the maximum benefit in terms of reduction in risk of CV events. Although diabetic patients have multiple complex lipid abnormalities based on currently available evidence from large RCTs, most national and international guidelines recommend treatment with moderate-to-high intensity statins in all patients with diabetes regardless of the presence or absence of CV disorder. Additional therapy with fibrates might be needed in select individuals to control hypertriglyceridemia.

CHOICE OF ANTIHYPERTENSIVE THERAPY IN YOUNG INDIVIDUALS: ARE THERE ANY DIFFERENCES FROM THE USUAL PRACTICE?

Dr HK Chopra, New Delhi

"Individualize your patient and create your own protocol"

New AHA/ACC guidelines suggest BP >130/80 mmHg is high; thus, HT burden is further increased especially in India. The trend of uncontrolled HT is high (NCHS Data 2017; AHA/ACC Guidelines for HT Management 2017).

In a study published by our group in IHJ 2007, 65% individuals had obesity (metabolic syndrome). Of these, 78% were hypertensive in hospital-based population aged 40-60 years. It is a "Red Alert" for Indians with 140 million suffering from HT equal to 14% of global burden of uncontrolled HT. WHO data 1980, which showed 80 millions of Indians suffering from HT, which has almost doubled now.

HT is most common cause of premature heart attack, brain attack, abdominal attack and leg attack. It can dissect any vessels at any time and may cause renal failure. Our objective should be to control BP at any cost by any approach. CV events are high with uncontrolled HT, especially in diabetics, obese and young.

Younger hypertensives have higher sympathetic nerve activity, plasma renin activity, norepinephrine levels, high levels of leptins and insulin resistance, especially in obese, increase CO and more compliant vessels vs. elderly with decreased sympathetic nerve activity, plasma renin activity, decreased cardiac output and increased vascular stiffness with increase peripheral vascular resistance and higher mortality and morbidity in both the groups (*Cruickshank et al. JDRT 2016, Framingham Heart Study 2005, Meta-analysis of 18 Studies 2005-2017. HK Chopra et al CDU 2017*). β blockers, especially super selective β_1 receptor blockers lower CVD risk (death, MI, stroke) and mortality in young by reducing sympathetic nerve activity and plasma renin activity (which is also increased by diuretics, ARBs, ACEIs, CCBs) (*Meta-Analysis data from 1960-2017 including ESC, Canadian Hypertension Society, API, CSI, Asia-Pacific Consensus, IJC 2017*).

Despite safe anti-HT drugs, BP control in young is achieved in only 20-30%. AZL is more potent of all sartans and enhances tight BP control due to tight AT_1 receptor binding in diabetes and prediabetes vs. candesartan, valsartan, olmesartan and telmisartan (*Early Registry, Gitt et al. BMC 2016, White et al. JH 2016, Bonner G. et al. JHH 2013*). Target BP reduction, efficacy outcome and safety outcome are reported better with AZL. Recent

ongoing data has shown superiority of AZL over TELS by ABPM in % reduction of nocturnal nondippers, early morning surge, evening surge, persistent time elevation of BP, etc.

β blockers and ARBs are the drugs of 1st choice in young hypertensives. Amongst β blockers super selective β_1 receptor blockers and among ARBs, AZL has been reported to be more efficacious by ABPM and CBPM.

STATINS IN PRIMARY AND SECONDARY PREVENTION OF CAD: ARE THEY FULLY UTILIZED?

Dr K Jai Shankar, Chennai

Primary prevention refers to delaying or preventing the onset of CVD. Secondary prevention relies on early detection of disease process and application of interventions to prevent progression of disease. Primary prevention reduces the risk of MI and HF, decreases the need for coronary revascularization procedures, and extends and improves QoL. It should start with lifestyle modification, including smoking cessation, weight management, diet and physical activity.

The 2013 AHA/ACC guidelines on the management of elevated blood cholesterol no longer specify LDL-C and non-HDL-C targets for the primary and secondary prevention of ASCVD.

The AHA/ACC expert panel found evidence supporting the use of statins for the prevention of ASCVD in many higher-risk primary- and all secondary-prevention individuals without NYHA Class II-IV HF not receiving hemodialysis. In the RCTs reviewed, initiation of moderate-intensity therapy (lowering LDL-C by ~30% to <50%) or high-intensity statin therapy (lowering LDL-C by ~≥50%) was a critical factor in reducing ASCVD events. Moreover, statin therapy reduces ASCVD events across the spectrum of baseline LDL-C >70 mg/dL. For secondary prevention, individuals aged <75 years with clinical ASCVD should be started on high-intensity statin therapy unless contraindicated. In individuals with clinical ASCVD with contraindications to high-intensity statin therapy, but who would otherwise benefit from it, or in persons predisposed to statin-associated adverse effects, a second-line option is moderate-intensity statin therapy, if tolerated. The lipid goal is achieving LDL-C <100 mg/dL; if TGs are >200 mg/dL, non-HDL-C should be <130 mg/dL.

Assess fasting lipid profile in all patients and within 24 hours of hospitalization for those with an acute CV or coronary event. For hospitalized patients, before discharge, initiate lipid-lowering medication as recommended below:

- LDL-C should be <100 mg/dL, and further reduction of LDL-C to <70 mg/dL is reasonable.
- If the baseline LDL-C is 100 mg/dL, initiate LDL-C-lowering drug therapy.
- If the patient is on treatment and LDL-C is 100 mg/dL, intensify LDL-C-lowering drug therapy (may require drug combination [standard dose of statin with ezetimibe, bile acid sequestrant or niacin]).
- If the baseline LDL-C is 70-100 mg/dL, treating to an LDL-C level <70 mg/dL is reasonable.
- If the TGs are 200-499 mg/dL, non-HDL-C should be <130 mg/dL, and further reduction of non-HDL-C to <100 mg/dL is reasonable.

Secondary prevention trials in older persons with CAD and hypercholesterolemia suggest that statins reduced all-cause mortality, CV mortality, coronary events, coronary revascularization, stroke and intermittent claudication.

Raal et al found that lipid-lowering therapy is associated with delayed CV events and prolonged survival in patients with homozygous familial hypercholesterolemia.

DRUGS THAT I CAN'T AVOID KNOWING ABOUT: CANAGLIFLOZIN

Dr Dharmendra Jain, Varanasi

The uniqueness of SGLT2 inhibition is the β-cell independent mechanism of action. Regarding CV risk factor reduction, canagliflozin is now confirmed to be CV beneficial with potential renoprotection in a diverse patient population. It lowers blood glucose levels and BP via osmotic diuresis. It increases urinary caloric loss with reductions in body weight and reduces albuminuria possibly due to alterations in tubuloglomerular feedback. It has shown HF benefits over and above β-blocker and diuretic usage in CANVAS Program. Canagliflozin can be the treatment of choice for diabetic nondippers as it suppress sodium overload during daytime to reduce evening BP and albuminuria.

The safety and efficacy in Indian T2DM patients is well-established. Adverse events leading to discontinuation were similar to placebo. Increased risk of (class effect) UTI, genital mycotic infection and volume depletion related AEs. No increase in the risk of hypoglycemia, acute kidney injury, hyperkalemia, cancer, pancreatitis or VTE was seen with canagliflozin vs. placebo.

LDL-C LEVEL <40 mg/dL: IS IT HARMFUL?

Dr Ananda Bagchi, Kolkata

Every incremental LDL-C level is associated with significant increase in the risk of ASCVD. The potential risk of lowering LDL-C to very low levels (<40 mg/dL) has not been confirmed and its association with conditions like cancer, hemorrhagic stroke, depression, preterm birth, etc. are still under debate as evidences are lacking. It is said that good health may co-exist with prolonged exposure to very low LDL-C levels. Umbilical cord measurements suggest that fetal growth and development occur in the setting of LDL-C <40 mg/dL. Investigators at Brigham and Women's Hospital have shown that PCSK9 inhibitor (evolocumab) when added to statin can lower LDL-C level even to <10 mg/dL, which safely causes additional lowering of CV events without much side effects.

In the recently published FOURIER trial (total 25,982 patients), where again evolocumab has been used for progressive lowering of LDL-C, 10% patients achieved LDL-C level <0.5 mmol/L (20 mg/dL), 31% patients achieved LDL-C level 0.5 mmol/L to <1.3 mmol/L, which showed that there is a monotonic relationship between achieved LDL-C level and major CV outcomes down to LDL-C <0.2 mmol/L and there was no safety concerns over a median period of 2.2 years. Very low LDL-C also did not have a negative impact on cognition, reaction time or memory. So in future, our guidelines may suggest a further lowering of LDL-C goal.

ARNI (LCZ696): ANGIOTENSIN RECEPTOR NEPRILYSIN INHIBITOR

Dr Anil Bharani, Indore

ARNi is a novel drug, first in class, which delivers simultaneous neprilysin inhibition and AT_1 receptor blockade. It is indicated to reduce the risk of CV death and hospitalization for heart failure in patients with HFrEF (NYHA Class II-IV). As per the ACC/AHA and ESC Guidelines 2016, replacement by an ARNi is recommended in patients with chronic symptomatic HFrEF NYHA Class II or III who tolerate an ACEI or ARB, to further reduce morbidity and mortality.

ARNi should not be co-administered with ACEI or within 36 hours of the last dose of an ACEI because of risk of angioedema and should not be administered to patient with a history of angioedema. Hypotension, angioedema, worsening renal functions and hyperkalemia are infrequent untoward effects.

CARDIAC MRI

Dr Vimal Raj, Bengaluru

Cardiac magnetic resonance (CMR) imaging is a one-stop shop for all cardiac problems. It is the gold standard for LV and RV functional assessment. The high spatial resolution make CMR a great method to assess viability.

Cardiac masses can be comprehensively assessed by CMR and it can differentiate between restrictive and constrictive cardiomyopathy.

ULTRATHIN BIOABSORBABLE POLYMER DES: NEW BENCHMARK IN THE FIELD OF DES

Dr Thomas Pilgrim, Switzerland

Ultrathin strut biodegradable polymer sirolimus-eluting stents (Orsiro) are noninferior to newer generation DES with durable polymers (Xience, Resolute) with regards to composite clinical endpoints. Recent evidence suggests superiority of Orsiro vs. Xience with regards to target lesion failure at 12 months.

Patients treated with Orsiro stents were shown to have a lower rate of definite stent thrombosis than those treated with Nobori stents. This difference may be related to the thickness of the metallic stent scaffold. An observed benefit in the subgroup of patients with STEMI in patients treated with Orsiro vs. Xience warrants confirmation in dedicated trials.

TRANSRADIAL ANGIOPLASTY TRUMPS FAILED CABG WITH SUCCESSFUL CTO REVASCULARIZATION

Dr Sanjay Chugh, Jaipur

Complex angioplasty can be done successfully transradially, which is more comfortable for patients because it allows early mobilization and also saves more lives. Risk of bleeding and vascular complications is extremely low with radial access. Radial access should be preferred over femoral access, even for angioplasty in CTO. Angina can recur in post-bypass patients from ungrafted coronaries or failed grafts.

