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Court has a Duty to Strike Down Law if it Violates Fundamental Right: SC

"Courts cannot wait for a "majoritarian government" to decide on enacting, amending or striking down a law if it violates fundamental rights", state the Supreme Court of India while reserving the verdict on the petitions challenging the validity of Section 377 of the Indian Penal Code (IPC) and seeking decriminalization of homosexuality.

The five-judge Constitution bench headed by Chief Justice Dipak Misra, however, made clear that it may not strike down the law completely and deal with it to the extent it relates to consensual acts between two adults.

"If Section 377 of the IPC goes away entirely, there will be anarchy. We are solely on consensual acts between man-man, man-woman. Consent is the fulcrum here. You cannot impose your sexual orientation on others without their consent."

"We would not wait for the majoritarian government to enact, amend or not to enact any law to deal with violations of fundamental rights."

The observations came when lawyer Shyam George, appearing for Apostolic Alliance of Churches and Utkal Christian Association, said that it was not the job of the court and rather it fell under the domain of the legislature to decide whether to enact, amend the existing law as the decriminalizing it would have the impacts on many other statutes which deal with matrimonial and civil rights of men and women.

The issue here is separation of the powers of the three branches of the government, namely the Legislature, Executive and Judiciary.

The Legislature i.e., the Parliament, enacts the laws; the Executive i.e., the Govt. enforces the laws, while the Judiciary interprets the laws and is responsible for administering the constitutional law.

The Supreme Court is the highest judicial forum and final court of appeal under the Constitution of India, the highest constitutional court, with the power of constitutional review. The laws of the Parliament are subject to judicial review. The Supreme Court can either strike down or uphold a law passed by the Govt.

The Constitution of India gives powers to the Supreme Court under Articles 136 and 142 to form laws in the interest of complete justice without any jurisdictional difficulties.

"*136. Special leave to appeal by the Supreme Court. (1) Notwithstanding anything in this Chapter, the Supreme Court may, in its discretion, grant special leave to appeal from any judgment, decree, determination, sentence or order in any cause or matter passed or made by any court or tribunal in the territory of India.*" But, these provisions do not apply to Armed Forces as per Clause 2 of this article.

Article 142 empowers the Supreme Court to "*pass such decree or make such order as is necessary for doing complete justice in any cause or matter pending before it, and any decree so passed or orders so made shall be enforceable throughout the*

territory of India in such manner as may be prescribed by or under any law made by Parliament and, until provision in that behalf is so made, in such manner as the President may by order prescribe" in the exercise of its jurisdiction.

Two judgments of the Supreme Court of India on fundamental rights are noteworthy in that they upheld the Constitution as above all and denied absolute powers to the Legislature.

In 1967, in the matter of **Golaknath v. State of Punjab**, the 11-member bench of the Supreme Court ruled that "*Parliament cannot take away or abridge and amend any of the fundamental rights, even cannot touch, because these are sacrosanct in nature.*"

To regain its supremacy, the Parliament overruled its verdict vide the 24th and 25th Amendment Acts in 1971 stating that its powers to amend the Constitution were unrestricted and unlimited under Article 368.

"*… (1) Notwithstanding anything in this Constitution, Parliament may in exercise of its constituent power amend by way of addition, variation or repeal any provision of this Constitution in accordance with the procedure laid down in this article.*

(4) No amendment of this Constitution (including the provisions of Part III) made or purporting to have been made under this article whether before or after the commencement of Section 55 of the Constitution (Forty-second Amendment) Act, 1976 shall be called in question in any court on any ground.

(5) For the removal of doubts, it is hereby declared that there shall be no limitation whatever on the constituent power of Parliament to amend by way of addition, variation or repeal the provisions of this Constitution under this article…"

The matter of **His Holiness Bharati Sripadagalvaru and Ors vs. State of Kerala and Anr** in 1973 challenged the power of the Parliament to amend the Constitution. In this case, the 13-judge Constitutional Bench of the Supreme Court said that while the Govt. had the power to amend the Constitution, this did mean the power to amend the fundamental rights. The bench of the Supreme Court also outlined the 'Basic Structure Doctrine' of the Constitution in this judgment, which can neither be amended nor destroyed by the legislature (the Parliament). While the Bench did not limit the powers of the Parliament, it held that amendments that affect the 'Basic structure of the Constitution' are subject to judicial review.

Amongst the various elements of the 'Basic Structure Doctrine' is the supremacy of the Constitution, freedom and dignity of the individual.

Right to equality is one of the six fundamental rights guaranteed by the Constitution of India.

Article 14 guarantees the right to equality, meaning that every citizen is equal before the law and is equally protected by the laws of the country, which cannot be denied by the state.

"*14. Equality before law: The State shall not deny to any person equality before the law or the equal protection of the laws within the territory of India.*"

Article 15 prohibits discrimination on grounds of religion, race, caste, sex or place of birth.

Over the years, **Article 21** "Right to life and personal liberty" has been widely interpreted to also include right to health, right to clean environment, right to live with dignity, right to adequate nutrition, right to education. In **Maneka Gandhi vs. Union of India** 25th January, 1978, the Supreme Court held the right to travel and go abroad as a part of right to personal liberty guaranteed under Article 21. Last year, the Supreme Court declared right to privacy as a fundamental right under Article 21. Many more fundamental rights are implied under this Article. The scope of Article 14 has been addressed in various judgments of the Supreme Court.

In **E.P. Royappa vs. State of Tamil Nadu**, the Supreme Court altered the concept of equality which was traditionally based on reasonable classification and said, "*Equality is a dynamic concept with many aspects and dimensions and it cannot be 'cribbed, cabined and confined' within traditional and doctrinaire limits. From a positivistic point of view, equality is a antithesis to arbitrariness. In fact equality and arbitrariness are sworn enemies; one belong to the rule of law in a republic while the other to the whim and caprice of an absolute monarch. Where an act is arbitrary it is implicit in it that it is unequal both according to political logic and constitutional law and is therefore violative of Art. 14… Arts. 14 strike at arbitrariness in State action…*"

Reiterating this in **Maneka Gandhi vs. Union of India**, the Apex Court again held "*…Equality is a dynamic concept with many aspects and dimensions and it cannot be imprisoned within traditional and doctrinaire limits. Article 14 strikes at arbitrariness in State action and ensures fairness and equality of treatment. The principle of reasonableness which legally as well as philosophically, is an essential element of equality or non-arbitrariness, pervades Article 14 like a brooding omnipresence and the procedure contemplated by Article 21 must answer the best of reasonableness in order to be in conformity with Article 14. It must be "right and just and fair" and not arbitrary,*

fanciful or oppressive; otherwise, it would be no procedure at all and the requirement of Article 21 would not be satisfied..."

With this background, it would perhaps be fair to state that the Supreme Court, as the Regulator, has the right to strike down any unconstitutional law formed by the Legislator, the Govt. So, the Legislator cannot legislate any unconstitutional law. The Administrators are the Bureaucrats and Ministries.

It also has implications for health.

All laws which the government makes, if violating basic rights, should be challenged in the court of law.

A legal approach and not a political approach may be the answer to resolve all issues and concerns raised by the medical fraternity. Will Article 14 or even Article 15 help?

Can the scope of these articles be expanded further to address the many concerns of the doctors?

■■■■

Make sure

DURING MEDICAL PRACTICE

SITUATION: A hypertensive patient with positive family history of type 2 diabetes was put on amlodipine therapy.

LESSON: Make sure to remember that compared with amlodipine, valsartan reduces the risk of developing diabetes mellitus in high-risk hypertensive patients as shown in the Valsartan Antihypertensive Long-term Use Evaluation (VALUE) trial.

J Hypertens. 2006;24(7):1405-12.

AMERICAN FAMILY PHYSICIAN

Chronic Pelvic Pain in Women

LINDA M. SPEER, SAUDIA MUSHKBAR, TARA ERBELE

ABSTRACT

Chronic pelvic pain in women is defined as persistent, non-cyclic pain perceived to be in structures related to the pelvis and lasting more than six months. Often no specific etiology can be identified, and it can be conceptualized as a chronic regional pain syndrome or functional somatic pain syndrome. It is typically associated with other functional somatic pain syndromes (e.g., irritable bowel syndrome, nonspecific chronic fatigue syndrome) and mental health disorders (e.g., post-traumatic stress disorder, depression). Diagnosis is based on findings from the history and physical examination. Pelvic ultrasonography is indicated to rule out anatomic abnormalities. Referral for diagnostic evaluation of endometriosis by laparoscopy is usually indicated in severe cases. Curative treatment is elusive, and evidence-based therapies are limited. Patient engagement in a biopsychosocial approach is recommended, with treatment of any identifiable disease process such as endometriosis, interstitial cystitis/painful bladder syndrome, and comorbid depression. Potentially beneficial medications include depot medroxyprogesterone, gabapentin, nonsteroidal anti-inflammatory drugs, and gonadotropin-releasing hormone agonists with add-back hormone therapy. Pelvic floor physical therapy may be helpful. Behavioral therapy is an integral part of treatment. In select cases, neuromodulation of sacral nerves may be appropriate. Hysterectomy may be considered as a last resort if pain seems to be of uterine origin, although significant improvement occurs in only about one-half of cases. Chronic pelvic pain should be managed with a collaborative, patient-centered approach.

Keywords: Chronic pelvic pain, regional pain syndrome, somatic pain syndromes, pelvic ultrasonography, medroxyprogesterone, hysterectomy

Chronic pelvic pain in women is defined as persistent, non-cyclic pain perceived to be in structures related to the pelvis.[1] An arbitrary duration of six months is usually considered chronic. A systematic review found only seven studies that reported the prevalence of chronic pelvic pain among women worldwide, with rates of 6% to 27%, although there was a lack of consensus on the definition of chronic pelvic pain.[2] Studies generally did not exclude dysmenorrhea.

It usually is not possible to identify a single etiology or definitive cure for chronic pelvic pain. In at least one-half of cases, there are one or more associated entities, such as irritable bowel syndrome, interstitial cystitis/painful bladder syndrome, endometriosis, or pelvic adhesions.[3,4] The presence of both endometriosis and interstitial cystitis is not unusual.[5] Comprehensive guidelines for the diagnosis and treatment of chronic pelvic pain have been developed by the European Association of Urology.[1] They include a description of the current understanding of pathophysiology and psychosocial aspects, as well as classification, diagnosis, and treatment.

Expert opinion suggests that in the absence of a single clear etiology, chronic pelvic pain can be conceptualized as a complex neuromuscular-psychosocial disorder consistent with a chronic regional pain syndrome (e.g., reflex sympathetic dystrophy) or functional somatic pain syndrome (e.g., irritable bowel syndrome, nonspecific chronic fatigue).[1,6,7] The pathophysiology is unclear, but it may include aspects of hyperesthesia/allodynia and pelvic floor dysfunction.[7]

The psychosocial context of the patient is important. Nearly one-half of women seeking care for chronic pelvic pain report a history of sexual, physical, or emotional trauma, and about one-third have positive screening results for post-traumatic stress disorder.[8]

EVALUATION

The International Pelvic Pain Society has developed a detailed history and physical examination form for evaluation of women with chronic pelvic pain (available at http://www.pelvicpain.org/Professional/Documents-and-Forms.aspx). It includes tools for quantification and

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Source: Adapted from Am Fam Physician. 2016;93(5):380-387.

mapping of pelvic pain, screening questionnaires, and an extensive review of the reproductive, urologic, and gastrointestinal systems. Table 1 lists findings from the history and physical examination that are associated with specific diagnoses.[9-12] Red flag findings that may indicate systemic disease include post-coital bleeding, postmenopausal bleeding or onset of pain, unexplained weight loss, pelvic mass, and hematuria.[9] Figure 1 shows a suggested approach to patients with chronic pelvic pain.

History

The patient history should include questions about precipitating and alleviating factors; association between pain and menses, sexual activity, urination, and defecation; and response to any prior treatments. Pain mapping may be helpful; the patient should localize the pain on a visual representation of the body. This may identify other areas where the patient experiences pain or may reveal a dermatomal distribution, suggesting a non-visceral source.

The review of systems should emphasize symptoms of urogynecologic diseases and gastrointestinal, musculoskeletal, and psychoneurologic disorders. The clinician should be familiar with visceral and somatic pain referral patterns, and the nerves that correspond to the region.

The clinician should inquire about patient perspectives on possible origins of the pain, and validate her concerns and anxiety. Effects on quality of life and function

Table 1. Select Clinical Clues in Women with Chronic Pelvic Pain

Finding	Possible significance
History	
Crampy pain	Inflammatory bowel disease, irritable bowel syndrome
Hot, burning, or electric shock–like pain	Nerve entrapment
Pain fluctuates with menstrual cycle	Adenomyosis, endometriosis
Pain fluctuation unassociated with menstrual cycle	Adhesions, interstitial cystitis, irritable bowel syndrome, musculoskeletal etiologies
Pain with urge to void	Interstitial cystitis, urethral syndrome
Post-coital bleeding*	Cervical cancer
Postmenopausal bleeding*	Endometrial cancer
Postmenopausal onset of pain*	Malignancy
Prior abdominal surgery or infection	Adhesions
Unexplained weight loss*	Malignancy, systemic illness
Physical examination	
Adnexal mass*	Ovarian neoplasm
Enlarged or tender uterus	Adenomyosis, chronic endometritis
Lack of uterine mobility on bimanual examination	Adhesions, endometriosis
Pain on palpation of outer back or pelvis	Abdominal/pelvic wall source of pain
Pelvic floor muscle tenderness	Interstitial cystitis/painful bladder syndrome, piriformis/levator ani syndrome
Point tenderness of vagina, vulva, or bladder	Adhesions, endometriosis, nerve entrapment
Positive Carnett sign (Figure 2)	Myofascial or abdominal wall source of pain
Suburethral mass, fullness, or tenderness	Urethral diverticulum
Uterosacral ligament abnormalities	Adenomyosis, endometriosis, malignancy
Vulvar/vestibular pain	Vulvodynia
Diagnostic testing	
Gross or microscopic hematuria*	Severe interstitial cystitis, urinary system malignancy
Mass on ultrasonography*	Malignancy

*Red flag finding for serious systemic disease.

Information from references 9 through 12.

should be assessed using a validated questionnaire, such as the Quality of Life Scale.[13] A pain log can be useful for understanding the pattern of pain and its impact on the patient's life. The log might include dates of pain episodes, a numeric rating from zero to 10, pain location and severity, associated factors (e.g., menses, mood, bowel/bladder function, coitus, physical activity), and use of analgesic medications.

Physical Examination

The goal of the physical examination is to identify the dermatome, tissues, nerves, muscles, and organs that reproduce the patient's pain symptoms in an attempt to determine the underlying cause. Findings are rarely normal in women with chronic pelvic pain. However, they can be nonspecific and thus inconclusive.

Physical examination, including a speculum examination, should be performed gently to limit exacerbation of pain. The abdomen and pelvis should be examined for any trigger points, surgical scars, vaginal discharge, pelvic organ prolapse, uterine enlargement, or masses. A one-handed, single-digit examination of the pelvis and abdomen using the flat tip of the index finger of the dominant hand may be helpful to identify the structures related to focal tenderness. Alternatively, a cotton swab may be used.

The external genitalia should be examined for signs of infection, inflammatory dermatologic conditions, vulvar

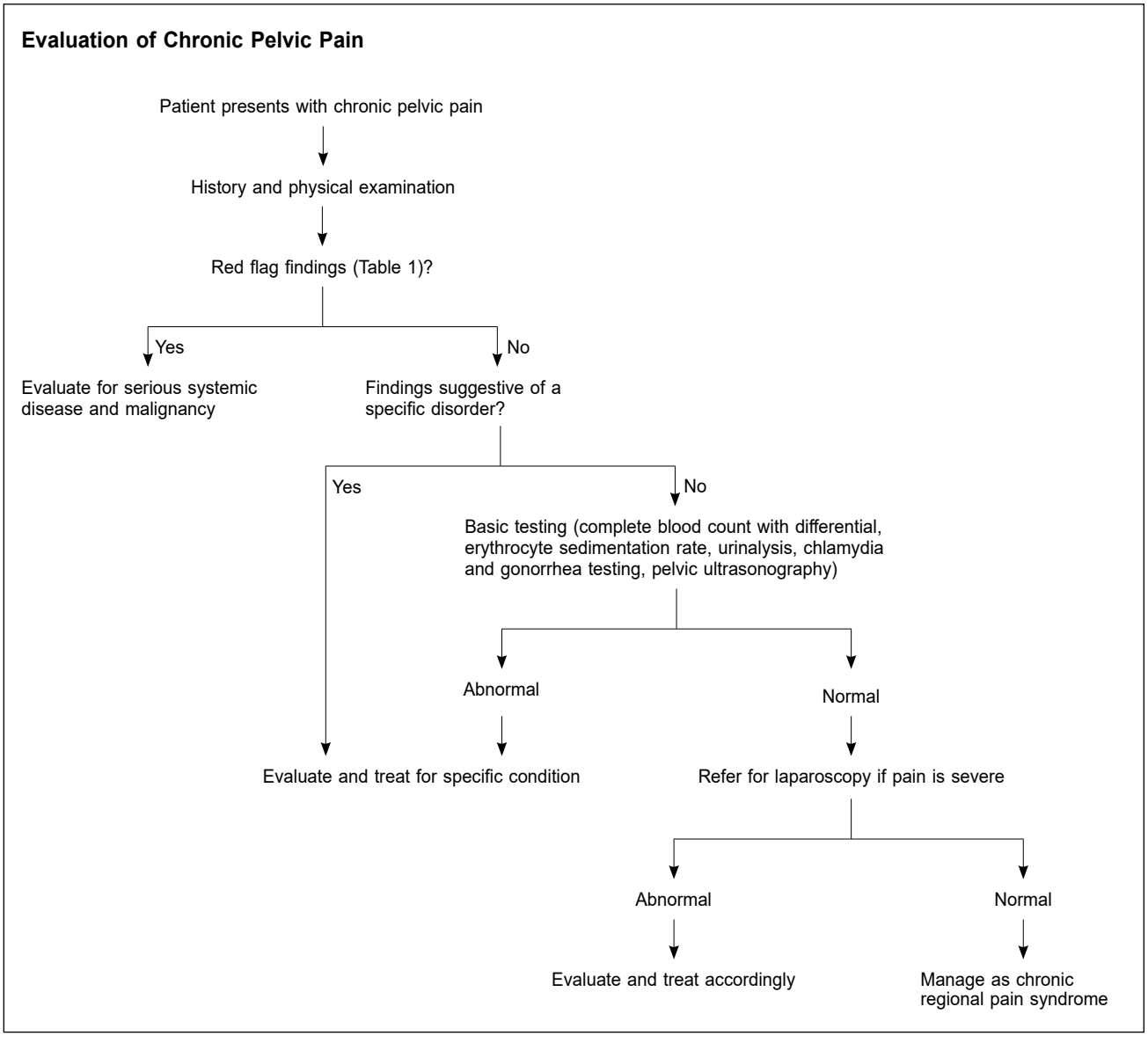

Figure 1. Algorithm for the evaluation of chronic pelvic pain.

malignancy, and neurogenic etiologies. Examination of the pelvic floor musculature may reveal hypertonicity, tenderness, or trigger points.