Chronically totally occluded arteries can be revascularized successfully transradially even in post-bypass patients, if they are culprits for angina. A CTO can be approached both antegradely and retrogradely. Antegrade attempt should be made first.

Appropriate guiding catheter and wire selection is important for success. CTO revascularization can be done using slender techniques with 5F guide catheters in patients with small diameter radials in small

individuals including women. Slender techniques are important because a third of our patients are either women or small.

2D STRAIN IN VALVULAR HEART DISEASE: READY FOR PRIME TIME?

Dr Satish C Govind, Bengaluru

Role of 2D strain in echocardiography of valvular heart disease has gained lot of attention over the last few years. Global longitudinal strain (GLS), a robust parameter of 2D strain is used to measure LV function. Circumferential and radial strain have proved to be less reliable and not recommended for routine use. GLS provides incremental information over and above LVEF. It has been widely studied in AS, MR and AR (especially AS) and also in transcatheter interventions like TAVI and Mitraclip procedures.

2D strain as an application and GLS as a measurement tool have shown to be useful in patients having valvular heart disease for studying cardiac mechanics, assessment of risk, predicting adverse events, for prognosis and in selecting patients for valve surgery or percutaneous valve procedures. 2D strain has also been studied in a limited way for RV and LA function in valvular heart disease, but not advocated for routine use though it shows potential to be a useful tool in the future. These are some limitations: Inter-vendor variability, dependence on image quality, affected by age, gender and load, and some technical challenges. 2D strain has shown value, it is robust and is a proven parameter, but due to certain limitations in its methodology and also lack of data in certain areas, it needs to be used with certain care and thought. Guidelines do make a mention, but suggest caution while using it in clinical scenarios. 2D strain in valvular heart is ready for prime time, can be used in routine clinical practice, but should be used in an integrated way and not to be used as the sole or primary parameter to make important decisions in valvular heart disease.

FUNCTIONAL MR IN ISCHEMIC LV DYSFUNCTION: CHALLENGING TO ASSESS AND EVEN MORE CHALLENGING TO TREAT

Dr Niteen V Deshpande, Nagpur

Secondary (functional) MR in patients with ischemic LV dysfunction is a marker of poorer prognosis. It is important to assess mechanism contributing to MR, which should be further evaluated. Although medical therapy is the most common therapy offered, its impact on prognosis is far from satisfactory. Surgical interventions have superior outcomes as compared to medical therapy, either alone or with CRT. MV repair/MVR needs to be considered for patients with severe MR with LV dysfunction. Percutaneous approaches are promising but need more data.

MYOCARDIAL VIABILITY BY MRI

Dr Johann Christopher, Hyderabad

Myocardial viability assessment is essential prior to revascularization of dysfunctional myocardium. Myocardial viability can be assessed by multiple techniques each of which has pros and cons. Cardiac MRI is a noninvasive and nonradiation-based technique. It looks at wall thickness, myocardial perfusion, delayed enhancement and contractile reserve.

The ability to look at all these parameters makes it extremely sensitive and specific compared to all the other competing techniques. MRI scanners are now available across the length and breadth of the country. The scan requires only 1 hour and is extremely cost-effective. I would consider cardiac MRI as the gold standard for the assessment of myocardial viability.

CTO: TIPS & TRICKS

Dr AB Mehta, Mumbai

CTO is encountered in 10-15% of all the cases who undergo coronary angiography for coronary disease. Till about a decade ago, it was the second commonest cause for coronary disease to undergo bypass surgery after valvular heart disease.

Success rate of recanalization of totally occluded major epicardial vessel is close to 90%. Advances in hardware, development of skill and better understanding of pathophysiology have improved the success rate. Restenosis rates after stenting are not very different from non-totally occluded significant coronary lesions.

ATRIAL FLUTTER: A DIFFERENT ARRHYTHMIA FROM ATRIAL FIBRILLATION

Dr Samuel J Asirvatham, USA

Atrial flutter and fibrillation tend to co-exist in the same patient. However, the electrophysiological mechanisms and approach to treatment are very different.

Typical atrial flutter is one of the "conquered" arrhythmias in the field of electrophysiology. However, an entire new genre of atrial flutters has now been discovered and is essentially iatrogenic, occurring in patients who have had ablation for atrial fibrillation or prior surgical procedures.

APICAL DILATATION OF LEFT VENTRICLE

Dr Aniruddha De, Kolkata

A 9-year-old boy presented with cyanosis, clubbing, shortness of breath (Class III) and mild hepatomegaly.

Echo showed large apical VSD with separation of RV apex from the remaining RV by excessive trabeculations, thereby eliminating any left to right shunt across the VSD; a rare and distinct type of morphology and physiology. Physiologically, there was no apparent hemodynamic disturbance. Right ventricular basal cavity size and inflow (tricuspid annular diameter: 16 mm Z score-1.86) and outflow tract were normal. Normal aorta and main pulmonary artery with confluent and good-sized branch pulmonary arteries. Apical segment distal to moderator band was integrated to LV and resultant apical dilatation of LV. Large apical muscular defect of ventricular septum closed by the moderator band.

Cyanosis and clubbing is due to resultant functional hypoplastic RV cavity with increased RV end-diastolic pressure and increased RA pressure with right to left shunt across large ASD. This type of apical VSD constitutes a rare and distinct type of morphology and physiology and has to be considered in patients with suspected LV aneurysm, absence of CAD and lack of any heart murmur.

Our patient was symptomatic with shortness of breath, cyanosed and failed to gain weight with a real challenge in planning his management.

DOES REDUCING LDL TO ULTRA-LOW LEVEL (<25 MG/DL) HAVE ADDITIONAL BENEFIT ON CVD EVENTS OR SAFETY CONCERNS?

Dr AK Pancholia, Indore

Patients achieving very low LDL levels (<25 mg/dL) do not show any increase in clinical and lab side effects vs. those with higher LDL-C or control groups in properly randomized studies.

The CVD events and IVUS data show additional benefits from low (<40 mg/dL) and very low (<25 mg/dL) levels of LDL and increase CVD events when LDL remained elevated.

These evidences are derived from recent PCSK9 inhibitor trials, ODYSSEY LONG TERM (Alirocumab) and FOURIER (Evolocumab). Based on current evidence, the real safety concern is undertreatment of LDL rather than very low LDL. It is very hard to argue that we should reduce the dose of statin simply because the LDL is very low.

FROM HISTOLOGY TO PHYSIOLOGY, CMR HAS ALL THE ANSWERS

Dr Mona Bhatia, New Delhi

Cardiac MRI (CMR) with its high spatial and temporal resolution is excellent for ventricular morphology and functional assessment and is currently the gold standard for both right and left ventricular (RV and LV) volumetric analysis and myocardial mass quantification. The hallmark of CMR is myocardial tissue characterization and gadolinium-enhanced images assist in characterization of myocardial pathology and help differentiate ischemic from nonischemic cardiomyopathy. CMR has a growing role in myocarditis and other infective and inflammatory cardiomyopathies.

In ischemic myocardial involvement, CMR has amongst the highest sensitivity and specificity to answer the 3 critical questions of cardiac function, perfusion and viability for risk stratification, management and prognostication of these patients. In hypertrophic cardiomyopathy, CMR enables accurate LV mass assessment and detailed characterization of HCM phenotype including atypical forms. Myocardial fibrosis detected on CMR has a clinical significance and may reclassify risk prediction and management.

The superior myocardial tissue characterization makes it extremely sensitive in the detection of amyloidosis, noncompaction, arrhythmogenic RV cardiomyopathy and other cardiomyopathies.

Preablation CMR assessment is extremely useful in localization and characterization of myocardial scars, prediction of successful ablation sites and reduction of procedure and fluoroscopy times.

DYSLIPIDEMIA IN YOUNG WITH LDL-C >190 MG/DL

Dr B Kesavamoorthy, Thanjavur

Most patients with LDL >190 mg/dL have polygenic hypercholesterolemia. They are at a very high risk of first and recurrent ASCVD events because of lifetime exposure to markedly elevated LDL-C levels. 10-year ASCVD risk assessment is not indicated in this high-risk population. ≥50% LDL-C reduction on maximal tolerated statin therapy and lifestyle modification are the initial goals.

Ezetimibe PCSK9 inhibitors as initial agent; addition of other as second agent, if needed. Cholesterol absorption inhibitors (ezetimibe) primarily ↓ LDL-C 10-18% ↓ Apo B 11-16%. In combination with statins,

additional ↓ LDL-C 25%, total ↓ LDL-C 34-61%. PCSK9 inhibitors (alirocumab, evolocumab) ↓LDL-C 48-71%, ↓ non-HDL-C 49-58%, ↓ TC 36-42%, ↓ Apo B 42-55%.

In patients with familial hypercholesterolemia unresponsive to drugs and dietary management, lipid apheresis producing acute reduction in LDL-C performed weekly or biweekly should be considered. Lifestyle interventions with high level of evidence to reduce LDL-C and TC include reduction of dietary trans fats, saturated fats and increased intake of dietary fiber, functional foods enriched with phytosterols, red yeast rice supplements and reduction of excessive body weight.

NATIVE COARCTATION IN ADULTS: BALLOON/STENT/ SURGERY?

Dr Sushil Azad, New Delhi

Management of adult coarctation of aorta continues to evolve. Balloon angioplasty alone is associated with less favorable hemodynamic results with more incidence of complications.

Significant improvement in both outcomes and avoidance of acute/intermediate complications have been observed in stent treatment of coarctation of the aorta over the past 10 years. At this time, acute and intermediate follow-up results favor stent treatment of coarctation in adults, though long-term results remain speculative.

Accurate comparisons between the stent/surgery are limited by the paucity of long-term imaging and clinical follow-up data. Further follow-up is required to determine which treatment a particular patient (and coarctation anatomy) should undergo to obtain the best results.

ECHOCARDIOGRAHY IN TETRALOGY OF FALLOT

Dr Munesh Tomar, Haryana

Tetralogy of Fallot (TOF) is a congenital cyanotic heart disease comprised of four anatomic features: Anterior malalignment of the infundibular septum leading to RV outflow obstruction (pulmonic stenosis), VSD, overriding aorta and RV hypertrophy. Echocardiography is the primary imaging method to examine a child with suspected TOF. Important views are: Subcostal coronal and subcostal sagittal, subcostal paracoronal, apical four-chamber, suprasternal long- and short-axis.

2D echo identifies intracardiac anomalies, including pulmonary stenosis (infundibular, valvular, supravalvular), VSD location and size, position of the aortic root over-riding the VSD, ASD, pulmonary annulus size, branch pulmonary arteries confluence and size, coronary artery origin, systemic venous anomaly as bilateral SVC and side of arch.

Color Doppler mapping is used to look for direction of shunt across VSD/ASD, additional VSD (need to reduce color scale), RVOT flow turbulence, PDA/collateral flow and any associated valve regurgitation (AV valve, aortic valve, pulmonary valve in case of TOF absent pulmonary valve), systemic and pulmonary venous connection.

Doppler interrogation of the pulmonary outflow tract is used to measure the velocity gradient in the RVOT and to differentiate severe stenosis from atresia. In small children, echo provides complete information and decision about surgical intervention (single stage or two stage) can be taken on the basis of echo alone.

In small number of children (suspicion of additional VSD, collaterals) and grown up children where acoustic windows are not good, cardiac catheterization or CT pulmonary angiography will be required before surgical intervention.

A DISCIPLINED APPROACH TO HYPERTENSION MANAGEMENT

Dr Saroj Mondal, Kolkata

Treating hypertension reduces the risk of cardiovascular disease (CVD) outcomes. Systolic BP targets to reduce CV morbidity and mortality among persons without diabetes still remain uncertain.

ACC/AHA new guidelines published in *Hypertension* and simultaneously presented at the 2017 AHA Scientific Sessions held from November 11-15 in Anaheim, California have now defined hypertension as a BP ≥130/80 mmHg. Previously published guidelines in 2003 categorized hypertension diagnosis as a BP ≥140/90 mmHg. These new guidelines essentially increase the proportion of hypertensive adults in the United States as well as India.

The 2017 ACC/AHA guidelines also recommend lifestyle modifications, especially for the 9.4% of adults with hypertension who are not appropriate candidates for antihypertensive medications. These include weight loss, smoking cessation, moderation of alcohol consumption and increased physical activity.

A study in *JACC* found that 45.6% of US adults have hypertension under the new ACC/AHA guidelines. Using the expanded definition for hypertension, the researchers theorized that a greater number of individuals will be diagnosed with high BP and will subsequently be prescribed more potent antihypertensive medications.

The investigators of the study suggested that patients are not meeting the new BP target and "a substantial [cardiovascular disease] risk reduction benefit should occur with more intensive antihypertensive medication treatment."

Azilsartan is the latest ARB to be approved by US FDA for hypertension and has been proven to play an important role in reducing the need for treatment compromise in hypertensive patients as well as patients with comorbidities. Despite use of existing ARBs, patients often remained uncontrolled and required a potent, superior and more efficacious ARB for the treatment of hypertension, which was essentially the rationale behind the discovery of Azilsartan.

Clinical trials demonstrated that Azilsartan is more effective at lowering systolic BP by ambulatory BP monitoring than other ARBs (Olmesartan and Valsartan) as well as the ACEI Ramipril. Another trial also demonstrated that addition of Azilsartan to the CCB amlodipine effectively lowers systolic BP while reducing incidence of peripheral edema. In patients with comorbid hypertension along with diabetes or other kidney disorders, Azilsartan has proved to be more effective at BP control than Olmesartan. Azilsartan is a useful and good choice of drug for lowering BP in patients with essential hypertension, particularly for those not able to tolerate ACEIs. The outlook for treating comorbid hypertension also looks positive with use of Azilsartan.

KNOW YOUR DRUG: AZILSARTAN

Dr Sudeep Kumar, Lucknow

As a potent ARB, azilsartan offers greater BP reduction (in mmHg); greater response rate/target BP goal achievement; consistent and larger magnitude of BP reduction over 24 hours; high smoothness index; suppression of sympathetic nervous system; significant reduction in LV mass index; significant reduction in variability of nocturnal SBP.

CIRCADIAN RHYTHM AND TIMING OF ANTIHYPERTENSIVE DRUGS: ANY RELEVANCE?

Dr Mrinal Kanti Das, Kolkata

Concept of circadian variation of BP has entered the clinical domain in 21st century. BP is highest in early to mid-morning and falls progressively all through the day. BP is lowest at night (nocturnal dip) and BP rises before waking (morning surge).

ABPM has consistently shown that sleep-time BP mean is a better predictor of CVD events than daytime or 24-hour BP means. Modification of timing of the drug alters the cicardian rhythm → converts nondippers to dippers (*J Am Soc Nephrol*. 201;22(12):2313-21).

RAAS blockers have been well tried to modify this physiological phenomenon where shifting from morning dose to evening dose is done. Several of pathophysiologic systems responsible for the circadian BP variability, especially salt-balance and the RAAS, can be modulated by appropriate long-term therapy.

The physiological basis of the concept is so overwhelming that it has been appreciated by the Nobel Committee this year to recognize three Physiologists with the Nobel Award in Medicine in 2017.

ABCD OF PHARMACOLOGICAL THERAPY IN HEART FAILURE

Dr VK Chopra, Gurugram

ACEI/ARBs/ARNI and β blockers are neurohormonal modulators and should be used in all HFrEF patients unless contraindicated, as they have been shown to reduce mortality and morbidity.

β blockers should be instituted when the patient is euvolumeic. Both ACEI/ARB/ARNI and β blockers should be uptitrated to the recommended or maximally tolerated dose while watching for their side effects, even if the patients are asymptomatic to reduce mortality. ARNI has been shown to be superior to ACEI in HFrEF. It should be used if patient is symptomatic despite the full dose of ACEI/ARB or *de novo*, if a patient can afford it.

Diuretics are used in volume overloaded patients. Their dose should be gradually reduced after decongestion to the required minimum. Aldosterone antagonists are to be used in patients who continue to be symptomatic despite adequate doses of ACEI/ARB/ARNI, β blockers and diuretics.

Frequent monitoring of BP, heart rate, electrolytes and renal function tests are required in patients on HF therapies. Influenza and pneumococcal vaccinations carry a Class I indication but are underused. For HFpEF patients, apart from diuretics to reduce symptoms, no specific therapy has been shown to reduce mortality and morbidity. As the etiology of HFpEf is varied, treatment of comorbidities improves long-term results.

HFmREF is a newly described entity. Its treatment is being formulated. However, in many patients the treatment is similar to HFrEF.

58th Annual Conference of the Indian Society of Gastroenterology (ISGCON 2017)

GI BLEED UPDATES: NEW TOOLS AND TECHNIQUES

Dr TS Chandrasekar, Chennai

- Endoscopic interventions are the first-line therapy.
- Rebleeding rate increases in-hospital mortality despite optimal endoscopic therapy.
- Newer endoscopic and procedural techniques are needed to improve patient outcomes.
- Cap mounted clips, topical hemostatic agents, fully covered self-expanding metal stents, EUS-guided interventions are getting established in refractory cases.
- Research and randomized controlled trials are needed to assess their efficacy and safety.

FRONTIERS IN SUBMUCOSAL ENDOSCOPIC SURGERY

Dr GV Rao, Hyderabad

- Submucosal space/3rd space: Potential for voluminous increase of space; loose areolar tissue; elastic fibers and collagen that allows the space to stretch.
- Advances in translational science: Removal of mucosal lesions; drug delivery; biopsy of nerve and muscle; removal of intramural lesions; harvesting tissue; placement of stimulating or monitoring devices; reshaping anatomy (e.g. myotomy).
- Submucosal endoscopic surgery: The scope of interventions is expanding; better understanding of the anatomy, physiology and pathology; the outcomes are comparable to surgery; endoscopic techniques and technology are limited; Endoscopy Cooperative Surgery is fast emerging; endoscopists and MIS surgeons are working closely; TEM technology is supportive; robotics could play a vital role in future; opening avenues for metabolic procedures, stem-cell therapy; submucosal implants, stimulating devices, drug delivery modules are under trial.

OPTIMAL TREATMENT FOR UNRESECTABLE HCC

Dr Subrat Kumar Acharya, New Delhi

- Globally, improvement in diagnosis and treatment (curative/palliation) is impressive with 5-year survival reaching 70-75% with curative option and 30% with palliative options.
- In India, the proportion of patients offered any form of treatment in few reported series varies from 15% to 50%, of whom only 25% were eligible for curative options and 75% received palliative options.
- Select patients receive liver transplant.
- Treatment of early HCC - Surgery: Offered to 5-10% patients; 5 year survival after resection can exceed 50%; recurrence rate varies from 27% to 73%; most powerful predictors of recurrence - Presence of microvascular invasion, additional tumor sites besides the primary lesion, tumor free margins.
- Liver transplant seems to have the best results: 5-year survival - 75-80%.
- Need of the hour: Awareness, team, access; screening of high risk to detect early HCC with good liver function - Surgery/Ablation/Transplant; alternative cheaper strategies should be evaluated - Affordability is a problem; downstaging and neoadjuvant therapy.
- The terms neoadjuvant therapy and downstaging are loosely used synonymously; both terms are different and should be specific. The treatment may be same but the aim and objectives are different.

DILEMMA IN DIAGNOSIS OF INTESTINAL TUBERCULOSIS

Dr Vineet Ahuja, New Delhi

- Existing diagnostic tests have poor sensitivity.
- TB PCR, if available, may be done on tissue sample in the diagnostic evaluation of abdominal TB.
- Positive PCR in intestinal tissue sample must be interpreted in light of other clinical, endoscopic and histologic findings.
- Combination of increased visceral fat and long segment involvement is almost exclusive for Crohn's disease (CD); can differentiate CD and intestinal TB with excellent specificity.

- PCR: As a standalone investigation may not be considered diagnostic for intestinal TB.
- Genexpert test: Very specific but has very low sensitivity; more data are required.
- IGRA, Mantoux: Supportive but not definitive.
- Endoscopy: Supportive but not definitive.
- CT/MR: Lymph nodal necrosis; chest CT - PTB; long segment involvement + visceral fat/subcutaneous fat >0.63.
- ATT trial: Mucosal + symptomatic response.
- MDR TB: Multiple biopsies to be taken.
- Isolated small bowel stricture: TB in one-fourth.
- TB stricture resolution: Only in one-fourth after ATT.

DIFFICULT BILIARY AND PANCREATIC CANNULATION

Dr Randhir Sud, Gurugram

- Difficult biliary cannulation: Inability to achieve selective biliary cannulation by standard ERCP techniques within 10 minutes or up to 5 cannulation attempts or failure of access to the major papilla.
- Standard cannulation - Cannula, sphincterotome and wire-guided cannulation is standard.
- Cannulation is intentional continuous contact with ampulla.
- Increased cannulation time, attempts and pancreatic injections increase the risk of post-ERCP pancreatitis (PEP).
- What to do when you fail - Patient safety precedes our desire to succeed. Take preventive steps for PEP: rectal indomethacin, pancreatic stent, hydration; change your cannulation device; repeat procedure after 24-48 hours; seek help of more experienced colleague.
- Advanced techniques: Increase your competence level - Get yourself trained in various cannulation techniques; securing pancreatic duct and cannulating BD: guide wire, stent; pre-cut papillotomy; EUS-guided; PTC-guided.

WHAT TO DO TO GET THE BEST OUTCOME IN EUS-GUIDED FNA?

Dr Vivek Kaul, Rochester, NY

- Goals of optimal EUS-FNA/FNB: Achieve accurate tissue diagnosis; provide adequate tissue for staining: NETs, metastatic lesions from remote organs; minimize false negatives; provide tissue core when needed/indicated; minimize complications.
- Factors impacting diagnostic accuracy of EUS-FNA: Nature and location of lesion; presence of necrosis/inflammation/desmoplasia; ability to visualize lesion adequately; needle size/type and technique used; specimen processing technique; experience of Endoscopist and Cytopathologist.
- EUS-FNA techniques: The best technique is unknown. The best technique is the one that works for you. Customize the technique to the case at hand. General principles: Shortest distance from transducer; short scope position; target periphery in larger lesions; "Fanning" technique usually productive; 5-10 actuations per pass (fast in, slow out).
- Recommendations - Based on current data and best practice: Review patient and case details; confirm indication; proper training and credentialing; no specific technique shown superior to another; use FNB for appropriate indications (including salvage); specimen processing/labeling is critical; general anesthesia may be better.