Tenderness to palpation over the lower back, sacroiliac joints, or pubic symphysis may indicate a musculoskeletal origin of pain. The Carnett test can be used to differentiate visceral pain from abdominal wall pain (Figure 2).[10]

A cotton swab applied to the abdominal skin can be used to identify a cutaneous source of pain. A case-control study found that a cotton-tipped applicator test had 73% sensitivity and 100% specificity to diagnose cutaneous allodynia in patients with chronic pelvic pain.[14] However, the study used inter-rater reliability as the only reference standard, and it is unclear whether the raters were blinded.

Diagnostic Testing

The history and physical examination are the most important components of the diagnostic evaluation. Limited laboratory testing and imaging are also indicated, with possible referral for laparoscopic or urologic evaluation as warranted by the clinical findings.

Laboratory testing is of limited value in evaluating women with chronic pelvic pain. A complete blood count with differential, erythrocyte sedimentation rate, urinalysis, chlamydia and gonorrhea testing, and pregnancy test may be ordered to screen for a chronic infectious or inflammatory process and to exclude pregnancy.

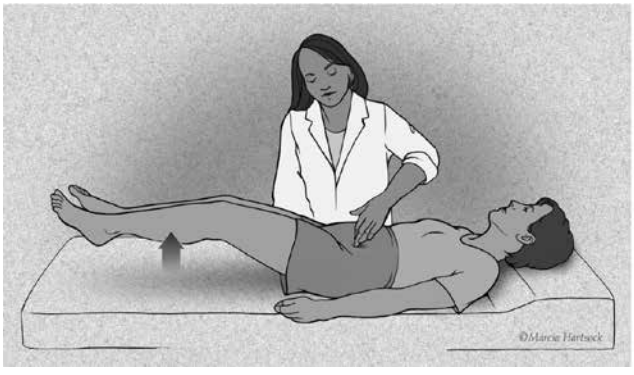

ILLUSTRATION BY MARCIA HARTSOCK

Figure 2. The Carnett test for patients with pelvic pain. The patient raises both legs off the table while supine. Raising only the head while in the supine position can serve the same purpose. The examiner places a finger on the painful abdominal site to determine whether the pain increases during the maneuver when the rectus abdominis muscles are contracted. The assumption is that it potentially increases myofascial pain such as trigger points, entrapped nerve, hernia, or myositis, whereas true visceral sources of pain may be less tender when abdominal muscles are tensed.

Reprinted with permission from Ortiz DD. Chronic pelvic pain in women. Am Fam Physician. 2008;77(11):1538.

Transvaginal ultrasonography is helpful to identify pelvic masses and adenomyosis.[15,16] It is particularly useful for detecting pelvic masses less than 4 cm in diameter, which often cannot be palpated on bimanual examination. Ultrasonography is also useful for detection of hydrosalpinx, an indicator of pelvic inflammatory disease.[16] Follow-up magnetic resonance imaging may be useful to define an abnormality detected on ultrasonography.[17]

When the pain is severe, the patient should be referred for laparoscopy if the diagnosis remains unclear after the initial evaluation.[1,9,18] Laparoscopy may be useful to confirm and possibly treat endometriosis or pelvic/abdominal adhesions, but it is negative in nearly 40% of cases.[19] Pain mapping may be useful while the patient is conscious and under local anesthesia during the procedure. The tissues should be probed and pulled with surgical instruments while the patient is asked about the severity and nature of any pain she perceives. This approach can help target medical and surgical treatments, although less than one-half of patients can expect a reduction in pain.[20]

TREATMENT

The goal of treatment is to maximize patient quality of life and overall function, with an emphasis on engaging the patient in self-management. Evidence-based therapy for chronic pelvic pain remains limited and is often focused on symptom relief.[21] Any obvious disease process should be treated, though even targeted treatment may not result in resolution of pain. The cause and consequence of pain can involve multiple mechanisms, so treatment requires a holistic approach addressing physical, behavioral, psychological, and sexual components.[6] Guidelines by the European Association of Urology provide greater detail regarding treatment of chronic pelvic pain.[1] Figure 3 shows a suggested treatment algorithm.

Medications

Medical management should address the underlying cause of pelvic pain, if known. If treatment is inadequate or the cause of pain is not known, pharmacologic therapy is aimed at symptom relief. Table 2 summarizes potentially useful medications for the treatment of nonspecific chronic pelvic pain.[1,10,22,23]

Analgesics such as acetaminophen and nonsteroidal anti-inflammatory drugs are usually well tolerated,

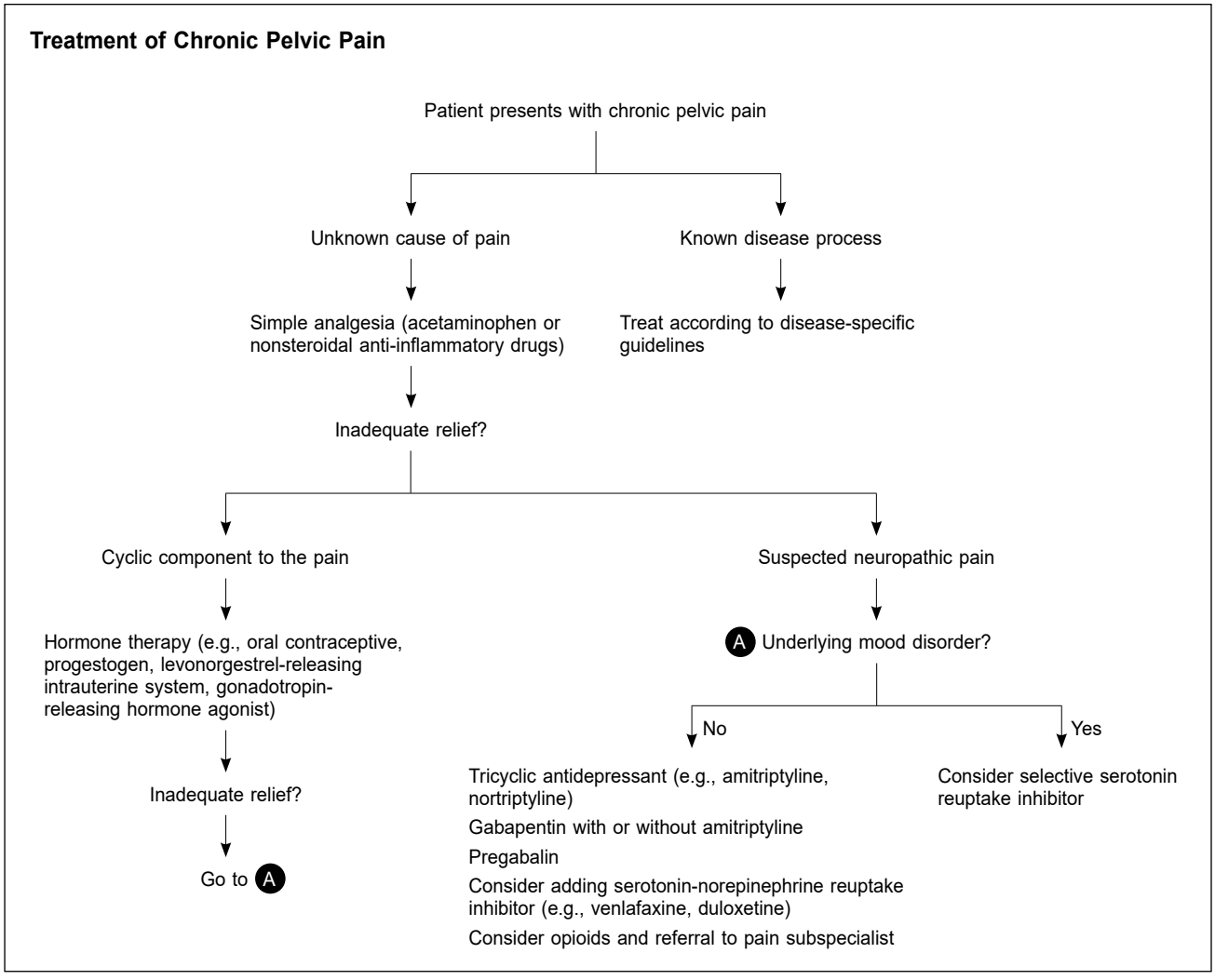

Figure 3. Algorithm for the treatment of chronic pelvic pain.

although a Cochrane review concluded that nonsteroidal anti-inflammatory drugs are not effective for treating chronic pelvic pain associated with endometriosis.[23]

Oral contraceptives are effective for the treatment of dysmenorrhea associated with endometriosis, with only limited evidence that they are useful for non-menstrual pelvic pain.[24] A Cochrane review concluded that there is moderate evidence to support progestogen treatment for chronic pelvic pain (e.g., depot medroxyprogesterone, 150 mg intramuscularly every 12 weeks).[21] If the patient has endometriosis, injectable gonadotropin-releasing hormone agonists such as goserelin provide longer-lasting effects than depot medroxyprogesterone.[25,26] Hypoestrogenic adverse effects can be mitigated with hormone therapy. The levonorgestrel-releasing intrauterine system has been shown to reduce the recurrence of dysmenorrhea if placed after laparoscopic treatment of endometriosis.[27] However, in women with pain of unknown etiology, it is associated with only short-term pain relief and low satisfaction because of the adverse effects of progesterone.[21]

If neuropathic pain is suspected, tricyclic antidepressants, serotonin-norepinephrine reuptake inhibitors, or anticonvulsants (e.g., gabapentin, pregabalin) may be helpful.[1,21] Although data regarding their effectiveness in treating chronic pelvic pain are limited, there is evidence of benefit for treating neuropathic pain in general. A Cochrane review of tricyclic antidepressants for the treatment of neuropathic pain concluded that they are effective (number needed to treat = 3).[28] There is some evidence of benefit for serotonin-norepinephrine reuptake inhibitors (e.g., venlafaxine, duloxetine).[1] Gabapentin provides good relief of neuropathic pain, with a low number needed to treat.[1] A study of chronic pelvic pain in women suggested that gabapentin used alone or in combination with amitriptyline is more

Table 2. Medications Used to Treat Nonspecific Chronic Pelvic Pain

Agent	Pain type	Comment
Acetaminophen	Somatic	Evidence based on arthritic pain
Gabapentin, pregabalin	Neuropathic	Evidence supports use for general neuropathic pain, with low number needed to treat; limited studies on chronic pelvic pain
Gabapentin plus amitriptyline	Neuropathic	Small study in women with chronic pelvic pain showed combination was more effective than amitriptyline alone[22]
Nonsteroidal anti-inflammatory drugs	Inflammatory	Good evidence of benefit for dysmenorrhea; Cochrane review indicates lack of effectiveness for endometriosis[23]
Opioids	Chronic nonmalignant	Controversial for long-term use
Oral contraceptives, progestogens, gonadotropin-releasing hormone agonists	Cyclic	Good evidence of benefit for endometriosis; limited evidence for noncyclic pelvic pain
Selective serotonin reuptake inhibitors	Pain with underlying depression	Good evidence of benefit for depression; insufficient evidence for pain
Tricyclic antidepressants, serotonin-norepinephrine reuptake inhibitors	Neuropathic	Most evidence based on neuropathic pain; few studies specifically on chronic pelvic pain

Information from references 1, 10, 22, and 23.

effective than amitriptyline alone.[22] A positive response to gabapentin or pregabalin may be a predictor of response to neuromodulation (described later). Data are insufficient to recommend selective serotonin reuptake inhibitors for neuropathic pain, but they are effective if there is underlying depression.[1]

Opioids may be considered for long-term management of non-malignant pain when other options have been exhausted. Their use in functional somatic pain syndromes is controversial, and referral to a pain management subspecialist should be considered.[6]

Surgical Interventions

Surgical intervention should be guided by the underlying diagnosis, although some options may be diagnostic. Pain is likely to improve after laparoscopic surgery to treat endometriosis.[18] Hysterectomy is a last resort because of its high morbidity and limited benefit. About one-half of women with uterine tenderness on pelvic examination will have improvements in mental health, physical health, and social functioning after hysterectomy.[29] However, up to 40% will have persistent pain, and at least 5% will have worse pain.[30]

Local injection of steroids may be therapeutic as well as diagnostic when peripheral nerves are involved.[6] If there is sacral nerve involvement, pain relief may be possible with sacral nerve blocks or neuromodulation by means of a surgically implanted device that stimulates the nerve with electric pulses.[31,32] However, neuromodulation may not be readily available. Studies are ongoing to investigate the specific role of these modalities in the treatment of chronic pelvic pain.[1]

Physical Modalities

Pelvic floor physical therapy has been proposed as a treatment for chronic pelvic pain. Its proponents cite benefits for diagnosis and treatment.[33] Referral should be considered when there is pelvic floor tenderness. Although physical therapy has shown promise in small, well-designed studies when myofascial pain is identified, a systematic review concluded that the current evidence base is too limited to guide practice.[34,35]

Multiple small studies support the use of biofeedback for chronic pelvic pain.[1] Biofeedback helps patients recognize the action of the pelvic floor muscles and has been shown to provide better pain relief than electrostimulation or massage.[1]

Behavioral Interventions

Behavioral health is a critical component of care for women with chronic pelvic pain, regardless of the underlying cause. One promising treatment method is a hybrid of cognitive psychotherapy and physiotherapy, referred to as somatocognitive therapy. Its goal is to promote awareness of one's own body, develop coping strategies, and manually release muscular pain.[36] When combined with specific gynecologic care, somatocognitive therapy improves distress, pain experience, and motor function.[37]

Diagnosis and treatment of comorbid depression are important for therapeutic success. Women with

depression are three to five times more likely to have persistent pain after surgical intervention.[29]

One small study showed that women were more likely to report improvements in pain when they were offered "reassurance" ultrasonography compared with those who were followed with a "wait-and-see" policy.[21]

Complementary and Alternative Therapies

Limited evidence suggests that ear acupuncture may be helpful for some causes of gynecologic pain, and is likely more effective than Chinese herbal medicine for endometriosis.[38]

Monitoring

The goal of treatment is to reduce symptoms and improve quality of life. Treatment plans should account for patient expectations of pain relief and functional ability. Monitoring of mood, pain, and function will help guide the treatment plan. A numeric pain scale can help quantify and measure any change in pain. The validated Quality of Life Scale is useful to monitor patient function.[13] The Patient Health Questionnaire-9 is another validated tool that is used to screen for and monitor depression symptoms[39]; it is available at http://www.integration.samhsa.gov/images/res/PHQ%20-%20Questions.pdf.

REFERENCES

1. Engeler D, Baranowski AP, Borovicka J, et al.; European Association of Urology. Guidelines on chronic pelvic pain. http://uroweb.org/wp-content/uploads/EAU-Guidelines-Chronic-Pelvic-Pain-2015.pdf. Accessed May 29, 2015.
2. Ahangari A. Prevalence of chronic pelvic pain among women: an updated review. Pain Physician. 2014; 17(2):E141-E147.
3. Williams RE, Hartmann KE, Sandler RS, Miller WC, Steege JF. Prevalence and characteristics of irritable bowel syndrome among women with chronic pelvic pain. Obstet Gynecol. 2004;104(3):452-458.
4. Haggerty CL, Peipert JF, Weitzen S, et al.; PID Evaluation and Clinical Health (PEACH) Study Investigators. Predictors of chronic pelvic pain in an urban population of women with symptoms and signs of pelvic inflammatory disease. Sex Transm Dis. 2005;32(5):293-299.
5. Tirlapur SA, Kuhrt K, Chaliha C, Ball E, Meads C, Khan KS. The 'evil twin syndrome' in chronic pelvic pain: a systematic review of prevalence studies of bladder pain syndrome and endometriosis. Int J Surg. 2013; 11(3): 233-237.
6. Engeler DS, Baranowski AP, Dinis-Oliveira P, et al.; European Association of Urology. The 2013 EAU guidelines on chronic pelvic pain: is management of chronic pelvic pain a habit, a philosophy, or a science? 10 years of development. Eur Urol. 2013;64(3):431-439.
7. Potts JM, Payne CK. Urologic chronic pelvic pain. Pain. 2012;153(4):755-758.
8. Meltzer-Brody S, Leserman J, Zolnoun D, Steege J, Green E, Teich A. Trauma and posttraumatic stress disorder in women with chronic pelvic pain. Obstet Gynecol. 2007;109(4):902-908.
9. Royal College of Obstetricians and Gynaecologists. The initial management of chronic pelvic pain. May 2012. https://www.rcog.org.uk/globalassets/documents/guidelines/gtg_41.pdf. Accessed May 29, 2015.
10. Ortiz DD. Chronic pelvic pain in women. Am Fam Physician. 2008;77(11):1535-1542.
11. DynaMed Plus. Chronic pelvic pain in women. http://www.dynamed.com/topics/dmp~AN~T114601/Chronic-pelvic-pain-in-women [subscription required]. Accessed May 29, 2015.
12. Howard F. Evaluation of chronic pelvic pain in women. UpToDate. http://www.uptodate.com/contents/evaluation-of-chronic-pelvic-pain-in-women [subscription required]. Accessed May 29, 2015.
13. Burckhardt CS, Anderson KL. The Quality of Life Scale (QOLS): reliability, validity, and utilization. Health Qual Life Outcomes. 2003;1:60.
14. Nasr-Esfahani M, Jarrell J. Cotton-tipped applicator test: validity and reliability in chronic pelvic pain. Am J Obstet Gynecol. 2013;208(1):52.e1-52.e5.
15. Holland TK, Cutner A, Saridogan E, Mavrelos D, Pateman K, Jurkovic D. Ultrasound mapping of pelvic endometriosis: does the location and number of lesions affect the diagnostic accuracy? A multicentre diagnostic accuracy study. BMC Womens Health. 2013;13:43.
16. Meredith SM, Sanchez-Ramos L, Kaunitz AM. Diagnostic accuracy of transvaginal sonography for the diagnosis of adenomyosis: systematic review and meta-analysis. Am J Obstet Gynecol. 2009;201(1):107.e1-107.e6.
17. Cody RF Jr, Ascher SM. Diagnostic value of radiological tests in chronic pelvic pain. Baillieres Best Pract Res Clin Obstet Gynaecol. 2000;14(3):433-466.
18. Jacobson TZ, Duffy JM, Barlow D, Koninckx PR, Garry R. Laparoscopic surgery for pelvic pain associated with endometriosis. Cochrane Database Syst Rev. 2009;(4):CD001300.
19. Kang SB, Chung HH, Lee HP, Lee JY, Chang YS. Impact of diagnostic laparoscopy on the management of chronic pelvic pain. Surg Endosc. 2007;21(6):916-919.
20. Swanton A, Iyer L, Reginald PW. Diagnosis, treatment and follow up of women undergoing conscious pain mapping for chronic pelvic pain: a prospective cohort study. BJOG. 2006;113(7):792-796.
21. Cheong YC, Smotra G, Williams AC. Non-surgical interventions for the management of chronic pelvic pain. Cochrane Database Syst Rev. 2014;(3):CD008797.