INHERITED LIVER DISEASES IN ADULTS

Dr Aabha Nagral, Mumbai

- Diagnosis of inherited-metabolic liver diseases requires a high index of suspicion.
- Facilities for diagnosis are improving - trend towards genetic studies rather than enzyme analysis.
- Some diseases are treatable using simple dietary interventions.
- Caution about transplanting patients with multisystem involvement. Genetic counseling is important.

PREDICTING OUTCOME IN SEVERE UC

Dr Ravinder Ogra, New Zealand

About 15-25% of ulcerative colitis (UC) will develop severe colitis. Severe UC is a medical emergency requiring hospitalization. Mortality has reduced from 24% to about 1% with steroid use. About 31-35% are steroid refractory. Nearly 18% of all flares are acute severe UC (ASUC).

Severe UC: Early identification of nonresponders may prevent use of potentially hazardous and futile therapies; help avoid unnecessary delays in surgery.

Ulcerative Colitis Endoscopic Index of Severity (UCEIS) and Salvage: Score ≥7/8: 79% need salvage therapy; score ≥5/8: 50% need salvage; score ≤5/8: only 23% need salvage.

SURGERY IN ULCERATIVE COLITIS

Dr Sujoy Pal, New Delhi

- Indications for surgery in UC: *Emergency* - Refractory ASUC; toxic megacolon; perforation: spontaneous/iatrogenic; massive lower GI bleeding; large bowel obstruction (rare, underlying cancer); *Elective* - Steroid dependent/refractory disease; side effects of steroid/immunosuppressive therapy; high-grade dysplasia/DALM/cancer; noncompliant or cannot afford therapy.
- Timing of surgical intervention is crucial - Early colectomy within 7 days for failed medical therapy for ASUC.
- Procedure of choice in India: Subtotal colectomy (STC) with mucus fistula; restorative proctocolectomy with ileal pouch anal anastomosis (IPAA) (J pouch); minimally invasive surgery techniques: evolving.

HOW TO DO RESEARCH AND HOW TO PUBLISH?

Dr BS Ramakrishna, Chennai

- We all do research every day, but not everyone is interested in or is equipped to do medical research. You need a critical mass of people on whom to bounce your thoughts and hypotheses. Identify funders: Private agencies; Government funding agencies; Pharmaceutical companies.
- Simple principles of good research: clearly state your goal; follow a specified protocol; collect data systematically; analyze data appropriately; review your conclusions and avoid overstatement.
- Write the first draft of your work: Start with methods, then write results, discussion; go back and review.
- Choose the journal: Journal's stated preferences; impact factor of the journal; review cycle for the journal; is the journal open access; is the journal predatory?

MANAGEMENT OF ASCITES: HAS IT BEEN CHANGED?

Dr Virendra Singh, Chandigarh

- Salt restriction and diuretics are the mainstay of treatment.
- Refractory ascites - Discontinue β blockers, add midodrine, therapeutic paracentesis.
- Post-paracentesis circulatory dysfunction - albumin and (?)vasopressors.
- TIPS - better control of ascites, but higher frequency of hepatic encephalopathy.
- Automated low flow ascites (ALFA) pump - requires more trials.
- Liver transplantation.

EXTRAINTESTINAL MANIFESTATIONS OF IBD: INDIAN PERSPECTIVE

Dr AS Puri, New Delhi

- Extraintestinal manifestations (EIM) of IBD - Arthritis; ocular; cutaneous; hepatobiliary and DVT.
- EIM occur in a minority of patients with IBD. Arthritis is the commonest EIM.
- EIM are associated with significant morbidity and mortality. Early recognition and prompt therapy is the key to success. Combined approach with other specialists optimizes the outcome.

INTERPRETATION OF ESOPHAGEAL HIGH RESOLUTION MANOMETRY

Dr Rajesh Sainani, Mumbai

- High resolution esophageal manometry is a gastrointestinal motility diagnostic system that measures intraluminal pressure activity from the pharynx to the stomach using a series of closely spaced pressure sensors.
- Integrated relaxation pressure [IRP] (mmHg): Mean of 4 secs of maximal deglutitive relaxation in the 10 secs window beginning at upper esophageal sphincter (UES) relaxation (contiguous or noncontiguous and referenced to gastric pressure).
- Distal contractile integral [DCI] (mmHg-s-cm): Amplitude × duration × length (mmHg-s-cm) of the distal esophageal contraction >20 mmHg from the transition zone (T) to proximal margin of the LES.
- Contractile deceleration point [CDP] (time, position): The inflection point along the 30 mmHg isobaric contour where propagation velocity slows demarcating peristalsis from ampullary emptying. It must be within 3 cm from the proximal LES margin.

- Distal latency [DL] (sec): Interval between UES relaxation and the CDP.

LIVER REGENERATION AND ITS IMPACT

Dr Ashok Choudhury, New Delhi

- Management of liver failure - Regenerative medicine in hepatology is an unmet need.
- Mechanisms of regeneration - the cells, the niche and the mediators.
- Strategies for liver regeneration - Amelioration of injury; augmentation of regeneration; cell replacement/therapy and tissue engineering.
- Three tier hepatic regeneration orchestra: Tier I - liver cells; tier II - hepatic progenitor cells (HPCs); tier III - bone marrow.

Strategy	Status
Amelioration of injury: Hepatocyte replication; HPCs proliferation; stellate cell dedifferentiation; angiocrine - SDF 1, HGF 1	Not in clinical practice Promising therapies for future
HSC mobilization: G-CSF; G-CSF + EPO	Strong evidence for use
Hepatocyte transplant: Unsorted and sorted	Not in clinical practice
Bioartificial liver: Cryogel based and spheroid	Promising therapies for future
Decellularized liver	Promising therapies for future
Reprogramming of IPSC	Promising therapies for future

ICU CARE IN CIRRHOTICS

Dr Manav Wadhawan, New Delhi

- Identify and reverse precipitating factors to prevent further deterioration of liver functions.
- Support failing organs.
- Infections - Give antibiotics to all cirrhotics needing ICU admission. Choice of antibiotics is as per local antibiogram.
- Management of AKI: *Step 1:* Intravascular volume expansion; 1 g/kg of 20% albumin on Day 1; 20-40 g/day subsequently. *Step 2:* Assess renal functions at 12-24 hours (urine output); improvement - volume responsive prerenal AKI. *Step 3:* No improvement - HRS/ATN; routine urinalysis.
- Coagulopathy - INR and platelet counts are not reflective of true coagulopathy; all replacements should be thrombelastography (TEG)-based.
- Consider TIPS for GI bleed/RA/HRS.
- Provide adequate nutrition and trace element replacement.
- Liver transplant should be considered early in these patients.

ASSESSMENT OF LIVER FIBROSIS: NEWER OPTIONS

Dr Ajay Duseja, Chandigarh

- Assessment of liver fibrosis: Histology; noninvasive biomarkers; elastography is a useful noninvasive tool; newer imaging modalities are still evolving; proteomics will be available in the future.
- Liver biopsy: Gold standard; invasive; complications (3%); sampling error (35%); labor intensive and time consuming; difficult to repeat.
- Liver biopsy: *Newer options* - Stereology; morphometry; quantitative information about the volume, area, length and numerical density in 3D structures using a simple point counting technique or a computer program; computerized image analysis system.
- Noninvasive biomarkers: Class 1 or direct biomarkers; Class 2 or indirect biomarkers.
- MR elastography: Acquisition performed during suspended respiration at full expiration, takes 12-15 seconds; repeated 4 times, total acquisition time <1 minute; processing generates elastograms; anatomic images and confidence images are also provided.
- New imaging modalities: Ultrasound - CEUS; CT - Perfusion CT, Fibro CT MRI; MRI - T1 mapping of liver, SPIO MRI, susceptibility weighted MRI, diffusion weighted MRI, perfusion MRI, MR spectroscopy.

ENDOSCOPIC CLOSURE DEVICES

Dr Mahesh Goenka, Kolkata

- Perforation: Acute full thickness defect in GI tract; Leak: Disruption at a surgical anastomosis resulting in a fluid collection; Fistula: Abnormal communication between two epithelialized surfaces.
- Endotherapy for leaks/fistula: *Limitations:* Large perforation; difficult endoscopic position; fibrosis at the edge; evidence of abscess; stool contamination and tension pneumoperitoneum.
- Choice of endotherapy - Small leak (<10 mm): Through the scope (TTS) clips; large leak (10-30 mm): OTS clip/stent; associated stricture: stent; leak with infective cavity: Endovac.

GENETIC SCREENING IN PANCREATITIS

Dr Rupjyoti Talukdar, Hyderabad

- WHO criteria for disease screening: Screening should be done only for diseases with serious consequences, so that screening tests could potentially have clear benefits to people's health; the test must be reliable enough and not harmful in itself; there must be an effective treatment for the disease when detected at an early stage - and there has to be scientific proof that that treatment is more effective when started before symptoms arise.
- Screening from pancreatitis perspective: Complex disease with heterogeneous natural history; no definitive modality to prevent progression of recurrent acute pancreatitis (RAP) to chronic pancreatitis (CP); no proven preventive strategy (except lifestyle change); no definitive treatment for CP. Of all genes implicated in idiopathic pancreatitis, PRSS1 R122H has >80% penetrance; associated with hereditary pancreatitis (HP) - 50-fold higher risk of developing pancreatic ductal adenocarcinoma (PDAC).
- It is UNLIKELY that genetic testing could confirm the cause of idiopathic recurrent AP. It is LIKELY that genetic testing could predict recurrence of acute episodes of AP (require validation in larger multicenter cohorts; require RCTs to evaluate the translational potential). It is POSSIBLE that genetic testing could predict progression of RAP to CP (require further multicenter large validated studies).
- Genetic testing: Whom and what: Children and young adults with idiopathic RAP (IRAP) with or without PD; family history of pancreatitis in a first or second relative; under approved research protocol: Gene-gene interactions, Gene-environment interactions.
- Genetic testing dos and don'ts: Understand and be clear about indication; be ready to interpret the results in the right perspective; conduct pre-test priming to the patient; provide post-test genetic counseling; be ready to handle the patients' questions.

PANCREATIC CYSTS: OBSERVE OR TREAT?

Dr Santhi Swaroop Vege, Rochester

- Pancreatic cancer is an extremely rare event in pancreatic cysts (Gardner TB, Wu B).
- Surveillance: Pancreatic cysts <3 cm without a solid component or a dilated pancreatic duct (PD) need MRI in 1 year and then every 2 years for 5 years, if no change in size or characteristics. MRI - no radiation, shows communication with PD better, less invasive than EUS. EUS needed for those with at least 2 high risk features (size >3 cm, associated solid component or dilated main pancreatic duct). EUS with FNA has a sensitivity of 60% and specificity of 90%; Those with no concerning features on EUS need MRI after 1 year, then every 2 years till 5 years to ensure no change in risk of malignancy. Sensitivity of EUS and FNA is modest but is counterbalanced by low prevalence of cancer in cysts; Discontinuing surveillance - Stop if no significant change in the characteristics of the cyst after 5 years of surveillance or if the patient no longer a surgical candidate
- When to offer surgery for pancreatic cysts - Those with both a solid component and a dilated PD and/or concerning features on EUS and FNA, to reduce the risk of mortality from cancer.
- Surveillance after surgery: Invasive cancer or dysplasia in a cyst after surgery needs MRI of remaining pancreas every 2 years. If there is no high grade dysplasia or cancer at surgery - no surveillance is required.

INFECTIVE HEPATITIS BEYOND VIRAL HEPATITIS

Dr Dharmesh Kapoor, Hyderabad

- Common causes of nonviral infective hepatitis: Malaria, dengue, *Leptospira, Salmonella* infections, scrub typhus.
- Nonviral hepatitides: Infectious causes; multi-system involvement; liver involvement common, though not dominant; outcome/prognosis may not be dependent on liver affection.
- Weil's disease - Liver involvement is a common feature of leptospirosis. Jaundice (when present) appears within initial 5-9 days of the clinical onset and lasts up to a month.
- Jaundice in leptospirosis: Hepatocellular necrosis; intrahepatic cholestasis; hemolysis; increased bilirubin load from absorption of tissue hemorrhage; marked elevations of bilirubin with mildly elevated transaminases; normal INR.
- Abnormal tests of liver function are common in a host of systemic infections.
- Liver may suffer more injury through systemic factors than the pathogen directly. Common thread runs through most of these infections.
- Presence of cholestasis may affect prognosis. ALF may rarely occur, though multiple causes may lead to the common final pathway.

EMERGING TREATMENT STRATEGIES FOR IRRITABLE BOWEL SYNDROME

Dr Satish SC Rao, Augusta, GA

- Irritable bowel syndrome (IBS) pathogenesis involves visceral hypersensitivity, brain-gut dysfunction, epigenetic factors and psychosocial distress.
- IBS can be diagnosed confidently with symptom-based criteria, and judicious use of diagnostic testing: Celiac serology, CRP, and/or fecal calprotectin may help; biomarkers are evolving for IBS.
- Emerging evidence supports a primary role of diet in managing IBS patients (low FODMAP, fructose or lactose or fructan free diets).
- Evidence-based treatments are directed at predominant symptoms - IBS-D: 5-HT3 agonists, tricyclic antidepressants, rifaximin, eluxadoline and peppermint oil; IBS-C: Linaclotide, plecanatide, lubiprostone, selective serotonin reuptake inhibitors (SSRIs); hypnotherapy and cognitive behavioral therapy are also effective.

I AM INDEBTED TO THE SOCIETY

Dr TS Chandrasekar, Chennai

I am Indebted to the Society - ISG and Society at Large

- I received the National Award "Best Individual for Serving Disabled" from Hon'ble President of India on December 3, 2017.
- We have launched the MedIndia Academy which has conducted 10 International conferences, 26 National Conferences, 14 crash courses in GI Endoscopy and 193 Weekly Gastroenterologists Meetings so far. We have trained over 450 doctors in GI Endoscopy.
- We have created a set of 14 Teaching CD-ROMs in Basic and Advanced GI Endoscopy.
- The post-doctoral fellowship in advanced GI endoscopy was initiated at the Tamil Nadu Dr MGR Medical University in 2011.
- The ISG has launched some state chapters such as the Punjab chapter in September 2017.
- The ISG has tie-ups with the American College of Gastroenterology, the British Society of Gastroenterology and the American Society of Gastrointestinal Endoscopy.
- We brought out the ISG Midterm Book in July 2017 - "Selected Topics in Gastroenterology".
- In a study published in the *Indian Journal of Gastroenterology* in 2013, we determined the predictors of immediate puncture site bleed on withdrawal of needle catheter during endoscopic glue injection without lipidiol. "Catheter pull sign" and "red catheter sign" were excellent predictors of immediate puncture site bleed during endoscopic glue injection.
- Technical determinants for a safe and effective glue therapy: Determinant to ensure complete delivery of glue into varix - Dead-space of injection catheter; Determinant to prevent premature solidification of glue within the injection catheter - Ideal liquid medium; Determinant to ensure complete glue solidification within varix before needle withdrawal - Needle indwelling time.
- In a case report published in 2016 in the *Indian Journal of Gastroenterology*, we demonstrated a new endoscopic method of retrieving a migrated and transmurally embedded intrauterine contraceptive device in the rectum.
- We published a study on novel endoscopic therapy for treatment of pill-induced esophageal ulcer in *Annals of Gastroenterology* in 2008.
- We have brought out a book for public on digestive system and diseases - "Know your digestive system and diseases". We have launched a multilingual website on digestive system and diseases - www.digestivediseasesinfo.com
- We have introduced a Braille chart on hygienic health tips. We have introduced an "Emergency Medical Care Card (emc^2)".
- Need of the hour for ISG: Amendment of constitution; electronic voting system; personal data of ISG members; enrolling of GE PGs to ISG; state members to become national members; ISG Task Force for several other GI disorders; best ISG State Chapter Award to be instituted; ISG shall strive to set an agenda for uniforming training in Gastroenterology across the nation; ISG guidelines shall get referred and cited like ASGE, AASLD, AGA and British Society guidelines.

PEDIATRIC GASTROENTEROLOGY: EXTENDED AND EXPANDED WINGS OF GASTROENTEROLOGY IN INDIA

Dr SK Yachha, Lucknow

- In the year 1984, Pediatric Gastroenterology was born in India with Professor Saroj Mehta conceiving this innovative idea.

- In the year 1987, the three eminent pediatric gastroenterologists Prof Saroj Mehta, Prof VS Sankaranarayanan and Prof SK Mittal launched the National Pediatric Gastroenterology Forum (NPGF).
- NPGF was later converted into Pediatric Gastroenterology subspecialty chapter of Indian Academy of Pediatrics.
- A recommendation was later sent to the Medical Council of India (MCI). A joint committee sent a proposal for starting DM Pediatric Gastroenterology to the MCI. There was a long journey to MCI recognition. The MCI recognized DM Pediatric Gastroenterology in 2002.
- MCI approved and notified in the Gazette of India in September, 2009. The first batch of DM was started in 2011.
- Training programs: *Sanjay Gandhi Postgraduate Institute of Medical Sciences (SGPGIMS), Lucknow:* Post-doctoral certificate course (PDCC) Pediatric Gastroenterology 2 seats/year in 2002 – Increased to 4 seats/year in 2009; DM Pediatric Gastroenterology 2 seats/year. *PGIMER, Chandigarh:* DM Pediatric Gastroenterology 2 seats/year. *ILBS, New Delhi:* DM Pediatric Hepatology 1 seat/year; PDCC Pediatric Hepatology 2-4 seats/year.
- A consensus report on neonatal cholestasis syndrome was published in *Indian Pediatrics* in 2000. Issues of EHPVO and celiac disease are being addressed in children.
- There are unique studies on complications of portal hypertension.
- We have a study on safety, complications and outcome of large volume paracentesis with or without albumin therapy in children with severe ascites due to liver disease, published in the *Journal of Hepatology* in 2015. There is exclusive pediatric literature on Budd-Chiari syndrome. We are looking at new dimensions in acute viral hepatitis.
- There is increased awareness for autoimmune liver disease in children. There is a dire need for special effort for hypoallergic formulations.

DIAGNOSTIC APPROACHES TO *CLOSTRIDIUM DIFFICILE* INFECTION

Dr Chetana Vaishnavi, Chandigarh

- *Clostridium difficile* infection (CDI) diagnostic testing is an important issue.
- A variety of testing methodologies are available: Endoscopy may show multiple yellow-white friable plaques; it can help avert emergency abdominal surgery. Radiology is most useful in PMC cases localized to proximal colon; may reveal colonic distension, thickening, pericolonic inflammation or free air. Culture - It is a low-cost, sensitive and good method; efficiency varies from lab to lab; but it is unattractive as a screening test. Tissue culture cytotoxin test - Gold standard test; detects toxin B; but it is cumbersome and expensive as well as time consuming; 30% patients are missed. Enzyme immunoassays (EIA) - Test for toxin A, toxin A/B, toxin B and GDH; necessitates batching of samples. Toxigenic culture - Gold standard; approved by US FDA. Molecular techniques - Rapidly detect toxin B gene in stool samples; highly accurate; sensitivity of PCR is greater than EIA.
- Best standard lab test for CD diagnosis has not been established for 30 years.
- Currently two reference assays are available with different targets: Cytotoxicity assay - detects free toxins; and toxigenic culture - organism with potential to produce toxin.
- Clinical laboratory professionals should use assays which give best performance for CDI detection.
- Laboratories may use >1 testing platform in reflexive or algorithmic approaches when assessing *C. difficile* diagnosis.
- Points to ponder: Testing of stool from patients without clinical indication of CDI is an unnecessary expense; testing for CDI should be based on age/LOS/antibiotic exposure; do not test formed stools when assessing for CDI; do not test children under 1 year of age; discourage repeat stool testing.

■■■■

News and Views

Half the World Lacks Access to Essential Health Services

At least half of the world's population cannot obtain essential health services, according to a new report "Tracking Universal Health Coverage: 2017 Global Monitoring Report" from the World Bank and WHO. And each year, large numbers of households are being pushed into poverty because they must pay for healthcare out of their own pockets.

Currently, 800 million people spend at least 10% of their household budgets on health expenses for themselves, a sick child or other family member. For almost 100 million people these expenses are high enough to push them into extreme poverty, forcing them to survive on just $1.90 or less a day. The report has been simultaneously published in *Lancet Global Health*. The report is a key point of discussion at the global Universal Health Coverage Forum 2017, currently taking place in Tokyo, Japan… (*WHO, December 13, 2017*).

Exposure to Terror may Increase Risk of Headaches Including Migraine

According to a study published online December 13, 2017 in the journal *Neurology*, people who survive a terror attack are at an increased risk of frequent migraine and tension headaches after the attack. The teens who had been exposed to terror were four times more likely to have migraines and three times more likely to have frequent tension headaches than the teens who were not exposed to terror.

New ACC Guidelines for Management of Bleeding in Patients on Oral Anticoagulants

The American College of Cardiology (ACC) has published an expert consensus decision pathway on management of bleeding in patients on oral anticoagulants in the December 19, 2017 issue of the *Journal of the American College of Cardiology*. The guideline includes decision pathways on how to assess severity and define bleeding, whether major or minor and how to manage them.

A New Tool to Get Updates on Antibiotics

The US Food and Drug Administration (FDA) has announced a new website to get critical updates regarding antibiotics and antifungal drugs to healthcare professionals as part of an overall effort to control antimicrobial resistance. A website that will provide direct and timely access to information about when bacterial or fungal infections are likely to respond to a specific drug. The information will help healthcare professionals in making more informed prescribing decisions that will both benefit their patients and prevent the spread of resistant bacteria.