22. Sator-Katzenschlager SM, Scharbert G, Kress HG, et al. Chronic pelvic pain treated with gabapentin and amitriptyline: a randomized controlled pilot study. Wien Klin Wochenschr. 2005;117(21-22):761-768.
23. Allen C, Hopewell S, Prentice A, Gregory D. Nonsteroidal anti-inflammatory drugs for pain in women with endometriosis. Cochrane Database Syst Rev. 2009;(2):CD004753.
24. Harada T, Momoeda M, Taketani Y, Hoshiai H, Terakawa N. Low-dose oral contraceptive pill for dysmenorrhea associated with endometriosis: a placebo-controlled, double-blind, randomized trial. Fertil Steril. 2008;90(5):583-1588.
25. Schlaff WD, Carson SA, Luciano A, Ross D, Bergqvist A. Subcutaneous injection of depot medroxyprogesterone acetate compared with leuprolide acetate in the treatment of endometriosis-associated pain. Fertil Steril. 2006;85(2):314-325.
26. Brown J, Pan A, Hart RJ. Gonadotrophin-releasing hormone analogues for pain associated with endometriosis. Cochrane Database Syst Rev. 2010;(12):CD008475.
27. Bayoglu Tekin Y, Dilbaz B, Altinbas SK, Dilbaz S. Postoperative medical treatment of chronic pelvic pain related to severe endometriosis: levonorgestrel-releasing intrauterine system versus gonadotropin-releasing hormone analogue. Fertil Steril. 2011;95(2):492-496.
28. Saarto T, Wiffen PJ. Antidepressants for neuropathic pain. Cochrane Database Syst Rev. 2007;(4):CD005454.
29. Hartmann KE, Ma C, Lamvu GM, Langenberg PW, Steege JF, Kjerulff KH. Quality of life and sexual function after hysterectomy in women with preoperative pain and depression. Obstet Gynecol. 2004;104(4):701-709.
30. Lamvu G. Role of hysterectomy in the treatment of chronic pelvic pain. Obstet Gynecol. 2011;117(5):1175-1178.
31. Fritz J, Chhabra A, Wang KC, Carrino JA. Magnetic resonance neurography-guided nerve blocks for the diagnosis and treatment of chronic pelvic pain syndrome. Neuroimaging Clin N Am. 2014;24(1):211-234.
32. Martellucci J, Naldini G, Carriero A. Sacral nerve modulation in the treatment of chronic pelvic pain. Int J Colorectal Dis. 2012;27(7):921-926.
33. Tu FF, Holt J, Gonzales J, Fitzgerald CM. Physical therapy evaluation of patients with chronic pelvic pain: a controlled study. Am J Obstet Gynecol. 2008;198(3):272.e1-272.e7.
34. Fitzgerald MP, Anderson RU, Potts J, et al.; Urological Pelvic Pain Collaborative Research Network. Randomized multicenter feasibility trial of myofascial physical therapy for the treatment of urological chronic pelvic pain syndromes. J Urol. 2013;189(1 suppl):S75-S85.
35. Loving S, Nordling J, Jaszczak P, Thomsen T. Does evidence support physiotherapy management of adult female chronic pelvic pain? A systematic review. Scand J Pain. 2012;3(2):70-81.
36. Haugstad GK, Kirste U, Leganger S, Haakonsen E, Haugstad TS. Somatocognitive therapy in the management of chronic gynaecological pain. A review of the historical background and results of a current approach. Scand J Pain. 2011;2(3):124-129.
37. Haugstad GK, Haugstad TS, Kirste UM, et al. Continuing improvement of chronic pelvic pain in women after short-term Mensendieck somatocognitive therapy: results of a 1-year follow-up study. Am J Obstet Gynecol. 2008;199(6):615.e1-615.e8.
38. Zhu X, Hamilton KD, McNicol ED. Acupuncture for pain in endometriosis. Cochrane Database Syst Rev. 2011;(9):CD007864.
39. Kroenke K, Spitzer RL, Williams JB. The PHQ-9: validity of a brief depression severity measure. J Gen Intern Med. 2001;16(9):606-613.

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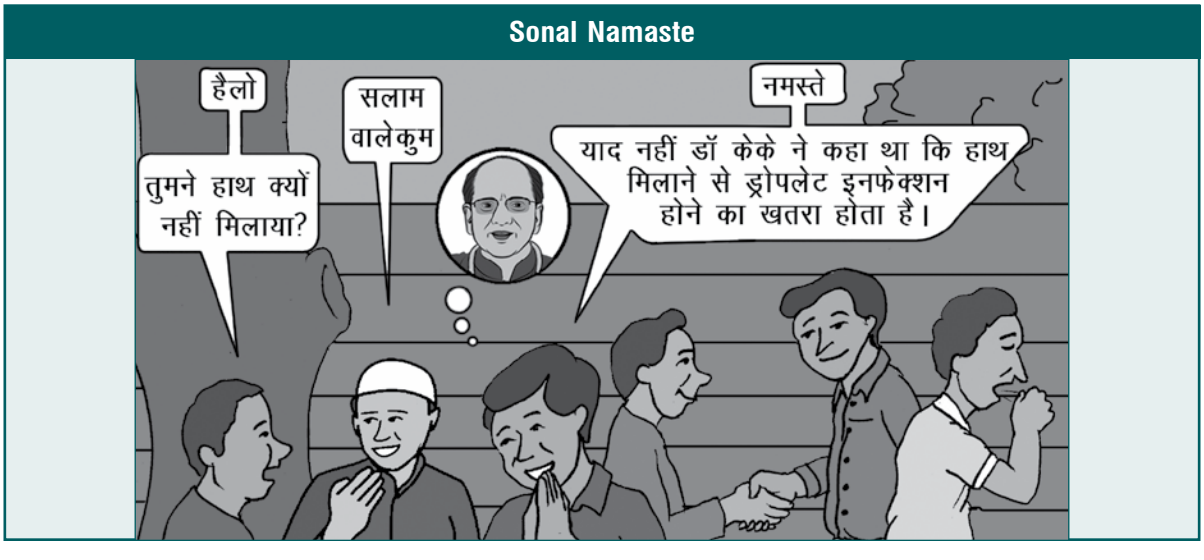
CHAT WITH DR KK



Practice Guidelines

AHA UPDATES GUIDELINES FOR CPR AND EMERGENCY CARDIOVASCULAR CARE

Providing cardiopulmonary resuscitation (CPR) effectively is dependent on a variety of factors, including immediate action taken by the rescuer and performance of high-quality maneuvers. The American Heart Association (AHA) has updated its 2010 guidelines on CPR and emergency cardiovascular care to highlight important changes. The 2010 guidelines changed the sequence of CPR from airway, breathing, compressions (ABC) to compressions, airway, breathing (CAB) to avoid delays in starting chest compressions; this remains unchanged in the update. Also, for untrained lay rescuers, chest compressions–only CPR is recommended. This summary practice guideline focuses on adult and child basic life support and CPR quality, as well as alternative CPR techniques. Additional changes from the AHA regarding cardiac life support, post–cardiac arrest care, acute coronary syndromes, special circumstances, and more can be found in the full guidelines.

New and Updated Recommendations

Basic Life Support and CPR Quality

Evidence has indicated that the most common mistakes that occur while providing CPR include not performing compressions deep or fast enough. Additionally, evidence shows improved survival rates with delivery of high-quality CPR, consisting of compressions of a sufficient rate and depth with minimal interruptions, allowing full chest recoil between compressions, and avoiding too much ventilation.

Adults

When providing CPR, 100 to 120 chest compressions per minute at a depth of at least 2 inches, but no greater than 2.4 inches, should be provided. Pauses in compressions should be as short as possible. A goal of a 60% or greater chest compression fraction may be reasonable in persons with an unprotected airway.

If the rescuer suspects that a patient with respiratory arrest has an opioid addiction, standard basic life support combined with intramuscular or intranasal naloxone should be provided, assuming the rescuer is appropriately trained. If the patient is at risk of overdose, opioid overdose response education can be provided at any point and may be combined with instructions on administering naloxone for prevention. If a patient has a spinal injury, manual spinal restriction such as placing hands on either side of the head is preferred over immobilization devices.

When cardiac arrest with a shockable rhythm occurs outside of a hospital, emergency medical services personnel can delay use of positive pressure ventilation by performing cycles of 200 continuous compressions (up to three cycles) combined with passive oxygen insufflation and airway adjuncts. Although routinely using passive ventilation is not recommended when providing conventional CPR because of questionable effectiveness, this is a reasonable method for emergency medical services personnel who typically provide this combined approach.

Emergency dispatchers should first find out where the event is occurring, and then ask if the patient is unconscious with abnormal or absent breathing, and, if so, it should be assumed that the patient is experiencing cardiac arrest. Training should be provided about how to recognize unconsciousness using signs such as abnormal or agonal gasps and various presentations. Dispatchers should provide callers with guidance on CPR using only chest compressions.

Health care professionals can perform chest compressions and ventilation in all patients presenting with cardiac arrest. A series of 30 compressions and two breaths is no longer necessary if there is an advanced airway, and, instead, one breath every six seconds should be given while chest compressions are provided continuously.

Evaluation of electrocardiography rhythm with artifact-filtering algorithms while performing CPR cannot be recommended; however, it could be useful for research or for emergency medical services personnel who use these algorithms already. Audiovisual feedback may be used to improve CPR performance.

Source: Adapted from Am Fam Physician. 2016;93(9):791-797.

Children

Although there are no major basic life support and CPR changes for children since the 2010 guidelines, new ideas about how to perform CPR were evaluated. For simplicity and consistency in training, it may be reasonable to keep the order of starting CPR as compressions, airway, and breathing vs. changing the order to airway, breathing, and compressions. Compression depth was affirmed as one-third or more of anterior-posterior diameter (i.e., about 1.5 inches in infants and 2 inches in children); however, evidence is lacking regarding the rate and, therefore, it was not assessed. Instead, the adult rate of 100 to 120 chest compressions per minute is recommended. Ventilation should be included when performing CPR, because 30-day outcomes were found to be worse when only compressions were performed. If the rescuer performing CPR is not willing or able to provide ventilation, then delivering compressions only is appropriate.

Alternative Techniques and Ancillary Devices

Since the 2010 guidelines, additional evidence about the effectiveness of alternatives and adjuncts to standard CPR has emerged; however, it should be noted that specialized equipment and training may be needed when alternative techniques are used.

There is no advantage to routinely using an impedance threshold device (a valve used to decrease intrathoracic pressure and increase venous return) as an adjunct to standard CPR (i.e., compressions and rescue breaths); however, combining its use with active CPR (i.e., compression-decompression) has been shown to improve neurologically intact survival and, therefore, may be a reasonable option, assuming equipment availability and proper training.

Although no studies have indicated that mechanical chest compression devices are better than standard CPR, they may be a reasonable option, again assuming proper training, and can be considered when performing high-quality manual compressions may be difficult or dangerous. It should be noted that interruptions in CPR should be limited when using and removing the device. There is no assessment of how extracorporeal CPR, also called venoarterial extracorporeal membrane oxygenation, affects survival.

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Photo Quiz

PERSISTENT LOWER-LIMB ULCERS IN A PATIENT WITH DIABETES

A 60-year-old woman presented with enlarging ulcers on her ankle and foot. Despite treatment, the ulcers worsened and became more painful, and she noted a new ulcer on her left shin. The problem started as a small ulcerated lesion on the lateral dorsal area of her foot that had developed two years earlier after she bumped into a dresser.

She had a history of diabetes mellitus, hypertension, hyperlipidemia, and myeloproliferative disease. At the time of presentation, her medications included enalapril, metoprolol, furosemide, fenofibrate, insulin aspart, insulin detemir, metformin, prednisone, dapsone, topical silver sulfadiazine, and clobetasol cream. She was previously taking hydroxyurea and anagrelide for her myeloproliferative disease. She was a non-smoker.

On examination, she was afebrile and had ulcers of varying size on her left lower leg over the lateral malleolus and foot (Figures 1 and 2). There were larger ulcerations exposing muscles and tendons, with sharp margins, an undermined and violaceous border, and granulation tissue over the ulcer beds. A smaller area of ulceration was noted in the left midpretibial area. A complete blood count revealed a white blood cell count of 17,200 per mm^3 (17.2×10^9 per L). Her blood glucose level was 126 mg per dL (7.0 mmol per L). Findings from Doppler ultrasonography and wound cultures were unremarkable.

Question

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

A. Cutaneous malignancy.

B. Factitial ulcers.

C. Infectious ulcers.

D. Pyoderma gangrenosum.

E. Venous stasis ulcers.

Source: Adapted from Am Fam Physician. 2016;93(9):783-784.

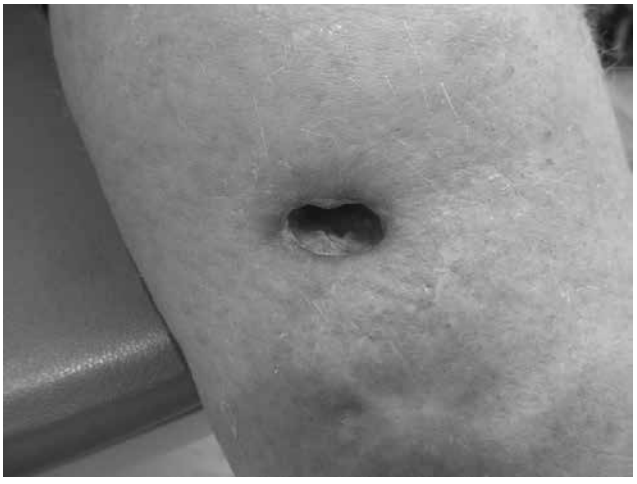

Figure 1.

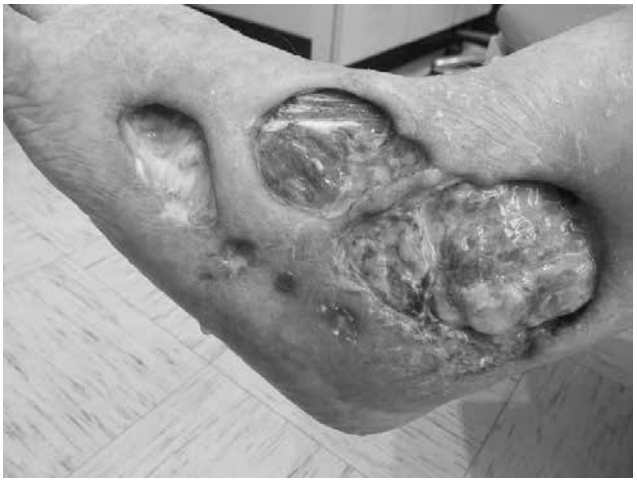

Figure 2.

Discussion

The answer is D: pyoderma gangrenosum. Pyoderma gangrenosum is an inflammatory, noninfectious, ulcerative skin disorder characterized by rapidly enlarging, painful lesions. Although the most common sites of involvement are the lower legs, buttocks, and abdomen, it may occur anywhere, including on mucosal surfaces.[1,2] Multiple lesions are usually present.[1] It is most common in adults 40 to 60 years of age.[3] It is rare in children, but head and anogenital involvement is more common in children than in adults.[1,2]

There are four variants: ulcerative, pustular, bullous, and vegetative. These variants may occur simultaneously.[1] Lesions begin as tender pustules or

Summary Table

Condition	Location	Characteristics
Cutaneous malignancies	Anywhere on skin	May be a result of squamous cell carcinoma, basal cell carcinoma, or melanoma; nonhealing ulcers
Factitial ulcers	More common on the extremities	Geometric, unusual shaped lesions; associated with psychiatric disease
Infectious ulcers	Anywhere on skin	May be caused by bacterial, deep fungal, parasitic, or atypical mycobacterial infections; diagnosed with tissue culture
Pyoderma gangrenosum	Most common on the lower leg	Sharply marginated, undermined ulcers with violaceous borders; associated with several chronic diseases such as inflammatory bowel disease; may occur after minor trauma
Venous stasis ulcers	Typically on the medial aspects of the lower legs	Nonhealing ulcers; associated with chronic venous insufficiency; comprise up to 80% of leg ulcers

erythematous nodules that enlarge, undergo necrosis, and then ulcerate.[2] A primary lesion is not always seen. Fully developed lesions are sharply marginated, undermined ulcers with violaceous borders.[3] The condition may develop spontaneously or at the site of trauma. Postsurgical pyoderma gangrenosum may be misdiagnosed as wound dehiscence or infection.[1] Because there are no diagnostic serologic or histologic features, pyoderma gangrenosum is diagnosed through exclusion.[3] An underlying chronic disease is present in around 50% of patients.[3] Inflammatory bowel disease is the most common association, but other conditions that have been reported include rheumatoid arthritis and myeloproliferative diseases.[4]

Cutaneous malignancies such as squamous cell carcinoma, basal cell carcinoma, and melanoma may develop in nonhealing ulcers, but there is often a history of a growth preceding the ulceration.[4] Biopsy is required for definitive diagnosis.[5]

Factitial ulcers may be suspected in patients with a history of psychiatric disease. The patient may present with geometric, unusual shaped lesions. These ulcers generally heal quickly if there is no repeated trauma.[5]

Bacterial, deep fungal, parasitic, and atypical mycobacterial infections can lead to ulcers. A travel history is important in considering tropical and parasitic diseases such as amebiasis and leishmaniasis. Tissue culture may be required for diagnosis.[5]

Venous stasis ulcers are nonhealing ulcers that are associated with chronic venous insufficiency. They are located on the medial aspects of the lower legs and comprise up to 80% of leg ulcers.[1,5] Stasis ulcers rarely occur below the level of the malleoli.[4]

REFERENCES

1. Pyoderma gangrenosum. In: Habif TP, et al., eds. Skin Disease: Diagnosis and Treatment. 3rd ed. Edinburgh, Scotland: Elsevier; 2011:624-627.
2. Pyoderma gangrenosum. In: Paller A, Mancini AJ, Hurwitz S. eds. Hurwitz Clinical Pediatric Dermatology: A Textbook of Skin Disorders of Childhood and Adolescence. 3rd ed. Philadelphia, Pa.: Elsevier Saunders; 2006:665-666.
3. Pyoderma gangrenosum. In: James WD, Berger TG, Elston DM, Odom RB, eds. Andrews' Diseases of the Skin: Clinical Dermatology. 10th ed. Philadelphia, Pa.: Elsevier Saunders; 2006:147-148.
4. Ulcers. In: Marks JG, Miller JJ, Lookingbill DP, eds. Lookingbill and Marks' Principles of Dermatology. 4th ed. Philadelphia, Pa.: Elsevier Saunders; 2006:255-259.
5. Hwang J, Wong E. Non-healing, non-tender ulcer on shin. J Fam Pract. 2015;64(7):421-424.