Ketamine Reduces Suicidal Ideation in Depressed Patients

Administration of adjunctive subanesthetic intravenous ketamine in patients on antidepressants reduced clinically significant suicidal ideation in patients with major depression within 24 hours compared with midazolam, partially independently of antidepressant effect. The study is published online December 5, 2017 in the *American Journal of Psychiatry*.

Noninvasive Cardiac Radioablation Effectively Ablates VT, Says Study

In five high-risk patients with refractory ventricular tachycardia, noninvasive treatment with electrophysiology-guided cardiac radioablation markedly reduced the burden of ventricular tachycardia, reported a study published December 14, 2017 in the *New England Journal of Medicine*.

Breathing Exercises Help Asthma Patients Improve QOL

According to a study published in the journal *The Lancet Respiratory Medicine*, teaching breathing exercises to patients with incompletely controlled asthma, even with standard treatment, improves their quality-of-life (QOL) despite having little effect on lung function or airway inflammation.

Up to 6,50,000 People Die of Respiratory Diseases Linked to Seasonal Flu Each Year

Up to 6,50,000 deaths annually are associated with respiratory diseases from seasonal influenza, according to new estimates by the United States Centers for Disease Control and Prevention (CDC), the World Health Organization (WHO) and global health partners. This marks an increase on the previous global estimate

of 2,50,000-5,00,000, which dates from over 10 years ago and covered all influenza-related deaths, including cardiovascular disease or diabetes. The new figures of 2,90,000-6,50,000 deaths are based on more recent data from a larger, more diverse group of countries, including lower middle income countries, and exclude deaths from nonrespiratory diseases.

According to US-CDC, most deaths occur among people aged over 75 years, and in the world's poorest regions. Sub-Saharan Africa accounts for the world's greatest flu mortality risk, followed closely by the Eastern Mediterranean and Southeast Asia. "These figures indicate the high burden of influenza and its substantial social and economic cost to the world," said Dr Peter Salama, Executive Director of WHO's Health Emergencies Programme. "They highlight the importance of influenza prevention for seasonal epidemics, as well as preparedness for pandemics."… (*WHO, December 14, 2017*).

Higher Blood Sugar in Early Pregnancy Raises Risk of Congenital Heart Disease

According to a study published online December 15, 2017 in the *Journal of Pediatrics*, higher blood sugar levels early in pregnancy increase the risk of congenital heart disease, even in mothers who do not have diabetes.

Exposure to Coarse Particulate Matter Increases Risk of Asthma in Children

Long-term exposure to coarse particulate matter (PM10-2.5) increased the risk of asthma by 0.6% in children independent of exposure to fine particulate (PM2.5) pollution, says a study published December 12, 2017 in the *American Journal of Respiratory and Critical Care Medicine*. Risk of hospitalizations for asthma increased by 2.3%. These children were 1.7 times more likely to require emergency care for asthma.

Active Surveillance as First-line Management in Low-risk Papillary Thyroid Carcinoma

According to findings of a 10-year study of more than 1,200 patients with low-risk papillary microcarcinoma (PMC) of the thyroid, active surveillance can be the first-line management in these patients. Of these, older patients with low-risk PMCs make the best candidates for active surveillance. The study is published in the January 2018 issue of the journal *Thyroid*.

2018 ADA Standards of Care Recommend BP Home Monitoring for Hypertensive Patients with Diabetes

The American Diabetes Association (ADA) 2018 Standards of Medical Care in Diabetes recommend that all hypertensive patients with diabetes should also monitor their blood pressure at home to identify white coat hypertension, masked hypertension or other discrepancies between office and home blood pressure, and also to improve adherence to medication.

Individualizing Glycemic Control Reduces Cost of Treatment

According to a study published online December 10, 2017 in the *Annals of Internal Medicine*, individualizing HbA1c goals for adults with type 2 diabetes reduces cost of treatment and also improves quality-of-life compared with a uniform intensive control for all patients.

Another Infliximab Biosimilar Approved by US FDA

The US Food and Drug Administration (FDA) has approved Ixifi (infliximab-qbtx) as a treatment for patients with rheumatoid arthritis (RA), Crohn's disease, pediatric Crohn's disease, ulcerative colitis, ankylosing spondylitis, psoriatic arthritis and plaque psoriasis. Ixifi is a chimeric human-murine monoclonal antibody against tumor necrosis factor.

Electronic Waste Poses 'Growing Risk' to Environment and Human Health, Says UN

The United Nations has warned that the growing volume of electronic waste, including discarded products with a battery or plug, such as mobile phones, laptops, televisions, refrigerators and electrical toys, poses a major threat to the environment and human health. The "Global E-Waste Monitor 2017", released by ITU, the UN University (UNU) and the International Solid Waste Association (ISWA), highlights increasing levels of e-waste and its improper and unsafe treatment and disposal through burning or at dumpsites. In 2016, 44.7 million metric tonnes of e-waste were generated, an increase of 3.3 million metric tonnes, or 8%, from 2014. Also, in 2016, only about 20%, or 8.9 million metric tonnes, of all e-waste was recycled. Experts foresee e-waste increasing a further 17% to 52.2 million metric tonnes by 2021… (*UN, December 13, 2017*).

A New Treatment Option for Raised Seborrheic Keratoses

The US Food and Drug Administration (FDA) has approved a high-concentration hydrogen peroxide topical solution (Eskata, Aclaris Therapeutics) for the treatment of raised seborrheic keratosis, which are noncancerous skin growths.

Study finds ED to be a Warning Sign for Early Heart Disease

A systematic review and meta-analysis of 28 studies has found a significant association of erectile dysfunction (ED) with impaired endothelial function and a 0.09-mm higher carotid intimal medial thickness (cIMT), an early manifestation of atherosclerosis suggesting a link between ED and early heart disease.

Ozenoxacin Cream Approved for Use in Impetigo in Infants

The US Food and Drug Administration (FDA) has approved ozenoxacin cream 1% for impetigo in patients aged 2 months and older. A quinolone antimicrobial, ozenoxacin cream is to be applied twice daily for 5 days.

Discontinuing bDMARDs Increases the Risk of Relapse in RA Patients

A study published online November 29, 2017 in the *Annals of the Rheumatic Diseases* has found that discontinuing biological disease-modifying antirheumatic drugs (bDMARDs) increases the risk of losing remission or low disease activity and radiographic progression in patients with rheumatoid arthritis (RA). Whereas tapering the dose of bDMARDs does not increase the risk of relapse or radiographic progression of disease, even though there is an increased risk of losing remission.

Blepharitis may be an Early Sign of Metabolic Syndrome

Blepharitis may be an early sign of metabolic syndrome, suggests a new study published online November 16, 2017 in the *British Journal of Ophthalmology*, which found increased chances of developing new metabolic syndrome in patients with blepharitis as also a higher association of hyperlipidemia and coronary artery disease in these patients.

Use of ABPM Identifies Different Types of Hypertension in Postpartum Period

A study of women with pre-eclampsia published November 13, 2017 in the journal *Hypertension* found on 24-hour ambulatory BP monitoring (ABPM) that 50% of pre-eclampsia women were still hypertensive in the postpartum period. Of these, 24.3% were still under antihypertensive treatment; 17.9% displayed a white-coat hypertension and 11.6% had masked hypertension.

Number of People with Dementia to Triple in Next Three Decades

As the global population ages, the number of people living with dementia is expected to triple from 50 million to 152 million by 2050. "Nearly 10 million people develop dementia each year, 6 million of them in low- and middle-income countries," says Dr Tedros Adhanom Ghebreyesus, Director-General of WHO. "The suffering that results is enormous. This is an alarm call: we must pay greater attention to this growing challenge and ensure that all people living with dementia, wherever they live, get the care that they need." The estimated annual global cost of dementia is US$ 818 billion, equivalent to more than 1% of global gross domestic product. The total cost includes direct medical costs, social care and informal care (loss of income of carers). By 2030, the cost is expected to have more than doubled, to US$ 2 trillion, a cost that could undermine social and economic development and overwhelm health and social services, including long-term care systems … (*WHO, December 7, 2017*)

Study Links HDL Cholesterol to Higher Risk of Infections

A study published online December 8, 2017 in the *European Heart Journal* has demonstrated a U-shaped association between concentrations of HDL cholesterol and risk of any infection, especially gastroenteritis and bacterial pneumonia.

VMR is Strongly Associated with Risk of Hip Fracture

A new study reported in the journal *Bone* has suggested that evaluating vitamin D status by incorporating assessment of 24,25(OH)D and the vitamin D metabolite ratio (VMR) provides information on bone health above and beyond 25(OH)D alone.

Tamsulosin Facilitates Passage of Larger Distal Ureteral Stones

A new study published online November 11, 2017 in *European Urology* has suggested a superior expulsion rate of tamsulosin for distal ureteral stones >5 mm in size. No such effect was noted for stones ≤5 mm. Tamsulosin was associated with a shorter time to expulsion, less recurrent colic and fewer analgesics.

FDA Reaffirms Concerns with the Use of Laparoscopic Power Morcellators to Treat Uterine Fibroids

FDA's Center for Devices and Radiological Health (CDRH)'s most recent assessment of using laparoscopic

power morcellators (LPM) to treat presumed uterine fibroids has confirmed the concerns outlined in our 2014 safety communication which discouraged the use of these products for this indication. Women with unsuspected uterine sarcoma who undergo morcellation of presumed benign fibroids are at risk for mechanical spread of cancerous tissue and worsened clinical outcomes.

PAHO/WHO Launches Regional Movement for Universal Health

A regional movement for universal health has been launched by representatives of government, academia, civil society and experts from some thirty countries and territories of the Americas to identify obstacles and generate alliances to help countries reach the goal of health for all by 2030, without leaving anyone behind. The Director of the Pan American Health Organization (PAHO), Carissa F. Etienne, affirmed that "universal health is more necessary than ever" and said that the way to achieve it "is not easy, but it is possible and urgent". Launched on the World Day of Universal Health Coverage, the initiative, called the Regional Universal Health Forum in the 21st century: 40 years of Alma-Ata, is composed of representatives of government, academia, civil society and experts from around thirty countries and territories of the region… (*PAHO/WHO, December 12, 2017*).

Children with Congenital Zika Virus Infection Face Serious Health and Developmental Challenges

Most children born with microcephaly and evidence of congenital Zika virus infection face severe health and developmental challenges at ages 19-24 months such as an inability to sit independently, difficulties with sleeping and feeding, seizures and hearing, says a study published December 14, 2017 in *Morbidity and Mortality Weekly Report (MMWR)*.

Cardiac Parasympathetic Autonomic Dysfunction Common in Inflammatory Joint Disorders

Patients with inflammatory joint disorders have cardiac parasympathetic autonomic dysfunction, which is related to inflammation. In a meta-analysis study published December 2, 2017 in the journal Seminars in Arthritis and Rheumatism, patients with rheumatoid arthritis and spondyloarthritis had lower markers of heart rate variability.