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Formula of 40

- An attack of asthma for the first time in life after the age of 40 unless proved otherwise is respiratory in origin.
- An attack of acidity occurring for the first time in life after the age of 40 is cardiac in origin unless proved otherwise.

Waveforms and Deflections in Toxicology

SUNTHARI RAJKUMAR*, VIJAYAKUMAR N†, NANJILKUMARAN A†, UMARANI R‡

ABSTRACT

Introduced as pieces of wires in the early 18th century, the electrocardiograph (ECG) machine has become an important clinical bedside tool. This easily available, user friendly, noninvasive, inexpensive investigation has spread its wings not only in the field of cardiology, but in almost all other medical fields. Herewith we present a synopsis of few case reports of drug overdose (digoxin, β-blockers, diazepam and tricyclic antidepressants) either accidental or by deliberate harmful intention who presented to our hospital, to highlight the importance of electrocardiogram (ECG) in toxicology field. One of the leading causes of mortality and morbidity is drug overdose and poisoning, more commonly in rural areas where sophisticated investigations like serum levels of toxins and treatment modalities may not be available. The cardiotoxic poisons bring changes in the ECG wave forms due to multiple effects, the most common being effects on ion channels. In such situations, ECG will help in early detection of life-threatening events, paving way for targeted and timely intervention.

Keywords: Waveforms, ion channels, cardiotoxic poisons, drug overdose

Electrocardiogram (ECG) is an important diagnostic tool in the field of cardiology as a patient with drug overdose and drug poisoning can present with typical ECG changes. Serial ECG is mandatory in patients with suspected exposure to cardiotoxic overdose.

Ionic current flow from cell to cell through the heart as a result of the activity of selectively permeable ion channels which, when activated transiently, open, allowing the movement of charged ions (Na^+, K^+, Cl^- and Ca^{2+}) across a muscle membrane that is otherwise impermeable. A sound knowledge of ECG interpretation and specific characteristics of cardiotoxic drugs is very much necessary to establish a good foundation for an early diagnosis and prompt management. Few case reports are presented here to highlight this fact.

CASE REPORT 1: BENZODIAZEPINE AND POTASSIUM CHANNEL

A 59-year-old female was brought to the emergency room (ER) with history of consumption of 10 mg diazepam tablets (unknown quantity). The patient was not a known case of hypertension, diabetes mellitus or coronary artery disease, had no other significant comorbid conditions and was not on any medications. There was no preceding history suggestive of any gastrointestinal disorders or underlying psychiatric disorders, trauma or similar weakness in the past. There was no significant family history.

At the time of presentation, the patient was slightly drowsy but was responding to oral commands. On examination, patient was afebrile, not anemic and not cyanosed and had no clubbing or pedal edema. She had a pulse rate of 90/min and blood pressure of 90/60 mmHg. Examination of cardiovascular system was normal. Bilateral air entry was present with no added sounds. Abdomen was not distended. Bowel sounds were present. Neurological examination revealed weakness of all four limbs with muscle power of Grade 3 with diminished deep tendon reflexes. There was no neck muscle weakness or ptosis. Pupils were equal and reacting to light. Fundus was normal. Bilateral plantars were flexors. Other modalities of neurological examination could not be elicited. Investigations revealed normal hemogram and renal parameters. Electrolyte analysis revealed sodium of 134 mEq/L, potassium of 2.5 mEq/L and chloride of 109 mEq/L. Arterial blood gas (ABG) analyses showed no evidence of acidosis or alkalosis.

ECG showed heart rate of 68 bpm, with normal sinus rhythm and no evidence of atrial enlargement or

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ventricular hypertrophy. There were no ST changes. However, prominent "U" waves were present in the precordial leads (V1-V3) (Fig. 1).

Following gastric decontamination, correction of potassium was done with potassium chloride. Figure 2 shows ECG after potassium chloride correction. Patient improved and was discharged on 7th day post-admission.

Diazepam

Diazepam, a prototype benzodiazepine, is the most commonly used drug for various effects acts on gamma-aminobutyric acid type A ($GABA_A$) receptor, as a positive allosteric modulator. It amplifies the inhibitory signal by opening the chloride ion channel, and thereby inhibits the neurons. With no risk of addiction and milder withdrawal symptoms, overdose is common and essentially never fatal. However, in a retrospective analysis of 53,931 people of diazepam poisoning, among the various side effects reported like hypotension, drowsiness, etc., 0.64% were found to have hypokalemia. Hypokalemia is more common in elderly females in the age group of 50-60 years. Several studies have found that the incidence of hypokalemia with diazepam overdose is maximum during the first few weeks and it steadily decreases with increasing duration of drug intake. The mechanism attributed to this includes the exhaustion of the $GABA_A$ receptors and resistance to diazepam on repeated exposures. If left unnoticed or untreated, diazepam can lead to major fatal outcomes such as impaired vision, ataxia, apnea, hypotension, respiratory depression, AV blocks and coma. Hypokalemia induced by diazepam is a rare yet a serious adverse effect, which is a completely reversible condition. Diazepam is the only benzodiazepine that does not cause QRS widening and oxazepam is the only one not causing prolongation of PR interval.

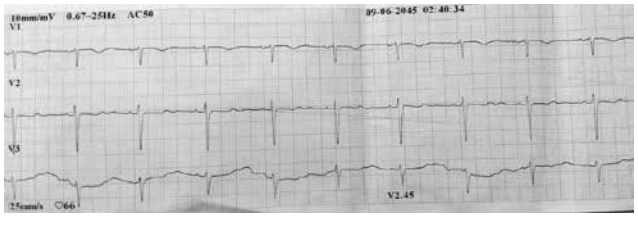

Figure 1. "U" waves.

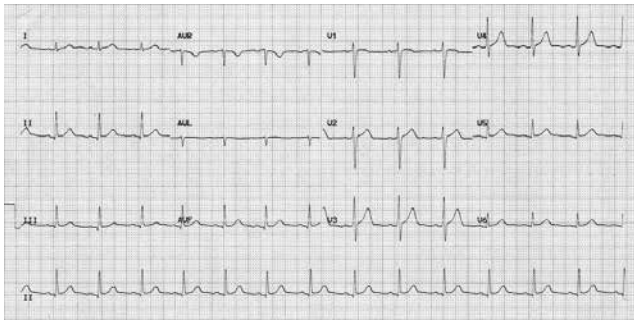

Figure 2. ECG taken after potassium chloride correction.

The use of flumazenil as an antidote for benzodiazepine poisoning is very less as the risks outweigh the benefits as it also acts as an inverse agonist. Hence, in the absence of a safe antidote, identifying the electrolyte imbalance by ECG and correcting them will be more relevant in diazepam poisoning.

CASE REPORT 2: TRICYCLIC-ANTIDEPRESSANT AND SODIUM CHANNEL

A 32-year-old female patient presented to ER after 3 hours of history of consumption of 10 tablets of amitriptyline (10 mg) and 10 tablets of clonazepam (0.5 mg). There was no preceding history of chest pain, palpitation, breathlessness, convulsions and loss of sensorium. She was a known case of psychogenic nonepileptic seizure for the past 1 year and was on regular treatment with amitriptyline 10 mg, clonazepam 0.5 mg and sodium valproate 600 mg. On examination, patient was drowsy, responding to deep painful stimuli and febrile. She had a pulse rate of 140/min and blood pressure of 100/60 mmHg. Pupils were equal and reacting to light. Fundus was normal. Plantar reflexes were flexors. Other modalities of neurological examination could not be elicited. Examination of cardiovascular system/respiratory system/abdomen was normal.

Investigations revealed a normal hemogram, renal parameters and metabolic acidosis (pH - 7.24, HCO_3^- - 11 mEq/L, pCO_2 - 35 mmHg). ECG was taken at the time of admission (Fig. 3 a-c).

Patient was treated with activated charcoal 1 g/kg and acidosis was corrected by sodium bicarbonate infusion.

Tricyclic Antidepressant Poisoning

Poisoning with tricyclic antidepressants (TCAs) is an important cause of drug-related poisoning with mortality of 1.3%. Neurological and cardiovascular toxicity, resulting in reduced levels of consciousness, reduced blood pressure and arrhythmias, are mainly responsible for mortality attributed to TCA overdose. It causes mild symptoms such as agitation, due to slow absorption in overdose, reduced by the cholinergic antagonist effects of TCA, which may worsen over time, leading to convulsions, coma and death.

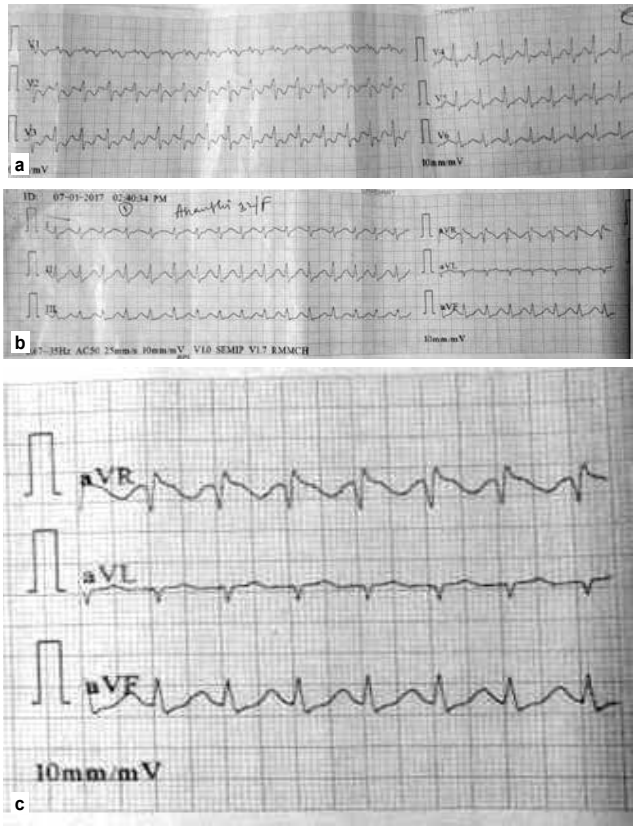

Figure 3 a-c. ECG figures reveal sinus tachycardia, right axis deviation, prolonged PR interval, QRS width prolongation with QTc interval of 0.506 sec, aVR was positive with deep S-wave.

Cholinergic antagonist effects of TCAs include delirium, widened pupils, reduced gut motility and retention of urine. Cardiovascular effects include α receptor blockage in vasodilatation, blockage of sodium channel resulting in increased depolarization time and the inhibition of potassium channels causing increased repolarization time and dysrhythmias. Neurological symptoms can include lowered levels of consciousness, due to antihistaminic effects and seizures due to TCA antagonist effects on the $GABA_A$ receptor.

ECG findings are used for:

- Risk stratification
- To guide subsequent therapy.

The typical ECG changes that can be found in a TCA overdose are QRS width >100 ms, QTc prolongation >430 ms and R/S ratio 0.7 in lead aVR, R in aVR of >3 mm and right axis deviation of 130-270° in the terminal 40 ms of the QRS. These ECG findings are identified as the most important risk stratification, more important than serum drug levels for the prediction of complications (seizure, dysrhythmias such as torsade de pointes) following a TCA overdose and thereby resolve by the administration of 1-2 units/kg of sodium bicarbonate. Sodium bicarbonate acts at three levels. It raises the sodium gradient across the affected sodium channel counteracting the drug-induced side effect of sodium channel blocking action, increases the pH, which promotes dissociation of TCA from cardiac sodium channels and finally TCAs bind more easily to protein in the higher pH range resulting in a lower pharmacologically active TCA concentration. Alkalinization to a pH of 7.45-7.55 is advised until normalization of the QRS interval, even in the absence of initial acidosis. When the PH becomes >7.6, the risk of dysrhythmias increases.

Similar ECG changes can occur in cocaine toxicity and class IA, IC antiarrhythmic drugs. Hence, these drugs should be avoided because of their ability to block cardiac sodium channels.

CASE REPORT 3: DIGITALIS AND CALCIUM CHANNEL

A 28-year-old male patient presented to ER with complaints of palpitation and giddiness of 2 hours duration. There was no history of chest pain, breathlessness, convulsions and loss of sensorium. He was a known case of rheumatic heart disease with atrial fibrillation for the past 2 years and was on regular treatment with digoxin 0.25. Inadvertently, he took 4 tablets of digoxin.

ECG was taken at ER which showed an irregular RR interval with controlled ventricular rate, absent P waves and inverse tick sign (Fig. 4).

Digoxin

A positive inotropic drug, digoxin inhibits the Na^+ K^+ ATPase, increases calcium concentration in the cell and thus, the effects of digoxin act through all 3 ions. Digoxin toxicity is most common in elderly patients with kidney injury and electrolyte imbalance like hypokalemia, hyperkalemia, hypercalcemia, calcium channel blockers and diuretics. Digoxin has very narrow therapeutic index (0.5-2 ng/mL).

Thus ECG helps us:

- *To find out toxicity versus effect*: Classical digoxin effect (Fig. 5): It appears as a down sloping of ST segment, also known as "Reverse tick"/"Reverse check sign."
- Digoxin toxicity (Fig. 6): The most common dysrhythmia associated with toxicity induced by

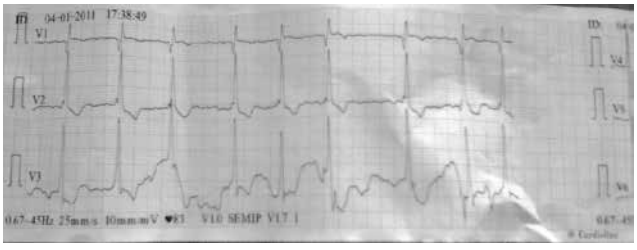

Figure 4. ECG showing irregular RR interval with controlled ventricular rate, absent P waves and inverse tick sign.

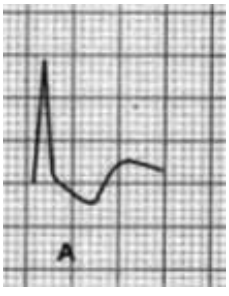

Figure 5. Digoxin effect - T wave rises above the baseline.

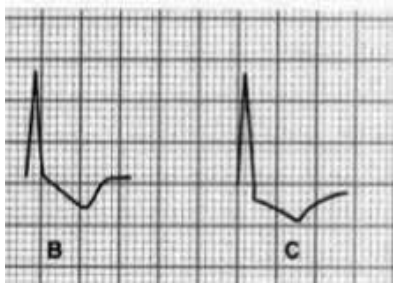

Figure 6. Digoxin toxicity - T wave does not rise above the baseline.

these agents is frequent premature ventricular beats, paroxysmal atrial tachycardia with variable block or accelerated junctional rhythm is highly suggestive of digitalis toxicity.

- *Help us to identify electrolyte disturbances*: Hyperkalemia is one of the indicator for Fab fragment treatment in digoxin toxicity, when estimation of serum digoxin level is not available or amount of ingested digoxin not known.

CASE REPORT 4: β BLOCKERS AND SODIUM, POTASSIUM CHANNELS

A 60-year-old female, known hypertensive, diabetic and dyslipidemic, on regular treatment, was brought to ER with history of giddiness since 2 hours duration. She had a dispute with her family members and consumed 10 tablets of antihypertensive drugs (bisoprolol). On examination, patient was conscious, responding to oral commands. She had a pulse rate of 45/min and blood pressure of 90/60 mmHg. Pupils were equal and reacting to light. Fundus was normal. Plantar reflexes were flexors. Other modalities of neurological examination could not be elicited. Examination of cardiovascular system/respiratory system/abdomen was normal.

ECG taken at ER showed heart rate of 42/min, NSR, no ST, T-wave changes (Fig. 7).

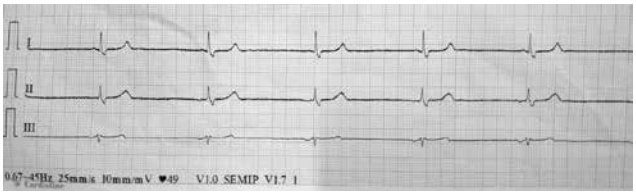

Figure 7. ECG showing no ST, T-wave changes.

β-blocker Toxicity

β blockers act mainly on cardiac β_1 receptors and produce decreased automaticity, negative chronotropic and inotropic effect. Hence, these drugs not only have a direct effect on the myocardium, but also exert an indirect effect by blocking the sodium and the potassium channels, thereby depressing sinoatrial and atrioventricular nodal activity.