Drinking Hot Tea Reduces Risk of Glaucoma

A study evaluating the association between consumption of coffee, tea or soft drinks, and glaucoma in the participants of the 2005-2006 National Health and Nutrition Examination Survey (NHANES) and published online in the *British Journal of Ophthalmology* has found that participants who consumed hot tea daily were less likely to have glaucoma than those who did not consume hot tea, while no significant associations were found between the risk of glaucoma and consumption of coffee, iced tea, decaffeinated tea and soft drinks.

BP Variability Predicts TOD in Elderly Hypertensive Patients

Blood pressure (BP) variability may be an important predictor of target organ damage in elderly patients with essential hypertension, says a study reported in the December 2017 issue of the journal *European Review for Medical and Pharmacological Sciences*. The 24 h systolic BP variability was associated with carotid artery intima-media thickness, left ventricular mass index and 24-hour microalbuminuria.

Study Finds Association of Relative Glycemia with Insulin Treatment with Adverse Outcomes Post-MI

Relative hyperglycemia during insulin treatment, but not absolute, is associated with mortality, heart failure, arrhythmia, cardiogenic shock following an acute myocardial infarction, according to a post-hoc analysis of HI-5 study published December 12, 2017 in the journal *Cardiovascular Diabetology*.

Younger Newly-diagnosed Patients with Type 2 Diabetes at High-risk of Complications

A new study published in the journal *Diabetes/Metabolism Research and Reviews* online December 12, 2017 has shown that younger persons newly-diagnosed with type 2 diabetes are at a high risk of delayed complications vs. type 2 diabetes patients who first contract the disease two decades later in life. Early signs of kidney damage were detected in 20% of the younger patients.

NPPA Fixes Prices of 65 Scheduled Formulations

NPPA has fixed/revised ceiling prices/Retail Prices of 65 scheduled formulations under Drugs (Prices Control) Order, 2013 in related Notification/order dated 18.12.2017. The list includes antibiotics and drugs used for the treatment of hypertension, diabetes, pain among others. The complete list of the 65 drugs is available on NPPA website (http://www.nppaindia.nic.in/)… (NPPA)

Abuse in Childhood Increases Risk of Future Heart Disease

Children and teens who are abused, witness violence, are bullied or face other adversities are more likely to develop heart and blood vessel diseases as adults, according to a new scientific statement by the American Heart Association published December 18, 2017 in the journal *Circulation*. This increased risk has been attributed to unhealthy responses to stress (such as overeating), mental health problems and disruptions in basic biologic processes.

Bortezomib Fails in Cases of Late Antibody-mediated Kidney Transplant Rejection

In a trial of kidney transplant recipients with late antibody-mediated rejection, treatment with bortezomib failed to improve the function of transplanted kidneys and prevent immunologic tissue injury, says a study published online December 14, 2017 in the *Journal of the American Society of Nephrology*. Bortezomib treatment was also associated with gastrointestinal and hematologic toxicity.

US FDA Approves Tofacitinib for Active Psoriatic Arthritis

The US Food and Drug Administration (FDA) has approved tofacitinib for treatment of adults with active psoriatic arthritis (PsA) who have failed to respond adequately or are intolerant to methotrexate or other disease-modifying antirheumatic drugs (DMARDs). Tofacitinib is a selective oral Janus kinase (JAK) inhibitor, which acts by interrupting signaling of several cytokines involved in immune response.

ACAAI Guidelines Say No Special Precautions Needed for Flu Shots for People with Egg Allergy

In an update to its guidelines on administration of influenza vaccines to egg allergic recipients, the American College of Allergy, Asthma and Immunology (ACAAI) has said that no special precautions are required or recommended for those with egg allergy and stresses that people with egg allergy should receive their annual flu vaccination. The updated practice parameter is published online December 19, 2017 in the *Annals of Allergy, Asthma and Immunology*.

EMA Grants Marketing Authorization to Alkindi for Treatment of Primary Adrenal Insufficiency

The European Medicines Agency's (EMA) Committee for Medicinal Products for Human Use (CHMP) has recommended granting a paediatric-use marketing authorization for Alkindi (hydrocortisone) for the treatment of primary adrenal insufficiency, a rare hormonal disorder, in infants, children and adolescents

High Uric Acid Levels Predict Progression of Prehypertension to Hypertension

Increased serum uric acid is a strong risk marker for developing hypertension from prehypertension, says a 5-Year Japanese Cohort Study published December 4, 2017 in the journal *Hypertension*. The cumulative incidence of hypertension in the study participants with hyperuricemia was significantly higher than those without hyperuricemia; 30.7% versus 24.0%, respectively.

India Ranks 100 Out 119 Countries in Global Hunger Index

As per 2017 Global Hunger Index (GHI) Report, published by the International Food Policy Research Institute (IFPRI), India ranks 100 out 119 countries. The Global Hunger Index is a tool designed to comprehensively measure and track hunger at the global, regional, and national levels. The International Food Policy Research Institute (IFPRI) calculates GHI scores each year to assess progress and setbacks in combating hunger. To capture the multidimensional nature of hunger, GHI scores are based on four indicators as follows:

- Undernourishment: The share of the population that is undernourished (that is, whose caloric intake is insufficient);
- Child wasting: The share of children under the age of five who are wasted (that is, who have low weight for their height, reflecting acute under-nutrition);
- Child stunting: The share of children under the age of five who are stunted (that is, who have low height for their age, reflecting chronic under-nutrition); and
- Child mortality: The mortality rate of children under the age of five (in part, a reflection of the mix of inadequate nutrition and unhealthy environments).

In a written reply in the Lok Sabha, Minister of State (Health and Family Welfare), Sh Ashwini Kumar Choubey stated that Government has implemented following interventions to tackle the problem of hunger in the country and to improve the position in GHI:

- Provision of food grains at highly subsidized prices to the targeted population through State

Governments/UT Administrations under the Targeted Public Distribution System (TPDS) in terms of Nation Food Security Act, 2013 and Other Welfare Schemes (OWS) such as Mid-Day Meal Scheme, Integrated Child Development Services (ICDS) Scheme, Rajiv Gandhi Scheme for Empowerment of Adolescent Girls, Annapurna Scheme, etc.

- National Food Security Act (NFSA), 2013 provides for coverage of up to 70% of the rural and up to 50% of the urban population thus covering about two-third of the population, for receiving food grains at highly subsidized prices of Rs. 3, 2 and 1 per kg. for rice, wheat and coarse grain, respectively under TPDS. The Act also has a special focus on nutritional support to women and children.
- Recently National Nutrition Mission has been approved under MWCD for addressing malnutrition status of the country in a comprehensive manner.

(Press Information Bureau, Ministry of Health and Family Welfare, December 18, 2017)

US FDA Approves Novel Gene Therapy to Treat Patients with a Rare Form of Inherited Vision Loss

The US Food and Drug Administration has approved Luxturna (voretigene neparvovec-rzyl), a new gene therapy, to treat children and adult patients with an inherited form of vision loss - biallelic RPE65 mutation-associated retinal dystrophy - that may result in blindness. It is the first directly administered gene therapy approved in the US, which targets a disease caused by mutations in a specific gene.

USPSTF Draft Recommendations Say no to ECG Screen for CVD Risk and Atrial Fibrillation

In two draft statements posted on its website, the US Preventive Services Task Force (USPSTF) has recommended against ECG to screen for atrial fibrillation adults aged 65 and older without a prior diagnosis of the arrhythmia or screening for cardiovascular disease risk. As per the USPSTF, adults at low risk for heart attack or stroke should not be screened with ECG; there is insufficient evidence on ECG screening in adults at medium or high risk. The Task Force also found insufficient evidence on ECG screening for atrial fibrillation.

Varenicline Associated with Increased Risk of Adverse Cardiovascular Events

A study published December 20, 2017 in the *American Journal of Respiratory and Critical Care Medicine* has shown a 34% increase in the incidence of a cardiovascular event (hospitalizations and ER visits) with varenicline.

CABG Superior to PCI in Diabetic Patients with Multivessel CAD

According to a study published December 19, 2017 issue of the *Journal of the American College of Cardiology*, compared to PCI for both acute coronary syndrome and stable ischemic heart disease, coronary artery bypass grafting (CABG) surgery was associated with a lower rate of long-term major adverse cardiac or cerebrovascular events (MACCE) in diabetic patients with multivessel coronary artery disease (CAD).

Fecal Transplant is a Safe and Effective Treatment for Recurrent *C. difficile* Infection

In patients with recurrent *Clostridium difficile* infection, treatment with fecal microbiota transplantation resulted in faster improvement of bowel habits, less irregular bowel function and less upper GI symptoms in comparison to patients treated with antibiotics. The study is published online December 11, 2017 in *Alimentary Pharmacology & Therapeutics.*

'Critical Windows' During Youth to Prevent Adult Obesity

As per a study published in the January 2018 issue of the journal *Pediatrics*, compared to people who will develop adult obesity, people who avoid obesity as an adult had a lower BMI at age 6 and a lower yearly change in BMI in childhood. BMI levels were found to stabilize from 16 years for females and 21 years for males, while BMI kept increasing until age 25 (for males) and 27 (for females) for overweight or obese children who persisted with obesity into adulthood.

Survey on Prevalence of TB

Thirty-nine percent of India's population is not suffering from Tuberculosis. RNTCP is conducting a TB prevalence survey which will provide information specific for the country in the year 2018. The National Strategic Plan (NSP) for Tuberculosis (2017-25) has been formulated by the Ministry of Health and Family Welfare. In addition to the existing strategies under RNTCP, the NSP focusses on:

- Early diagnosis of all the TB patients, prompt treatment with quality assured drugs and treatment regimens
- Suitable patient support systems to promote adherence.

- Engaging with the patients seeking care in the private sector.
- Prevention strategies including active case finding and contact tracing in high risk/vulnerable population.
- Use of ICT tools for effective monitoring of patients.
- Multi-sectoral response for addressing social determinants.

(Press Information Bureau, Ministry of Health and Family Welfare, December 19, 2017)

Unmarried Heart Patients are at Higher Risk of Death

Compared to married heart disease patients, being unmarried was associated with a 24% higher risk of death from any cause, 45% higher risk of death from cardiovascular disease and 52% higher risk of cardiovascular death/heart attack, according to new research published December 20, 2017 in *Journal of the American Heart Association*.

Underactive Thyroid within Normal Range may Cause Unexplained Infertility

New research published December 19, 2017 in the *Journal of Clinical Endocrinology & Metabolism* suggests that a slightly underactive thyroid may affect a women's ability to become pregnant-even when the gland is functioning at the low-end of the normal range. Nearly twice as many women with unexplained infertility had a TSH >2.5 mlU/L than women whose partners had male factor infertility.

Eating Salads Daily may Slow Down Brain Aging

According to a study published online December 20, 2017 in the journal *Neurology*, people who ate at least one serving of green, leafy vegetables a day had a slower rate of decline on tests of memory and thinking skills than people who never or rarely ate these vegetables suggesting that eating about one serving per day of green, leafy vegetables may be linked to a slower rate of brain aging.