The hallmark of β-blocker poisoning is myocardial depression and decreased contractility leading to bradycardia, hypotension and in large dose, cardiogenic shock. Highly lipophilic β blockers like propranolol readily cross the blood-brain barrier and can produce central nervous system (CNS) effects such as seizures and coma. β blockers with membrane stabilizing property, such as propranolol or acebutolol, may prolong the QRS interval (>0.10 sec) and predispose to dysrhythmias. These inhibitory effects of propranolol on the fast inward sodium current producing prolongation of QRS may be used as predictors of propranolol-induced seizures. Prolonged PR can be an early sign of β-blocker overdose. Propranolol overdose has been associated with a higher mortality rate compared with other β blockers. Sotalol is a unique β-blocker in that it possesses the ability to block delayed rectifier potassium channels in a dose-dependent fashion.

General goals of therapy are aimed at improving the inotropic and chronotropic effect. Potential intervention utilized to manage severe toxicity includes intravenous fluid, atropine, glucagon, calcium and vasopressors.

CONCLUSION

To summarize, the myocardial resting and action potential depends mainly on sodium, potassium and calcium ion channels. Many cardiotoxic poisons have well-known effect on these channels producing varied ECG findings. Hence, toxidrome approach, in the management of poisoning, should also include ECG interpretation for guided, targeted, interventions.

Toxidrome approach: In patients with normal sinus rhythm (like TCA toxicity), subtle changes like prolonged QTC, etc. should be looked for. Bradycardia

in poisoned patients can be assessed with the toxidrome approach to search for signs of toxicity of drugs like digoxin overdose (PVC), β-blocker poisoning (AV block). ECG of tachycardia patients should be assessed for wide complexes (TCA poisoning, Na^+ channel blockade drugs) - R-wave in aVR, S in lead 1, aVL; QTc prolongation and ischemia.

Reasonable period of observation in patients with normal ECG without other signs of cardiotoxicity is usually 6-8 hours, but in patients exposed to sustained release preparations or drugs (like citalopram) with delayed toxicity may be beyond 24 hours. Serial ECGs should be performed in patients with suspected cardiotoxicity.

SUGGESTED READING

1. Zisterer DM, Williams DC. Peripheral-type benzodiazepine receptors. Gen Pharmacol. 1997;29(3):305-14.
2. Izgi C, Erdem G, Mansuroglu D, Kurtoglu N, Kara M, Gunesdogdu F. Severe hypokalemia probably associated with sertraline use. Ann Pharmacother. 2014;48(2):297-300.
3. Eizadi-Mood N, Montazeri K, Dastjerdi MD. Evaluation of cardiovascular manifestations in benzodiazepine poisoning. Iranian J Toxicol. 2011;4(4):373-6.
4. Mullins ME. First-degree atrioventricular block in alprazolam overdose reversed by flumazenil. J Pharm Pharmacol. 1999;51(3):367-70.
5. Boehnert MT, Lovejoy FH Jr. Value of the QRS duration versus the serum drug level in predicting seizures and ventricular arrhythmias after an acute overdose of tricyclic antidepressants. N Engl J Med. 1985;313(8):474-9.
6. McKinney PE, Rasmussen R. Reversal of severe tricyclic antidepressant-induced cardiotoxicity with intravenous hypertonic saline solution. Ann Emerg Med. 2003; 42(1):20-4.
7. McCabe JL, Cobaugh DJ, Menegazzi JJ, Fata J. Experimental tricyclic antidepressant toxicity: a randomized, controlled comparison of hypertonic saline solution, sodium bicarbonate, and hyperventilation. Ann Emerg Med. 1998;32(3 Pt 1):329-33.
8. Hoffman JR, Votey SR, Bayer M, Silver L. Effect of hypertonic sodium bicarbonate in the treatment of moderate-to-severe cyclic antidepressant overdose. Am J Emerg Med. 1993;11(4):336-41.
9. Høegholm A, Clementsen P. Hypertonic sodium chloride in severe antidepressant overdosage. J Toxicol Clin Toxicol. 1991;29(2):297-8.
10. Holstege CP, Eldridge DL, Rowden AK. ECG manifestations: the poisoned patient. Emerg Med Clin North Am. 2006;24(1):159-77, vii.
11. Ma G, Brady WJ, Pollack M, Chan TC. Electrocardiographic manifestations: digitalis toxicity. J Emerg Med. 2001; 20(2):145-52.
12. Reith DM, Dawson AH, Epid D, Whyte IM, Buckley NA, Sayer GP. Relative toxicity of beta blockers in overdose. J Toxicol Clin Toxicol. 1996;34(3):273-8.
13. Buiumsohn A, Eisenberg ES, Jacob H, Rosen N, Bock J, Frishman WH. Seizures and intraventricular conduction defect in propranolol poisoning. A report of two cases. Ann Intern Med. 1979;91(6):860-2.
14. Love JN, Howell JM, Newsome JT, Skibbie DF, Dickerson LW, Henderson KJ. The effect of sodium bicarbonate on propranolol-induced cardiovascular toxicity in a canine model. J Toxicol Clin Toxicol. 2000;38(4):421-8.

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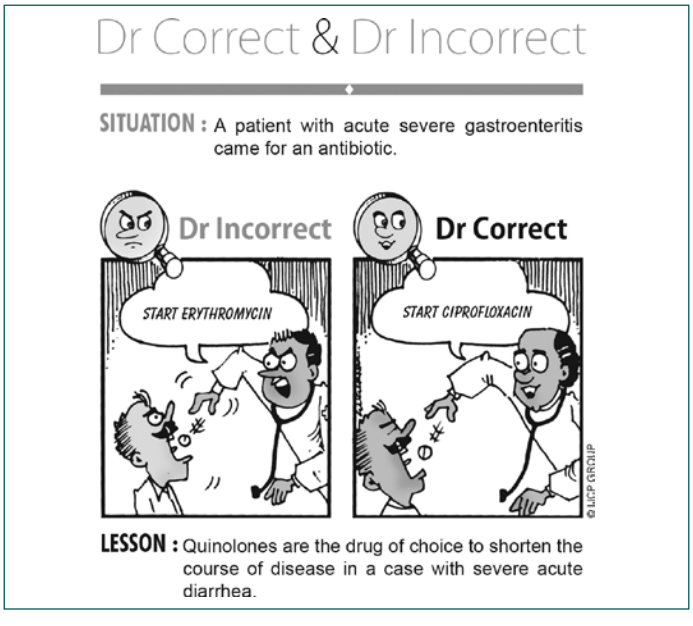

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A Frog in the Well's Score – Shortcomings of the Well's Score for Diagnosis of Acute Pulmonary Embolism

SANDEEP NATHANAEL DAVID*, SURESH SAMUEL DAVID†

ABSTRACT

Pulmonary embolism (PE) is one of the leading causes of undiagnosed deaths in patients worldwide due to its unpredictable clinical course and mimicry of various other diseases. The often over-used simplified Well's score and D-dimer test must be utilized with prudence to stratify the probability of PE. Astute interpretation of electrocardiography (ECG) signs and bedside echocardiography findings has helped Emergency Physicians narrow down a diagnosis of PE. PE remains a diagnostic challenge; nevertheless, with high index of suspicion, appropriate understanding of clinical probability scores and use of bedside screening tests like ECG and bedside echocardiography, PE can be rapidly diagnosed and managed in the Emergency Department.

Keywords: Emergency Department, pulmonary embolism, Well's score, bedside echocardiography, empirical heparin, CT pulmonary angiogram, McConnell's sign

Pulmonary embolism (PE) is one of the leading causes of undiagnosed deaths in patients worldwide due to its unpredictable clinical course, highly variable symptomatology, mimicry of various other diseases and difficulty in obtaining reliable diagnostic tests. The triad of cough, dyspnea and hemoptysis is found in abysmally low number of patients with PE. The often over-used simplified Well's score and D-dimer test must be utilized with prudence to stratify the probability of PE prior to confirmation with a computed tomography pulmonary angiography (CTPA), which is the gold standard diagnostic test for PE. However, high cost, unavailability in all medical centers, reliance on a normal renal function and high radiation output often make it unfeasible for all patients. Astute interpretation of pathognomonic electrocardiography (ECG) signs and characteristic bedside echocardiography findings have shown promise in helping Emergency Physicians narrow down a diagnosis of PE, as well as rapidly confirming the presence or absence of other conditions, which present in similar fashion. Studies have also shown that initiation of 'empirical heparin' in the Emergency Department (ED) greatly reduced morbidity and mortality in such patients for whom PE is suspected, but a CTPA is either delayed or not feasible. We present the case of a 76-year-old male with a different presentation from the usual described triad of PE. This shows how a broad suspicion and bedside echocardiography help in rapid diagnosis and treatment.

CASE REPORT

Mr KV, a 76-year-old man was brought to the ED, with a laceration measuring 7 cm, over the right parietal area of his scalp, associated with history of collapse in the bathroom early that morning. There were no witnessed seizures and he regained consciousness while in the ambulance towards the hospital, but vomited 4 times in quick succession. Over the last 1 month, he had suffered from recurrent fainting spells, which resolved spontaneously over half an hour and with no associated seizures or vomiting. He was not a smoker or consumer of alcohol, neither had he ever had any previous surgeries. There was no prior history of diabetes, hypertension, chronic kidney disease, ischemic heart disease, asthma or chronic obstructive pulmonary disease. On arrival, he was conscious and oriented (Glasgow Coma Scale [GCS] 15/15), with bilateral equally reactive pupils. He was

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afebrile with regular pulse rate of 116/min and blood pressure of 140/90 mmHg. Although he had no respiratory discomfort, his respiratory rate was 26/min with pulse oximetry of 88% on room air. There was a 7 cm horizontal laceration over his right parietal region and the rest of systemic examination was unremarkable.

Arterial blood gas analysis demonstrated hypoxia (PaO_2 = 68% with an SaO_2 of 86%), but no other significant findings. His chest X-ray was unremarkable. Plain computed tomography (CT) brain was undertaken on account of sudden collapse in the toilet with multiple episodes of vomiting as well as similar episodes of collapse, in the past. However, it was a normal study. Baseline blood investigations indicated leukocytosis of 16,100/mm^3, with serum creatinine of 1.7 mg/dL. Due to his "comfortable hypoxia", the absence of clinical chest findings and persistent tachycardia, a diagnosis of PE was considered. Well's score was calculated to be 4.5 and bedside D-dimer assessment was found to be 4,910 ng/mL.

The ECG showed sinus tachycardia (Fig. 1). Bedside echocardiography showed dilated right ventricle and right atrium with positive McConnell's sign, i.e., regional right ventricular (RV) dysfunction, akinesia of the mid free wall, but normal motion at the apex. CTPA was deferred due to elevated creatinine. Unfractionated heparin therapy was empirically initiated with bolus dose of 5,000 units IV, and continued thereafter. The patient was admitted for further care and 3 days later, after normalizing the serum creatinine, CTPA was performed, confirming the diagnosis of PE - multiple filling defects involving the right pulmonary artery extending into the segmental branches. A representative image from the scan series is enclosed (Fig. 2). The patient was treated with 5 days of IV unfractionated heparin, after which he was discharged in a stable condition, on warfarin.

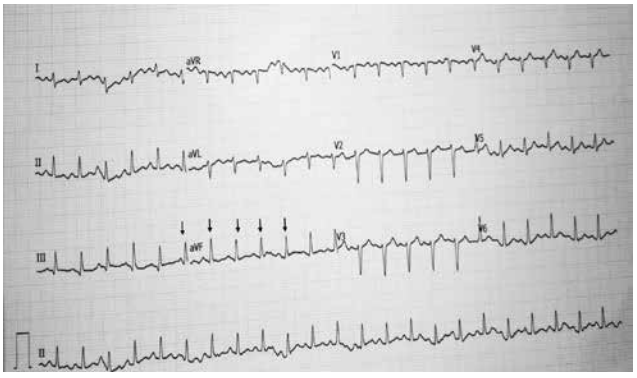

Figure 1. ECG of patient. Black arrows indicate sinus tachycardia.

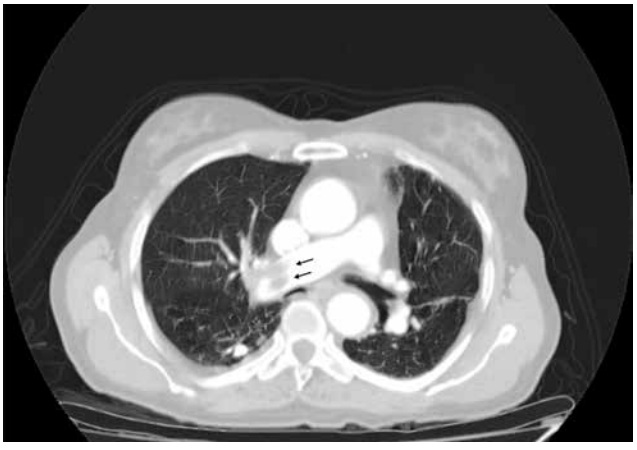

Figure 2. CTPA (*black arrows*) indicating multiple filling defects involving the right pulmonary artery extending into the segmental branches.

DISCUSSION

Acute PE is a major harbinger of death, a major cause of undiagnosed mortality worldwide. The diagnosis of PE has always been challenging, as it is the second leading cause of sudden death without a discernible cause, due to wide variety of presenting symptoms, quick progression and paucity of rapid diagnostic modalities with high sensitivity and specificity. The typical triad of 'Chest Pain, Dyspnea and Hemoptysis' is found in absurdly few number of patients, and presentation of PE can vary greatly. The presentation could be extremely subtle with rare occurrences such as seizures, as part of the symptom complex. In fact, PE was identified in nearly 1 of every 6 patients hospitalized for a first episode of syncope. The commonly employed Well's score, though a useful clinical screening tool, has limited diagnostic capacity in PE. Conditions such as pneumonia, pneumothorax, sepsis or even panic attacks would sufficiently satisfy the Well's score criteria and lead to over-investigation for PE. Further, the challenge for diagnosis is frequently compounded by significant delay in organizing CTPA, due to multiple factors including unstable hemodynamic status of patient, deranged renal function and delay in obtaining CT in centers, which do not have the privilege of 24 × 7 imaging services.

Role of ECG

The role of ECG in prognosticating PE is increasingly recognized. The ECG in addition to clinical acumen, steers the Emergency Physician towards the diagnosis. McGinn and White described the first association between acute PE and specific ECG changes when they noted the familiar 'S1Q3T3' pattern in 7 patients

with acute cor pulmonale. However, it is reported that patients with normal ECGs at admission revealed diagnostic features of embolism in serial ECGs carried out subsequently. ECG findings in PE range from sinus tachycardia (44% of patients), right axis deviation (16% of patients), right bundle branch block (18% of patients), inverted T waves in leads V1-V4 (right ventricular strain pattern - 18% of patients), and the "S1Q3T3" pattern (20% of patients), and any one of these findings doubles the probability of PE. The most common ECG changes when compared with previous ECG in the setting of PE are T-wave inversion and flattening, most commonly in the inferior leads, and occurring in approximately one-third of cases. It has been observed that approximately one-quarter of patients will have new-onset sinus tachycardia.

The fact that ECG provides invaluable information for PE prognostication was reaffirmed by a meta-analysis of 39 studies (9,198 patients). ECG signs that were good predictors of a negative outcome included S1Q3T3, complete right bundle branch block, T-wave inversion, right axis deviation and atrial fibrillation for in-hospital mortality. It was concluded that ECG is potentially valuable in prognostication of acute PE. Moreover, changes in right-sided chest leads occur frequently in PE. Routinely recorded right-sided ECG appears to possess the greatest potential for diagnosing acute PE in patients who have not manifested typical changes in their standard 12-lead ECGs. However, it needs to be emphasized that approximately one-quarter of patients with PE may have no changes in their ECG.

Fragmented QRS (fQRS) is a convenient marker of myocardial scar evaluated by 12-lead ECG and is defined as additional spikes within the QRS complex. The presence of fragmented QRS complex (fQRS), as a simple and feasible ECG marker, seems to be a novel predictor of in-hospital adverse events and long-term all-cause mortality in PE patient population. There is scarcity of data on the prognostic importance of fQRS on short- and long-term outcomes in patients with PE.

Bedside Echocardiography

Bedside echocardiography demonstrates right ventricular dilation, reduced contractility with apical sparing, which is known as McConnell's sign and is very specific in acute PE.

Both these tests are useful for patients who are too unstable to be shifted out of the ED for CTPA, or who have deranged renal parameters, which make the use of IV contrast risky. Thrombolytic therapy, based on bedside echocardiography, has also been shown to produce successful outcome in low-resource settings.

D-dimer

D-dimer is a fibrin breakdown product which is elevated whenever the fibrinolytic system of the body is activated. The usage of D-dimer as a diagnostic marker for PE is to be discouraged, since the differential diagnoses for elevated D-dimer values in the setting of dyspnea are numerous, including sepsis, hemothorax, myocardial infarction, congestive cardiac failure, etc. D-dimer has very high sensitivity (up to 95%), but low specificity (approximately 45%) for PE, and must only be used as a 'rule out' rather than diagnostic test for patients with a low pre-test probability of PE. In a recent study on 614 patients, it has been reported that ECG signs of right ventricular strain are strongly related to elevated cardiac biomarkers and echocardiographic signs of right ventricular overload.

However, rapid point-of-care testing for D-dimer in patients who have simplified Well's score of <4, would be beneficial to indicate the clinical pathway to investigate for PE. A triad of circulatory collapse, right ventricular dilatation and large alveolar dead space is proposed for the rapid diagnosis and treatment of massive PE.

Thrombolytic Therapy

The role of thrombolytic therapy in acute PE patients is still controversial and early-onset thrombolytic therapy in the ED for high-risk and hemodynamically worsening patients appears safe and life-saving. Short-term effects of thrombolytics are well-known, whereas long-term effects on cardiac electrophysiology have not been reported before. In the absence of contraindications, it is reasonable to administer a patient with suspected PE 'empirical heparin' before confirmatory imaging, as early anticoagulation therapy is vital for management of acute PE and delay of which increases mortality significantly. Low-molecular weight heparin (LMWH) has several advantages over unfractionated heparin; however, in cases of deranged renal function, as seen in this case, unfractionated heparin is preferred.