Combination of OCP and Bicalutamide is an Effective Treatment for Severe Hirsutism in PCOS

A combination of oral contraceptive pill (OCP) and bicalutamide (antiandrogen) is significantly more effective and well-tolerated compared to OCP alone as treatment for severe hirsutism in women with polycystic ovary syndrome (PCOS). These findings from a study were published December 1, 2017 in the *Journal of Clinical Endocrinology & Metabolism*.

New Guidelines on Management of Abnormal Liver Blood Tests

Updated guidelines on the management of abnormal liver blood tests have been published online December 12, 2017 in the journal *Gut*. New recommendations, led by experts at the University of Birmingham, have been published to improve the use of liver blood tests. The guidelines recommend that initial investigation for potential liver disease should include bilirubin, albumin, alanine aminotransferase (ALT), alkaline phosphatase (ALP) and γ-glutamyltransferase (GGT), together with a full blood count if not already done in the last 1 year. Also, the abnormal results should only be interpreted after review of the previous results, past medical history and current medical condition.

Updated EAU Recommendations for Treatment of Metastatic Clear Cell Renal Cancer

Updated EAU guidelines recommend a combination of ipilimumab and nivolumab as first-line treatment in intermediate- and poor-risk patients with metastatic clear cell renal cancer. A VEGF tyrosine kinase inhibitor should be used as second-line treatment when the use of this combination is not safe or feasible. These new recommendations are published online December 6, 2017 in *European Urology*.

WHO Develops a Draft Global Action Plan to Promote Physical Activity

WHO has developed a draft global action plan to promote physical activity after wide consultation with Member States, international experts and other stakeholders, which will be submitted to the 142nd WHO Executive Board in January 2018. As per the draft, there are multiple ways to be active, which offer multiple health benefits. The target for this global action plan is a 15% relative reduction in the global prevalence of physical inactivity in adults and in adolescents … (*WHO*).

US FDA Approves Giapreza to Treat Dangerously Low Blood Pressure

The US Food and Drug Administration (FDA) has approved Giapreza (angiotensin II) as intravenous infusion to treat dangerously low blood pressure in adults with septic or other distributive shock. Giapreza can cause dangerous blood clots with serious consequences, so, prophylactic treatment for blood clots should be used.

Women More Likely to have Mental Stress-induced Constricted Blood Vessels

In women with heart disease, constriction of peripheral vessels during mental stress affects the heart circulation more than men's, potentially raising women's risk of heart-related events and death, according to new research in Arteriosclerosis, Thrombosis and Vascular Biology.

ACOG Committee Opinion on Cascade Testing for Cancer Related Mutations

The American College of Obstetricians and Gynecologists (ACOG) has published a new Committee Opinion online December 21, 2017, on cascade testing and recommends that ob-gyns should be aware of and incorporate cascade testing and counseling into their practices to effectively respond to patients who have been informed that they have a relative with a genetic mutation. Cascade testing is the performance of genetic counseling and testing in blood relatives of individuals who have been identified with specific genetic mutations. Cascade testing may include screening, counseling or referral for a patient with a relative who has tested positive for a genetic mutation.

US FDA Removes Boxed Warning on LABA + ICS Combination for Asthma and COPD

In an updated drug safety communication released on December 20, 2017, the US FDA has removed the Boxed Warning about asthma-related death from the drug labels of medicines that contain long-acting beta agonists (LABAs) in combination with inhaled corticosteroids (ICS).

Another SGLT2 Inhibitor Approved for Type 2 Diabetes

Ertugliflozin, a SGLT2 inhibitor has been approved to improve glycemic control in adults with type 2 diabetes as an adjunct to diet and exercise. It is to be administered orally in once-daily doses. Two dose strengths will be available: 5-mg and 15-mg tablets.

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INSPIRATIONAL STORY

A Short Story on Self-confidence

There was a business executive who was deep in debt and could see no way out. Creditors were closing in on him. Suppliers were demanding payment. He sat on the park bench, head in hands, wondering if anything could save his company from bankruptcy.

Suddenly an old man appeared before him. "I can see that something is troubling you," he said.

After listening to the executive's woes, the old man said, "I believe I can help you."

He asked the man his name, wrote out a check, and pushed it into his hand saying, "Take this money. Meet me here exactly 1 year from today, and you can pay me back at that time."

Then he turned and disappeared as quickly as he had come.

The business executive saw in his hand a check for $500,000, signed by John D. Rockefeller, then one of the richest men in the world!

"I can erase my money worries in an instant!" he realized. But instead, the executive decided to put the uncashed check in his safe. Just knowing it was there might give him the strength to work out a way to save his business, he thought.

With renewed optimism, he negotiated better deals and extended terms of payment. He closed several big sales. Within a few months, he was out of debt and making money once again.

Exactly 1 year later, he returned to the park with the uncashed check. At the agreed-upon time, the old man appeared. But just as the executive was about to hand back the check and share his success story, a nurse came running up and grabbed the old man.

"I'm so glad I caught him!" she cried. "I hope he hasn't been bothering you. He's always escaping from the rest home and telling people he's John D Rockefeller." And she led the old man away by the arm.

The astonished executive just stood there, stunned. All year long he'd been wheeling and dealing, buying and selling, convinced he had half a million dollars behind him.

Suddenly, he realized that it wasn't the money, real or imagined, that had turned his life around. It was his newfound self-confidence that gave him the power to achieve anything he went after.

■■■■

Lighter Side of Medicine

HUMOR

WHAT'S FOR DINNER?

I have my changed my system for labeling homemade freezer meals. I used to carefully note in large clear letters, "Meatloaf" or "Pot Roast" or "Steak and Vegetables or "Chicken and Dumplings" or "Beef Pot Pie." However, I used to get frustrated when I asked my husband what he wanted for dinner because he never asked for any of those things. So, I decided to stock the freezer with what he really likes. If you look in my freezer now you'll see a whole new set of labels. You'll find dinners with neat little tags that say: "Whatever," "Anything," "I Don't Know," "I Don't Care," "Something Good" or "Food." My frustration is now reduced because no matter what my husband replies when I ask him what he wants for dinner, I know that it is there waiting.

FIRST DAY AT SCHOOL

A school teacher injured his back and had to wear a plaster cast around the upper part of his body.

It fit under his shirt and was not noticeable at all. On the first day of the term, still with the cast under his shirt, he found himself assigned to the toughest students in school.

Walking confidently into the rowdy classroom, he opened the window as wide as possible and then busied himself with desk work.

When a strong breeze made his tie flap, he took the desk stapler and stapled the tie to his chest.

He had no trouble with discipline that term.

FUNNY MEANINGS...

Conference: The confusion of one man multiplied by the number present.

Hypochondriac: A person wants to have her ache and treat it too.

Inflation: Cutting money in half without damaging the paper.

Smile: A curve that can set a lot of things straight!

PRINTER IS WORKING FINE

A woman customer called the Canon help desk with a problem with her printer.

Tech support: Are you running it under windows?

Customer: "No, my desk is next to the door, but that is a good point. The man sitting in the cubicle next to me is under a window, and his printer is working fine."

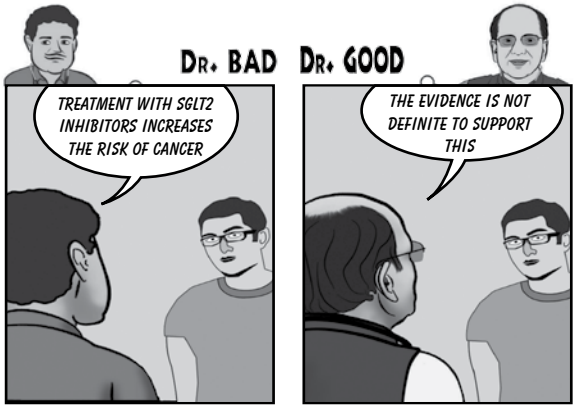
SMALLER VESSEL

The shipwrecked mariner had spent several years on a deserted island. Then one morning he was thrilled to see a ship offshore and a smaller vessel pulling out toward him.

When the boat grounded on the beach, the officer in charge handed the marooned sailor a bundle of newspapers and told him, "The captain said to read through these and let us know if you still want to be rescued."

Dr. Good and Dr. Bad

SITUATION: A type 2 diabetic individual has been treated with a SGLT2 inhibitor from the past 24 weeks.



LESSON: Information available from short-term RCTs has shown that the risk of overall cancer among individuals with T2DM using SGLT2 inhibitors is not significantly high.

Diabetologia. 2017 Jul 19. [Epub ahead of print]

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CLINICAL PRACTICE

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Manuscripts should be prepared in accordance with the 'Uniform requirements for manuscripts submitted to biomedical journals' compiled by the International Committee of Medical Journal Editors (Ann. Intern. Med. 1992;96: 766-767).

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- The introduction should state why the study was carried out and what were its specific aims/objectives.

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- These should be described in sufficient detail to permit evaluation and duplication of the work by others.
- Ethical guidelines followed by the investigations should be described.

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The following information should be given:

- The statistical universe i.e., the population from which the sample for the study is selected.
- Method of selecting the sample (cases, subjects, etc. from the statistical universe).
- Method of allocating the subjects into different groups.
- Statistical methods used for presentation and analysis of data i.e., in terms of mean and standard deviation values or percentages and statistical tests such as Student's 't' test, Chi-square test and analysis of variance or non-parametric tests and multivariate techniques.
- Confidence intervals for the measurements should be provided wherever appropriate.

Results

- These should be concise and include only the tables and figures necessary to enhance the understanding of the text.

Discussion

– This should consist of a review of the literature and relate the major findings of the article to other publications on the subject. The particular relevance of the results to healthcare in India should be stressed, e.g., practicality and cost.

References

These should conform to the Vancouver style. References should be numbered in the order in which they appear in the texts and these numbers should be inserted above the lines on each occasion the author is cited (Sinha[12] confirmed other reports[13,14]...). References cited only in tables or in legends to figures should be numbered in the text of the particular table or illustration. Include among the references papers accepted but not yet published; designate the journal and add 'in press' (in parentheses). Information from manuscripts submitted but not yet accepted should be cited in the text as 'unpublished observations' (in parentheses). At the end of the article the full list of references should include the names of all authors if there are fewer than seven or if there are more, the first six followed by et al., the full title of the journal article or book chapters; the title of journals abbreviated according to the style of the Index Medicus and the first and final page numbers of the article or chapter. The authors should check that the references are accurate. If they are not this may result in the rejection of an otherwise adequate contribution.
Examples of common forms of references are:

Articles

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.

Tables

– These should be typed double spaced on separate sheets with the table number (in Roman Arabic numerals) and title above the table and explanatory notes below the table.

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– The legend must include enough information to permit interpretation of the figure without reference to the text.

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– All photomicrographs should indicate the magnification of the print.

– Special features should be indicated by arrows or letters which contrast with the background.

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R.N.I. No. 50798/1990
Date of Publication 13th of Same Month
Date of Posting 13-14 Same Month

POSTAL REGISTRATION NO. DL (S)-01/3200/2018-2020
Posted in N.D. PSO New Delhi