CONCLUSION

Rapid diagnosis of PE in the ED greatly improves survival rates, but requires a systematic, multivariate approach involving high clinical suspicion, good understanding of pre-test probability with appropriate use of D-dimer, use of easily available bedside modalities such as ECG and bedside echocardiography and ideally, CTPA. Treatment can be started in the

ED on an empirical basis with unfractionated heparin, which can be continued or stopped depending on the angiography report. High Well's score is not diagnostic of PE in itself, neither is elevated D-dimer level. Appropriate clinical judgment must be used along with pre-test probability scoring and appropriate testing of D-dimer levels for all low-risk patients only. ECG and bedside echocardiography can be used for patients with elevated D-dimer levels to assess the right ventricular function and guide the Emergency Physician to start empirical heparin before shifting the patient for a CTPA.

SUGGESTED READING

1. Todd K, Simpson CS, Redfearn DP, Abdollah H, Baranchuk A. ECG for the diagnosis of pulmonary embolism when conventional imaging cannot be utilized: a case report and review of the literature. Indian Pacing Electrophysiol J. 2009;9(5):268-75.
2. Hashmani S, Tipoo Sultan FA, Kazmi M, Yasmeen A. Massive pulmonary embolism presenting as seizures. J Pak Med Assoc. 2016;66(12):1656-8.
3. Prandoni P, Lensing AW, Prins MH, Ciammaichella M, Perlati M, Mumoli N, et al; PESIT Investigators. Prevalence of pulmonary embolism among patients hospitalized for syncope. N Engl J Med. 2016; 375(16):1524-31.
4. Aydoğdu M, Topbaşi Sinanoğlu N, Doğan NO, Oğuzülgen IK, Demircan A, Bildik F, et al. Wells score and Pulmonary Embolism Rule Out Criteria in preventing over investigation of pulmonary embolism in emergency departments. Tuberk Toraks. 2014;62(1):12-21.
5. McGinn S, White P. Acute cor pulmonale resulting from pulmonary embolism. JAMA. 1935;104(17):1473-80.
6. Sreeram N, Cheriex EC, Smeets JL, Gorgels AP, Wellens HJ. Value of the 12-lead electrocardiogram at hospital admission in the diagnosis of pulmonary embolism. Am J Cardiol. 1994;73(4):298-303.
7. Patra S, Math RS, Shankarappa RK, Agrawal N. McConnell's sign: an early and specific indicator of acute pulmonary embolism. BMJ Case Rep. 2014;2014. pii: bcr2013200799.
8. Qaddoura A, Digby GC, Kabali C, Kukla P, Zhan ZQ, Baranchuk AM. The value of electrocardiography in prognosticating clinical deterioration and mortality in acute pulmonary embolism: A systematic review and meta-analysis. Clin Cardiol. 2017;40(10):814-24.
9. Akula R, Hasan SP, Alhassen M, Mujahid H, Amegashie E. Right-sided EKG in pulmonary embolism. J Natl Med Assoc. 2003;95(8):714-7.
10. Co I, Eilbert W, Chiganos T. New electrocardiographic changes in patients diagnosed with pulmonary embolism. J Emerg Med. 2017;52(3):280-5.
11. Cetin MS, Ozcan Cetin EH, Arisoy F, Kuyumcu MS, Topaloglu S, Aras D, et al. Fragmented QRS complex predicts in-hospital adverse events and long-term mortality in patients with acute pulmonary embolism. Ann Noninvasive Electrocardiol. 2016;21(5):470-8.
12. Mahajan AU, Laddhad DS, Bohara D, Laddhad SD, Dinde YT, Bhabad SS. Successful thrombolysis of a large pulmonary artery thrombosis. J Assoc Physicians India. 2016;64(6):80-1.
13. Kukla P, Kosior DA, Tomaszewski A, Ptaszyńska-Kopczyńska K, Widejko K, Długopolski R, et al. Correlations between electrocardiogram and biomarkers in acute pulmonary embolism: Analysis of ZATPOL-2 Registry. Ann Noninvasive Electrocardiol. 2017;22(4).
14. Gazmuri RJ, Patel DJ, Stevens R, Smith S. Circulatory collapse, right ventricular dilatation, and alveolar dead space: A triad for the rapid diagnosis of massive pulmonary embolism. Am J Emerg Med. 2017;35(6):936. e1-936.e4.
15. Beydilli İ, Yılmaz F, Sönmez BM, Kozacı N, Yılmaz A, Toksul İH, et al. Thrombolytic therapy delay is independent predictor of mortality in acute pulmonary embolism at emergency service. Kaohsiung J Med Sci. 2016;32(11):572-8.
16. Hayıroğlu Mİ, Keskin M, Uzun AO, Tekkeşin Aİ, Avşar Ş, Öz A, et al. Long-term antiarrhythmic effects of thrombolytic therapy in pulmonary embolism. Heart Lung Circ. 2017;26(10):1094-100.

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Formula of 10

- Start CPR within 10 minutes.
- Continue CPR for at least 10 minutes.
- Give at least 10 x 10, 100 compressions per minute.
- Assume the patient is in cardiac arrest if there is no breathing or abnormal breathing (e.g., gasping) or if a pulse cannot be readily palpated within 10 seconds.

Symptom Correlation in Patients Undergoing Ambulatory 24-hour pH Study

MAYANK JAIN,* M SRINIVAS*, JAYANTHI VENKATARAMAN*

ABSTRACT

Background: There is scarce data from India on symptom correlation in patients undergoing ambulatory 24-hour pH monitoring. **Aim:** Retrospective analysis of symptom correlation in patients undergoing ambulatory 24-hour pH study at our center. **Material and methods:** The study included patients who had 24-hour pH testing from 2015 to 2017 for typical or extra-esophageal symptoms of gastroesophageal reflux disease (GERD). Patient information included age, gender and indications for the pH study. Collected data included reflux details in upright and recumbent position, correlation with meals, duration and number of reflux events, Johnson/DeMeester score, symptom index (SI) and symptom sensitivity index (SSI). Descriptive analysis was carried out by median and range for quantitative variables, and frequency and proportion for categorical variables. Chi-square tests and Mann-Whitney *U* test were used. P value <0.05 was considered statistically significant. **Results:** Thirty-six of the 66 patients had Johnson/DeMeester score >14.7 (Group 1). Heartburn, regurgitation and extra-esophageal symptoms were significantly more common in Group 1. These patients also had significantly more reflux in both upright and supine position, with significant reflux episodes in both positions. They also had more reflux episodes lasting for more than 5 minutes. Post meal reflux episodes were common. SI was significantly high in Group 1. The positive symptom correlation, as assessed by SI >50% and SSI >10%, was higher for heartburn, regurgitation compared to chest pain and extra-esophageal symptoms, although not statistically significant. **Conclusion:** About 45% of patients undergoing pH study had no pathological reflux. 24-hour pH study is useful to identify pathological acid exposure with good symptom correlation for typical as well as extra-esophageal symptoms.

Keywords: Reflux, symptom, severity, esophagus

Newer techniques for esophageal functional testing, such as impedance testing and wireless pH capsule monitoring, are currently available in most centers in the West. With impedance testing, movements of liquid and air within the esophageal lumen, either in an antegrade or retrograde direction, can be monitored and reflux can be detected independently of the acid in the refluxate.[1] Combined pH impedance monitoring can identify the causative agent for extra-esophageal symptoms of reflux.[2] Wireless pH capsule is well-tolerated by most patients and improves symptom assessment in those with atypical reflux symptoms in comparison to 24-hour pH monitoring.[3,4]

In India, ambulatory 24-hour esophageal pH monitoring is most popular and widely used. It provides quantitative information on esophageal acid exposure and symptom correlation with acid exposure events. Indications for 24-hour pH testing in our setting include testing prior to fundoplication, evaluation of nonerosive reflux disease, extra-esophageal symptoms of gastroesophageal reflux disease (GERD) and poor response to medical management. Symptom correlation in these patients may guide us to appropriate management.

The present study is a retrospective analysis of symptom correlation in patients undergoing ambulatory 24-hour pH study at GI Motility Unit, Institute of GI and HPB Sciences, Gleneagles Global Health City, Chennai, Tamil Nadu, India. A Johnson/DeMeester score of >14.7 pH was considered as significant for acid reflux in patients with typical and extra-esophageal symptoms of GERD.[5]

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MATERIAL AND METHODS

The study was retrospective and included patients who had 24-hour pH testing from 2015 to 2017 for typical or extra-esophageal symptoms of GERD. Patient information included age, gender and indications for the pH study. Gastroesophageal reflux (GER) symptoms were categorized as: typical GER symptoms (heartburn, regurgitation, dysphagia or combination), noncardiac chest pain and extra-esophageal symptoms that included hoarseness of voice, chronic cough, otalgia, wheeze and constant throat clearance.

The procedure was done using single sensor pH probe using standard protocol. The localization of the lower esophageal sphincter (LES) was determined by high resolution esophageal manometry (HREM). The pH probe was then passed into the stomach and using pull-through technique was placed 5 cm above the LES. Patients were asked to note a symptom directed documentation in relation to meal and posture (upright or supine). In addition, they were asked to identify three predominant symptoms that they associated with GERD and accordingly to tap the code on the pH recorder when these occurred. The data was stored via an interface on a compatible computer. Analysis was performed using computerized software and was also reviewed manually.

Data obtained included reflux details in upright and recumbent position, correlation with meals, duration and number of reflux events. Johnson/DeMeester score was available in the final computerized analysis.

Correlation of symptoms with pH was done by calculating symptom index (SI) for all the symptoms mentioned by the patient using the computerized software and values >50% were taken as positive. Symptom sensitivity index (SSI) was calculated for all the cases manually and values >10% were considered positive.[6,7] Both SI and SSI provide data on the strength of the association between symptoms and severity of reflux. The SI does not incorporate the total number of reflux episodes into account. Likewise, SSI does not take into account the total number of symptom episodes.

The flow chart of the study is shown in Figure 1.

Statistical Analysis

The data was entered in Microsoft Excel sheet. Descriptive analysis was carried out by median and range for quantitative variables, and frequency and proportion for categorical variables. Chi-square tests and Mann-Whitney *U* test were used to assess statistical significance. A p value <0.05 was considered statistically significant.

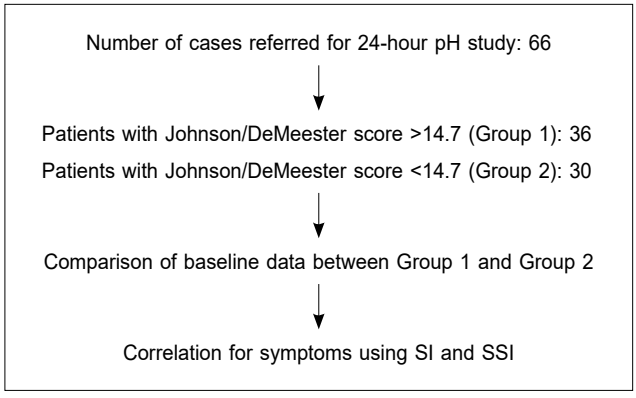

Figure 1. Flowchart of the study.

RESULTS

Sixty-six patients underwent upper endoscopy and ambulatory 24-hour pH monitoring during the study period. Endoscopy was normal in 52 (78.8%) and 13 of the remaining 14 had Los Angeles (LA) Grade A esophagitis. One patient had LA Grade B esophagitis. Thirty-six of the 66 patients had Johnson/DeMeester score >14.7 (Group 1).

Between Group 1 and Group 2, there was no difference in age and gender distribution (Table 1). Heartburn, regurgitation and extra-esophageal symptoms were significantly more common in Group 1. These patients also had significantly more reflux in both upright and supine position, with significant higher number of reflux episodes in both positions. They also had more reflux episodes lasting for more than 5 minutes. Post meal reflux episodes were common. SI was significantly high in Group 1.

Symptom Correlation as Noted by SI and SSI in Group 1

The positive symptom correlation, as assessed by SI >50%, was highest in patients with typical symptoms and least for those with extra-esophageal symptoms, but not statistically significant (p = 0.483) (Table 2). Similarly, the SSI was greater for heartburn, regurgitation compared to chest pain and extra-esophageal symptoms, although not statistically significant (Table 2).

DISCUSSION

The study highlights that 45% of patients undergoing pH study had no pathological reflux. Patients with pathological reflux presented with heartburn, regurgitation and extra-esophageal symptoms in both

Table 1. Comparison of Group 1 and Group 2

Parameter	Group 1 DM score >14.7 (n = 36)	Group 2 DM score <14.7 (n = 30)	P value
Age in years (median)	48 (25-72)	45 (24-69)	0.34
Sex (M:F)	22:14	24:6	0.09
Symptoms present in one or more combinations			
Heartburn	32 (88.8%)	14 (46.7%)	<0.0001
Regurgitation	28 (77.7%)	14 (46.7%)	0.002
Chest pain	7 (19.4%)	02 (6.6%)	0.08
Extra-esophageal symptoms	19 (52.7%)	06 (20%)	0.001
Upright pH <4 for >6.3% of time	18 (50%)	0 (0%)	<0.0001
Recumbent pH <4 for >1.2% of time	26 (72.2%)	6 (16.6%)	<0.0001
Median no. of reflux episodes in upright posture	63 (1-268)	23 (0-74)	<0.0001
Median no. of reflux episodes in recumbent position	18 (0-260)	3 (0-34)	0.002
Median no. of episodes >5 min	3 (0-23)	0 (0-1)	<0.0001
Median duration of longest episode of reflux in minutes	9 (0-781)	3 (0-17)	<0.0001
Median symptom index with meals	55.07% (0-100%)	21.2% (0-100%)	<0.0001
SI >50% (for all symptoms)	73/86 (84.8%)	18/36 (50%)	0.0001

DM: Johnson/DeMeester score.

Table 2. Correlation of SI and SSI with Symptoms

	Heartburn (n = 32)	Regurgitation (n = 28)	Chest pain (n = 7)	Atypical features (n = 19)	P value
Correlation of symptoms with SI					
Positive (>50%)	28 (87.5%)	25 (89.3%)	6 (85.7%)	14 (73.7%)	0.483
Negative <50%	4 (12.5%)	3 (10.7%)	1 (14.3%)	5 (26.3%)	
Correlation of symptoms with SSI					
Positive (>10%)	24 (67%)	22 (61%)	3 (43%)	9 (47.3%)	0.43
Negative (<10%)	12 (33%)	14 (39%)	4 (57%)	10 (52.7%)	

upright and supine position, with more frequent reflux episodes in either position lasting more than 5 minutes compared to those with a normal pH, with longer duration of reflux episodes with symptoms after a meal. Symptom correlation in those with pathological reflux was higher for typical GERD symptoms like regurgitation and heartburn.

Functional heartburn is characterized by the presence of symptoms of heartburn with physiological acid exposure while hypersensitive esophagus is characterized by normal acid exposure but positive correlation between symptoms and acid reflux events.[8] In our cohort of patients, 15 patients in Group 2 had normal acid exposure but an SI >50% and represent the hypersensitive esophagus subset. Addition of impedance monitoring to pH monitoring is likely to yield higher symptom correlation using various scoring systems.[9,10]

Ambulatory 24-hour esophageal pH monitoring has the ability to correlate symptoms with acid exposure events. SI and SSI are simple indices that assist in predicting response to proton pump inhibitors.[11] Despite these advantages, ambulatory pH monitoring has a few shortcomings too. It does not take into account the day-to-day variation in acid exposure[12] and the recommended

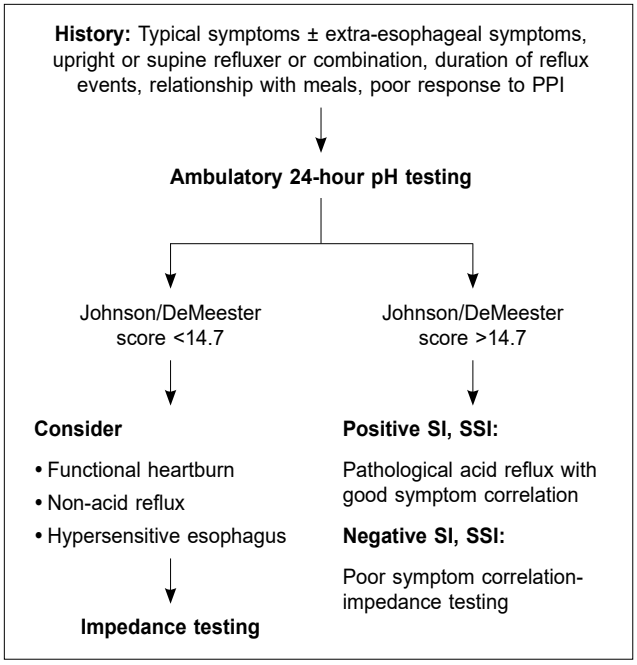

Figure 2. Interpretation of 24-hour ambulatory pH study.

cut-offs to distinguish pathological from physiological reflux differ considerably in various studies.[5,13,14] Furthermore, the available symptom indices rely on patient's recording of events. For example, frequent tappings or inappropriate pressing of position/symptom codes may lead to errors in analysis.

Earlier studies have highlighted a good correlation between pathological acid exposure time and symptoms like heartburn and regurgitation.[15] However, temporal relation of symptoms like globus sensation, hoarseness, chronic cough[9] and chest pain[10,16] with acid reflux is less clear. Furthermore, functional heartburn and hypersensitive esophagus can also coexist and interfere with symptom correlation.

Based on our preliminary observations and review of literature, we recommend an algorithmic approach for Indian patients undergoing ambulatory pH testing (Fig. 2).

To conclude, 24-hour pH study is useful to identify pathological acid exposure with good symptom correlation for typical as well as extra-esophageal symptoms. However, in those with physiological acid exposure with persistent symptoms and poor symptom correlation, impedance testing has an important role.

REFERENCES

1. Silny J. Intraluminal multiple electric impedance procedure for measurement of gastrointestinal motility. Neurogastroenterol Motil. 1991;3(3):151-62.
2. Sifrim D, Dupont L, Blondeau K, Zhang X, Tack J, Janssens J. Weakly acidic reflux in patients with chronic unexplained cough during 24 hour pressure, pH, and impedance monitoring. Gut. 2005;54(4):449-54.
3. Pandolfino JE, Richter JE, Ours T, Guardino JM, Chapman J, Kahrilas PJ. Ambulatory esophageal pH monitoring using a wireless system. Am J Gastroenterol. 2003;98(4):740-9.
4. Clouse RE, Prakash C, Haroian LR. Symptom association tests are improved by the extended ambulatory pH recording time with the Bravo capsule. Gastroenterology. 2003;124(4 Suppl 1):A537.
5. Johnson LF, Demeester TR. Twenty-four-hour pH monitoring of the distal esophagus. A quantitative measure of gastroesophageal reflux. Am J Gastroenterol. 1974;62(4):325-32.
6. Wiener GJ, Richter JE, Copper JB, Wu WC, Castell DO. The symptom index: a clinically important parameter of ambulatory 24-hour esophageal pH monitoring. Am J Gastroenterol. 1988;83(4):358-61.
7. Breumelhof R, Smout AJ. The symptom sensitivity index: a valuable additional parameter in 24-hour esophageal pH recording. Am J Gastroenterol. 1991;86(2):160-4.
8. Shay S, Sifrim D, Tutuian R, Zhang X, Vela M, Castell DO. Multichannel intraluminal impedance (MII) in the evaluation of patients with persistent GERD symptoms despite proton pump inhibitors (PPI): a multicenter study. Gastroenterology. 2003;124(4 Suppl 1):A537.
9. Wunderlich AW, Murray JA. Temporal correlation between chronic cough and gastroesophageal reflux disease. Dig Dis Sci. 2003;48(6):1050-6.
10. Breumelhof R, Nadorp JH, Akkermans LM, Smout AJ. Analysis of 24-hour esophageal pressure and pH data in unselected patients with noncardiac chest pain. Gastroenterology. 1990;99(5):1257-64.
11. Watson RG, Tham TC, Johnston BT, McDougall NI. Double blind cross-over placebo controlled study of omeprazole in the treatment of patients with reflux symptoms and physiological levels of acid reflux - the "sensitive oesophagus". Gut. 1997;40(5):587-90.
12. Wiener GJ, Morgan TM, Copper JB, Wu WC, Castell DO, Sinclair JW, et al. Ambulatory 24-hour esophageal pH monitoring. Reproducibility and variability of pH parameters. Dig Dis Sci. 1988;33(9):1127-33.
13. de Caestecker JS. Twenty-four-hour oesophageal pH monitoring: advances and controversies. Neth J Med. 1989;34 Suppl:S20-39.
14. Johnsson F, Joelsson B, Isberg PE. Ambulatory 24 hour intraesophageal pH-monitoring in the diagnosis of gastroesophageal reflux disease. Gut. 1987;28(9):1145-50.
15. Klauser AG, Schindlbeck NE, Müller-Lissner SA. Symptoms in gastro-oesophageal reflux disease. Lancet. 1990;335(8683):205-8.
16. Fass R, Tougas G. Functional heartburn: the stimulus, the pain, and the brain. Gut. 2002;51(6):885-92.

Piggyback Aspergillosis: Pulmonary Hydatid Cyst with Aspergillus Co-infection

SANJEET KUMAR SINGH*, KALPANA CHANDRA†, UMAKANT PRASAD‡, MONA LISA#, ANITA KUMARI¥

ABSTRACT

Aspergilloma is a saprophytic infection that colonizes pre-existing cavities in the lung. These cavities are caused by tuberculosis, bronchiectasis, lung cancer and other pulmonary diseases. Development of aspergilloma in the residual cavities after pulmonary hydatid cyst surgery is rarely described in terms of co-existence of the two conditions. Here we report co-infection of pulmonary hydatid cyst and aspergilloma in a 43-year-old male who had history of minor thalassemia and suffered from chest pain, dyspnea, non-productive cough for at least 5 months and hemoptysis for 20 days.

Keywords: Aspergillosis, hydatid cyst, pulmonary hydatid cyst

Aspergilloma infection consists of a mass of fungal hyphae, inflammatory cells, fibrin, mucus and tissue debris and can colonize lung cavities due to underlying diseases such as tuberculosis, sarcoidosis, bronchiectasis, cavitary lung cancer, neoplasms and bronchial cysts.[1,2] Active invasion and proliferation of fungi in the laminated ectocyst or sometimes the pericyst of the hydatid is very unusual.

CASE REPORT

A 43-year-old male presented to the Pulmonary Medicine OPD with nonspecific complaints of mild weakness, cough, dyspnea, hemoptysis and chest pain for last 5 months. There was no history of fever or night sweats. He had visited local doctors. He got no relief even after a course of antibiotics. On radiological examination, X-ray chest showed a large cavitary lesion involving left lung. Sputum examination for acid-fast bacilli did not reveal any bacilli and GeneXpert evaluation for tuberculosis too was negative. Computed tomography (CT) chest showed a large cavitary lesion (5 × 6 × 6 cm) involving left lower lobe of lung (Fig. 1). A diagnosis of hydatid cyst was suggested on radiology.

The patient underwent surgical excision of the cyst after a course of antihelminthic treatment. Grossly, a grey-white already punctured cyst was received. When cut open, there was a foci of dirty black soft tissue and few daughter cysts (Fig. 2).

On histopathological examination, the section revealed lamellated hyaline acellular ectocyst of hydatid cyst (Fig. 3). There were collections of acute angle branching septate hyphae along with inflammatory cells, fibrin, mucus and tissue debris, conforming to morphology of Aspergillus (Fig. 4). Thus, a final diagnosis of Piggyback aspergillosis on pulmonary hydatid cyst was made. Itraconazole 100 mg/day was given for 3 months. The patient

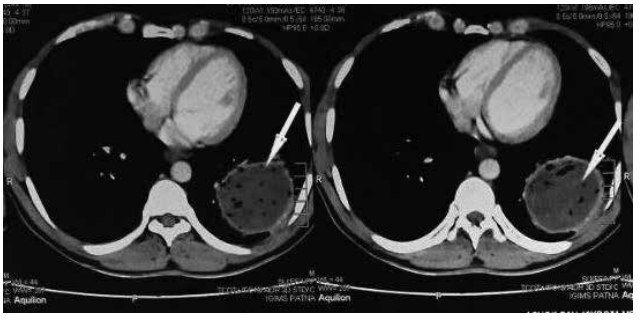

Figure 1. CT chest showing a large cavitary lesion (*white arrow*) in left lower lobe of lung.

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Figure 2. Grey-white already punctured cyst with foci of dirty black soft tissue (*gray arrows*) and few daughter cysts (*black arrows*).

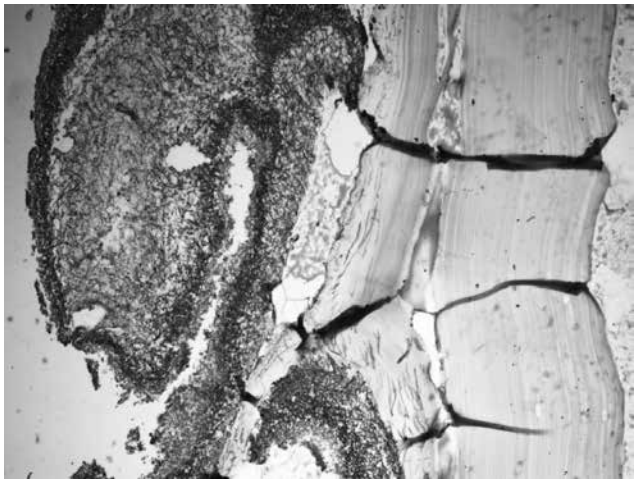

Figure 3. Lamellated hyaline acellular ectocyst of hydatid cyst with ball of Aspergillus attached (scanner view).

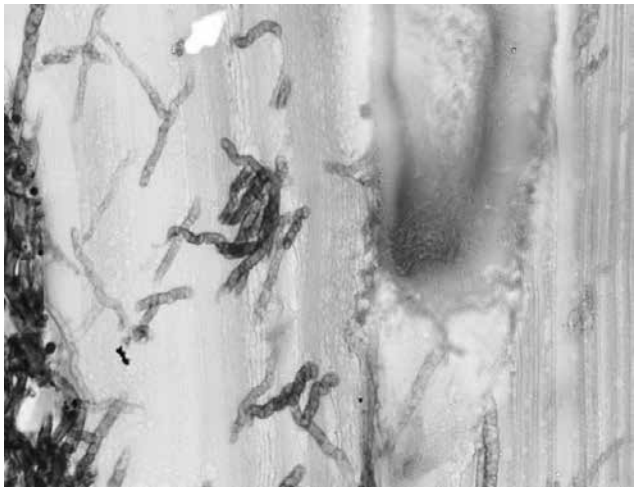

Figure 4. Acute angle branching septate hyphae along with fibrin, mucus and tissue debris (100x).

remained asymptomatic with normal radiological control after more than 9 months.

DISCUSSION

Pulmonary aspergilloma is a saprophytic infection which occurs as a colonizer of pre-existing pulmonary cavity lesions of any etiology such as sequelae tuberculosis, sarcoidosis, bronchiectasis, cavitatory neoplasia and lung abscess, producing a fungus ball or a mycetoma.[1-3]

Radiological diagnosisis made upon visualizing a well-defined heterogeneous density within a pre-formed cyst cavity, separated from the cyst wall by an air crescent. Aspergillosis and echinococcosis share the same symptoms and crescent signs on chest CT, making it difficult to distinguish.[4] CT usually reveals globules of gas within the hyphal ball, which may be loose or attached to the cavity wall by granulation tissue.[5]

Hydatid cysts containing fungi resembling Aspergillus are extremely rare. At present, such cases have been uncommonly reported. From 100 archival cases of hydatid disease, Koçer et al found two cases of simultaneous Aspergillus infection, and such infections were seen only in the lung.[6] The reason for such association still remains unclear.

The surgical treatment of lung hydatid cyst aims to avoid lung parenchyma resection. This surgery is based on the removal of the cyst membrane (cystectomy or pericystectomy), the closure of bronchial fistulas and eventually obliteration of the residual cavity with sutures (the capitonnage).[7]

Finally, aggressive surgical treatment with lung resection and antifungal therapy for pulmonary aspergilloma in residual hydatid cavities are safe and effective treatment options, and can achieve favorable outcomes.

CONCLUSION

As this co-infection is an incidental finding, a high-degree of suspicion is needed to predict the superimposed mycosis. Early diagnosis and treatment is important to prevent potential complications stemming from infection by these two pathogens.

Acknowledgment

I take this opportunity to extend my gratitude and sincere thanks to all those who helped me to complete this study.

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REFERENCES

1. Kabiri H, Lahlou K, Achir A, al Aziz S, el Meslout A, Benosman A. Pulmonary aspergilloma: results of surgical treatment. Report of a series of 206 cases. Chirurgie. 1999;124(6):655-60.
2. Daly RC, Pairolero PC, Piehler JM, Trastek VF, Payne WS, Bernatz PE. Pulmonary aspergilloma. Results of surgical treatment. J Thorac Cardiovasc Surg. 1986;92(6):981-8.
3. Bal A, Bagai M, Mohan H, Dalal U. Aspergilloma in a pulmonary hydatid cyst: a case report. Mycoses. 2008;51(4):357-9.
4. Pan JB, Hou YH, Yin PZ. A case report of hydatid cysts containing aspergillus. J Thorac Dis. 2013; 5(2):E25-7.
5. Tuncel E. Pulmonary air meniscus sign. Respiration. 1984;46(1):139-44.
6. Koçer NE, Kibar Y, Güldür ME, Deniz H, Bakir K. A retrospective study on the coexistence of hydatid cyst and aspergillosis. Int J Infect Dis. 2008;12(3):248-51.
7. Kuzucu A, Soysal O, Ozgel M, Yologlu S. Complicated hydatid cysts of the lung: clinical and therapeutic issues. Ann Thorac Surg. 2004;77(4):1200-4.

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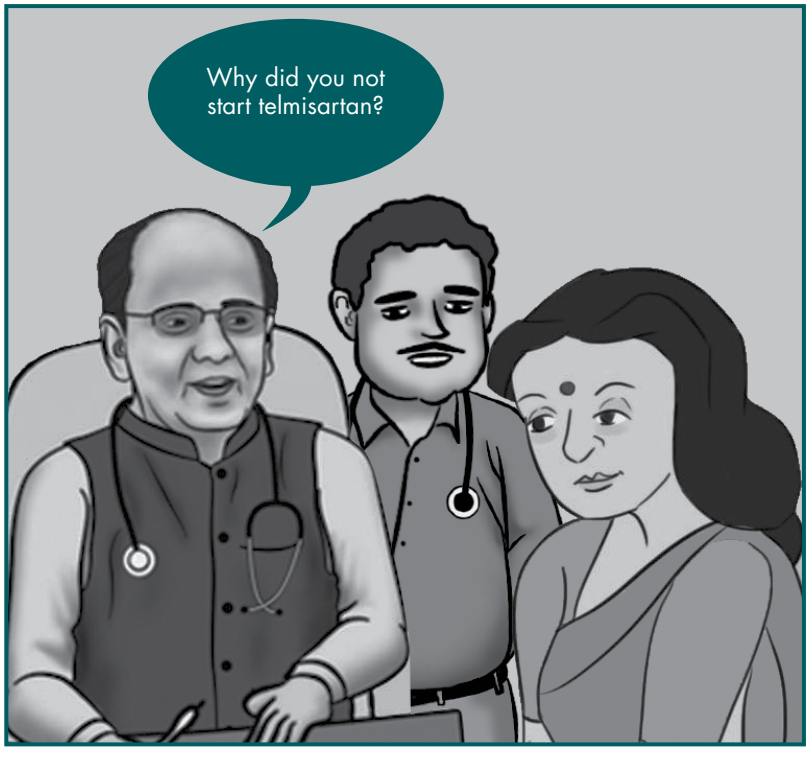

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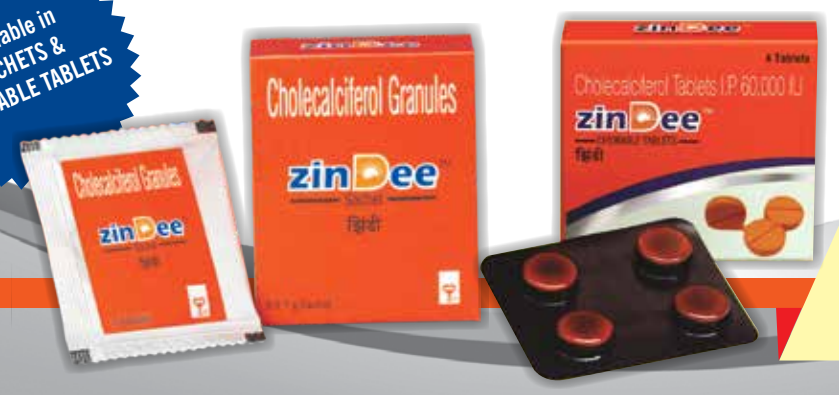

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Cervical Angina: An Unnoticed Cause of Noncardiac Chest Pain

RAJENDRA SINGH JAIN*, JAYDEEP KUMAR SHARMA†

ABSTRACT

Introduction: Cervical angina is one of the commonly unnoticed causes of chest pain with frequent presentation in cardiology outpatient department (OPD). **Objectives:** This is a retrospective study with the objective to analyze the symptoms and study the clinical, neurophysiological and radiological profile of patients with cervical angina. **Study design:** A retrospective study was carried out in the Dept. of Neurology, SMS Medical College and Hospital, Jaipur, from September 2015 to July 2018. In this study, records of 25 patients were analyzed who were admitted and diagnosed with noncardiac chest pain after normal cardiac investigations who underwent neurological work-up. **Results:** Out of 25 patients, 8 (32%) were found to have cervical radiculopathy and 2 (8%) had carpal tunnel syndrome. Chest pain accompanied with neck pain was the most common presentation (24%) followed by left arm pain (16%) and shoulder pain (8%). **Conclusion:** A good history taking by physicians and cardiologists should be the basis to reach at the diagnosis of cervical angina. Thus, a high index of suspicion is required in order to save the patient from the burden of unnecessary invasive investigations and stress.

Keywords: Cervical angina, cervical radiculopathy, chest pain, neck pain

"Cervical angina is defined as a paroxysmal precordialgia that resembles true cardiac angina resulting from cervical pathology and nerve root compression," also known as pseudoangina.[1,2]

Cervical angina mostly occurs due to cervical spine disorders mimicking true angina pectoris, i.e., manifesting as pain in upper chest and scapular areas.[3,4] Pathologies like cervical intervertebral disk diseases, ossified posterior longitudinal ligament (OPLL) or other spinal disorders frequently present with atypical chest pain and are misdiagnosed as cardiac pain, thus, are subjected to an exhaustive list of costly investigations.[5] These patients are sometimes started on antianginal medications with no relief of symptoms subsequently. Thus, to decrease the financial burden and to reach the appropriate diagnosis, other mimickers of anginal pain should be thought of, one of them being cervical angina. Physicians and cardiologists should be well-versed with the symptomatology of cervical angina and keep a high index of suspicion while referring any patient with atypical chest pain for further evaluation. In this study, the importance of clinical symptomatology of cervical angina has been emphasized in order to save the patient from unnecessary expenditure of investigations and medications.

It is difficult to determine the cause of chest pain as cervical angina. Cervical angina may present with dull aching to moderately severe type of anterior chest pain with radiation to back, scapular region and arms. Neurological examination is mostly normal except for cases with prominent disk displacement. Thus, it strongly mimics angina pectoris and such patients usually present directly, or are referred, to a cardiologist for ruling out ischemic heart disease.

MATERIAL AND METHODS

A retrospective study was performed in the Dept. of Neurology, SMS Medical College and Hospital, Jaipur, from September 2015 to July 2018. In this study, records of 25 patients who were admitted and diagnosed with noncardiac chest pain after normal cardiac investigations and found unresponsive to antianginal medications who underwent neurological work-up were included.

The patients with true cardiac chest pain, or with any abnormality in cardiac work-up and those with past history of cervical spine surgery were excluded.

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RESULTS

The age of the patients ranged from 40 to 84 years (mean age 57.24 years; Table 1). Out of 25 patients, 10 (40%) patients had neurological cause of chest pain, in which 8 (32%) patients (5 males, 3 females) had cervical nerve root compression and 2 (8%) female patients had carpal tunnel syndrome. One female patient had bilateral carpal tunnel syndrome and 1 female patient had left-sided carpal tunnel syndrome (Table 2). The mean duration of symptoms was 4.36 months. Chest pain accompanied with neck pain was the most common presentation (24%) followed by left arm pain (16%) and shoulder pain (8%) (Table 3). Out of 25 patients, 16 (64%) patients had dull aching type of pain, 8 (32%) patients had radiating type of pain and 1 (8%) patient had burning type of pain (Table 4).

Table 1. Age Group-wise Presentation of Noncardiac Chest Pain

Age group	Number of cases	Percentage (%)
40-50	7	28
51-60	8	32
61-70	9	36
71-80	0	0
81-90	1	4

Table 2. Cause of Noncardiac Chest Pain

Cause	Number of cases	Percentage (%)
Radiculopathy	8	32
Carpal tunnel syndrome	2	8
Non-neurological	15	60

Table 3. Presentation of Noncardiac Chest Pain as Neurological Cause

Presentations	Number of cases	Percentage (%)
Chest pain with neck pain	6	24
Left arm pain	4	16
Chest pain with shoulder pain	2	8

Table 4. Nature of Noncardiac Chest Pain

Nature	Number of cases	Percentage (%)
Dull aching	16	64
Radiating	8	32
Burning	1	8

DISCUSSION

In this study, the patients of chest pain with normal cardiac investigations, i.e., electrocardiography (ECG), 2D echocardiography and coronary angiography who underwent neurological evaluation in the form of electrophysiology and cervical magnetic resonance imaging (MRI) were included. In addition to normalcy of investigations, nonresponse to antianginal medications was a strong criteria to defer the diagnosis of angina pectoris and evaluate the patients for noncardiac causes like cervical angina. In this study, electrophysiology and spinal MRI proved to be useful tools to verify the cause of chest pain as cervical angina.

Our study revealed that cervical angina can have diverse presentations such as cervical radiculopathy and carpal tunnel syndrome. The clinical symptomatology

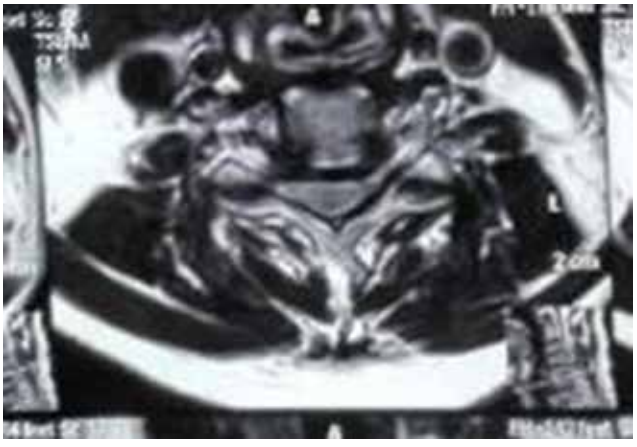

Figure 1. MRI T2W image axial section shows right C5 nerve root compression.

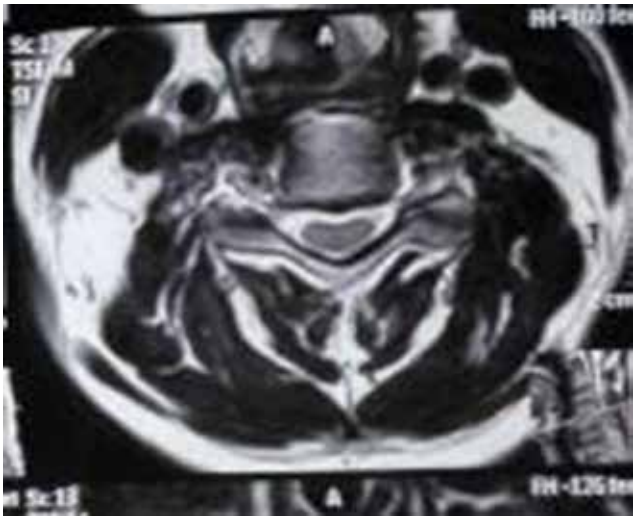

Figure 2. MRI T2W image axial section shows left C6 nerve root compression.

served as a guide to reach to a diagnosis. Patients had associated neck pain, left arm with shoulder pain in addition to chest pain. In many such cases, the clinician gets biased after hearing the symptomatology and suspect a diagnosis of coronary artery disease. Thus, one should keep all symptoms as well as neurological signs in mind before labeling the patient with a particular disease. Radicular pain occurs due to compression of the C5-C8 nerve roots, which carry sensorimotor supply to chest through medial and lateral pectoral nerves. C5-C6 and C6-C7 were the most common sites of pathological nerve root compression in our study (Figs. 1 and 2). MRI cervical spine may show disk desiccation, osteophytes formation, neuroforaminal compression and other age-related degenerative changes. This study demonstrates that cervical angina is an underdiagnosed and unnoticed entity which requires a high index of suspicion for diagnosis to prevent unnecessary financial and psychosocial burden.

CONCLUSION

Cervical angina is a strong mimicker of angina pectoris which requires a careful history taking by the physician and cardiologist. Unnecessary invasive investigations like coronary angiography can be prevented if a high index of suspicion is observed for cervical angina. This will lead to an early diagnosis thus saving the time and expenditure of patient, avoidance of transportation to higher center with catheterization laboratory facility and the most important of all, unnecessary stress to patient and family members.

REFERENCES

1. Ito Y, Tanaka N, Fujimoto Y, Yasunaga Y, Ishida O, Ochi M. Cervical angina caused by atlantoaxial instability. J Spinal Disord Tech. 2004;17(5):462-5.
2. Wiles M. Pseudo-angina pectoris of cervical origin: A case report. JCCA. 1980;24(2):74-5.
3. Constant J. The diagnosis of nonanginal chest pain. Keio J Med. 1990;39(3):187-92.
4. Grgić V. Vertebrogenic chest pain - "pseudoangina pectoris": etiopathogenesis, clinical manifestations, diagnosis, differential diagnosis and therapy. Lijec Vjesn. 2007;129(1-2):20-5.
5. Brodsky AE. Cervical angina: a correlative study with emphasis on the use of coronary arteriography. Spine (Phila Pa 1976). 1985;10(8):699-709.

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Outpatient Vaginal Administration of Isosorbide Mononitrate for Preinduction Cervical Ripening

T SHUBHAMANGALA*, RAMALINGAPPA C ANTARATANI†

ABSTRACT

Objective: The aim of the study was to determine whether isosorbide mononitrate (ISMN) 60 mg administered vaginally is effective for preinduction cervical ripening on an outpatient basis. **Material and methods:** The study was carried out at Karnataka Institute of Medical Sciences, Hubli, Karnataka from November 2007 to October 2008. Hundred women with singleton pregnancies with Bishop score ≤6 were randomized to receive either ISMN slow-release (ISMN-SR) 60 mg or vitamin C vaginally on an outpatient basis. Bishop score, proportions establishing spontaneous labor were assessed after 48 hours. Requirement of additional cervical ripening agent, need for oxytocin, admission-delivery interval, neonatal outcome (Apgar score 5 minutes, neonatal intensive care unit [NICU] admission and meconium-stained liquor) and side effects were compared. **Results:** In ISMN-SR group, there was a marked increase in the proportion of women establishing spontaneous labor (36% vs. 12%) and being favorable for induction of labor (40% vs. 9.09%). There was a significantly higher Bishop score (6.76 ± 2.65 vs. 4.6 ± 2.17) and decrease in proportion of subjects requiring further ripening (38% vs. 80%). Admission-delivery interval was shorter in ISMN group ($p < 0.001$). There were no significant differences in mode of delivery and fetal distress. Headache was seen in 22% of women in the ISMN group ($p < 0.01$). **Conclusion:** ISMN administered vaginally is effective for preinduction cervical ripening.

Keywords: Outpatient cervical ripening, isosorbide mononitrate, nitric oxide

Before the onset of labor, the cervix usually undergoes a process called 'ripening', in which it softens, dilates and effaces. These changes result in substantially decreased cervical resistance to labor pains. Sometimes, it is necessary to bring on labor artificially because of safety concerns for the mother or baby. Labor induction, when performed in a woman with unripe cervix often results in prolonged and difficult labor. Failed induction, secondary to ineffective labor or excessive uterine activity causing fetal distress are the main problems resulting in increased risk of cesarean delivery.

Nitric oxide (NO) is produced through NO synthetase (NOS) which is expressed in three isoforms: Neuronal, inducible and endothelial NOS,[1] all of which are present in the various cells of the uterine cervix.[2-4] The expression of NOS isoforms and the release of NO in the cervix have been shown to increase with advancing gestational age and during cervical ripening. Since, it does not cause uterine contractions, it may be suitable for outpatient use as against prostaglandins.

An ideal cervical ripening agent would induce ripening without causing contractions, since the lack of uterine contractions obviates fetal monitoring; such an agent could be used on an outpatient basis. There is increasing interest in carrying out cervical ripening on an outpatient basis, advantages of which are - patient convenience and reduced hospitalization costs. There is increasing interest in outpatient cervical ripening which is driven at least in part by financial costs associated with an inpatient stay in the labor ward. Additionally, there is a wish to 'deinstitutionalize' the process of labor, and, where appropriate, to offer women the opportunity to remain as an outpatient for a longer period of time.

The present study was conducted to determine the efficacy of NO donor: Isosorbide mononitrate (ISMN), as a preinduction cervical ripening agent on an outpatient basis.

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MATERIAL AND METHODS

This study was carried out in Karnataka Institute of Medical Sciences, Hubli during the period from November 2007 to October 2008. It included 100 patients with various indications for induction of labor with unripe cervix.

Study design: Randomized stratified (nulliparous/multiparous), placebo-controlled study. Active placebo treatment was allocated in a 1:1 ratio.

Each of the women selected had been subjected to detailed history, general and abdominal examination. Vaginal examination was done to examine the bony pelvis and to detect cervical score. Inducibility was predicted using the Bishop pelvic scoring system. Ultrasound examination was done to assess fetal viability, lie, presentation, position, fetal weight, fetal number, amniotic fluid volume, placental location and fetal well-being.

Indications for induction of labor were according to hospital protocols. Common indications for induction were to be postdated pregnancies, pregnancy-induced hypertension, intrauterine growth restriction, Rh-isoimmunization, fetus with major congenital anomaly, intrauterine death of fetus, etc.

Pregnant women were eligible for enrollment if they were: Between 37 and 43 week's gestation, singleton pregnancy with the fetus in cephalic presentation, unfavorable cervix, (defined as a Bishop score ≤6), had intact membranes and willing to participate in the study. Exclusion criteria were: Cephalopelvic disproportion (CPD), previous uterine scar, nonvertex presentation, multifetal pregnancy, significant vaginal bleeding, chorioamnionitis, severe pre-eclampsia, uncontrolled diabetes mellitus, contraindication to receive prostaglandins or NO (history of hypersensitivity, heart disease, glaucoma or asthma), prelabor rupture of membranes, established fetal distress, fetal compromise of sufficient degree that daily fetal monitoring is scheduled.

Eligible patients were taken for study. Procedure having been explained and having obtained their written consent for participation, subjects were randomly divided into two groups. The first group (A) consisted of 50 cases that used 60 mg ISMN tablet introduced into posterior vaginal fornix. The second group (B) consisted of 50 cases used as a placebo vitamin C tablet applied into posterior vaginal fornix. Subjects were examined after 48 hours or earlier if they came with any complaints. Cervix was defined as ripe if Bishop score was >6. After assessment of Bishop score, subjects received inpatient cervical ripening if Bishop score was ≤6 and oxytocin drip if Bishop score was >6. Cervical ripening was done with misoprostol 25 μg placed in posterior vaginal fornix every 6 hours till Bishop score was >6. After that cervical score and depending on the uterine contraction frequency and duration, augmentation with oxytocin was done.

If the cervical score was >6, augmentation of labor was done by oxytocin drip. When regular uterine contractions with a favorable cervix and a well-fitted vertex, amniotomy was performed. Intrapartum monitoring was continued. Failed labor induction was defined as the inability to achieve a cervical dilation of 4 cm and 90% effacement, or at least 5 cm (regardless of effacement) after a minimum of 12-18 hours of membrane rupture and oxytocin administration (with a goal of 250 MU or 5 contractions/10 minutes). Favorable cervix was defined as Bishop score of >6. Cesarean section was done for obstetric indications and documented.

Mode of delivery and neonatal outcome were recorded with respect to meconium staining, Apgar score at 1 minute and 5 minutes and admission to neonatal intensive care unit (NICU). Indications for operative deliveries were documented.

The analytic statistics was performed using the unpaired student test. To compare two rates or percentages, Chi-square test was used. Fisher's test was if numbers in the contingency table were very small (<5).

RESULTS

The clinical characteristics for women in both groups were comparable as regards to clinical criteria namely: Maternal age, parity, gestational age and initial Bishop score with no significant difference between both groups ($p > 0.05$) as shown in Table 1. Indications for induction of labor were presented in Table 2.

There were 34% unscheduled admissions in cases and 16% in controls ($p < 0.001$). Significant number of women in ISMN-treated group went into spontaneous labor <48 hours in cases (13 [26%] vs. 5 [10%]) (Table 3). Cases had improved Bishop score (6.76 ± 2.65 vs. 4.6 ± 2.18, $p < 0.001$), change in Bishop score (4.36 ± 2.83 vs. 2 ± 2.24, $p < 0.001$) as well as favorable Bishop score at 48-hour/next visit (31 vs. 10, $p < 0.001$).

Table 1. Clinical Characteristics of Women in Study Group

Clinical characteristics	ISMN group (n = 50)	Placebo group (n = 50)	P value	Significance
Maternal age (years)				
Range	18-29	18-29	>0.05	Not significant
Mean ± SD	23.12 ± 2.82	23.08 ± 2.78	>0.05	Not significant
Gestational age (days)				
Range	273-299	270-303	>0.05	Not significant
Mean ± SD	286.56 ± 5.89	286.28 ± 8.59	>0.05	Not significant
Bishop score				
Range	1-4	1-5	>0.05	Not significant
Mean ± SD	2.369 ± 0.72	2.62 ± 0.9	>0.05	Not significant

ISMN = Isosorbide mononitrate; n = Number of subjects.

Table 2. Indications for Induction of Labor

	Case (n = 50)	Control (n = 50)	Total
Postdated pregnancy	33 (66%)	25 (50%)	68 (68%)
Pre-eclampsia	12 (24%)	22 (44%)	34 (34%)
Oligohydramnios	5 (10%)	3 (6%)	8 (8%)
Others	—	—	—

The number of doses of additional cervical ripening was higher with controls (38% vs. 80%, $p < 0.05$). Inpatient induction/admission in labor to delivery was shorter in cases than controls (9.21 ± 4.55 hours vs. 12.9 ± 4.65 hours, $p < 0.001$).

There were no differences in duration of first, second and third stages of labor. Also, no differences were observed between both groups regarding the mode of delivery, for indications for operative delivery as well as fetal outcomes in both groups as found through Apgar score, meconium-stained liquor or admissions to NICU. Table 4 demonstrates maternal and fetal side effects and their incidence among both groups. Headache was more common in ISMN group (22% vs. 4%, $p < 0.05$).

DISCUSSION

The need to ripe the cervix prior to induction of labor has become a reality in our lives as induction especially with unfavorable cervix in a full-term pregnancy is still a problem to the obstetricians. NO donors were tried for the first time before surgical evacuation of the first trimester pregnancy' in the form of vaginal tablet by Thomson et al[5] and intracervically by Arteaga-Troncoso et al.[6]

The results from the current study show that ISMN is an efficient cervical ripening agent compared to placebo; especially on an outpatient basis. In ISMN group, there was increase in the proportion of women establishing spontaneous labor and having Bishop score favorable for induction of labor. In present study, in ISMN group there was a significantly higher Bishop score at 48-hour (6.76 ± 2.65 vs. 4.6 ± 2.17, $p < 0.001$), a higher change in score (4.36 ± 2.83 vs. 2 ± 2.24, $p < 0.001$) and decrease in proportion of subjects requiring further ripening (38% vs. 80%, $p < 0.001$) (Table 3).

In those who needed inpatient cervical ripening, doses in ISMN-treated group were less than in placebo-treated. Similar response was seen by Rameez et al[7] where proportion establishing spontaneous labor was (28% vs. 7.5%), score being favorable for induction of labor was (40% vs. 9%), an increase in Bishop score (3.8 vs. 1.3) and need for additional cervical ripening was seen in 32% versus 79% in placebo group. Admission to delivery interval was shorter in ISMN group in the present study (9.21 ± 4.65 hours vs. 12.91 ± 4.55 hours, $p < 0.001$).

No significant differences in cesarean delivery rates including any differences in fetal outcomes and admissions to intensive care unit were noted in the present study. Headache was the main side effect seen in 22% of women in the ISMN group but was not so severe to need analgesia. However, in the present study, women who had headache did not feel it to be significant.

Table 3. Comparison Between Study Groups

	Case (n = 50)	Control (n = 50)	P value	Significance
Unscheduled admissions	17 (34%)	8 (16%)	<0.001	Significant
Unscheduled admissions for cause other than labor	4 (8%)	3 (6%)	>0.05	Not significant
Established labor (<48 hours)	13 (26%)	5 (10%)	<0.05	Significant
Established labor (≥48%)	5 (10%)	1 (2%)	>0.05	Not significant
Bishop score at 48-hour/next visit				
Range	3-12	2-12	<0.001	Significant
Mean ± SD	6.76 ± 2.65	4.6 ± 2.18		
Change in Bishop score at 48-hour/next visit				
Range	0-10	0-10	<0.001	Significant
Mean ± SD	4.36 ± 2.83	2 ± 2.24		
Favorable score (>6)	31 (62%)	10 (20%)	<0.001	Significant
Unfavorable score (≤6)	19 (38%)	40 (80%)	<0.001	Significant
Bishop score favorable for induction with oxytocin	13 (40.6%)	4 (9.09%)	<0.001	Significant
Women who needed inpatient cervical ripening	19 (38%)	40 (80%)	<0.001	Significant
Requirement of oxytocin	47 (94%)	47 (94%)	>0.05	Not significant
Duration from inpatient induction/admission in labor to delivery				
Range	1.66-20.91 hours	1-23 hours	<0.001	Significant
Mean ± SD	9.21 ± 4.55 hours	12.9 ± 4.65 hours		
Duration of first stage				
Mean ± SD	6.193 ± 2.6 hours	5.7 ± 2.3 hours	>0.05	Not significant
Duration of second stage				
Mean ± SD	41.3 ± 19.9 minutes	40.42 ± 20.3 minutes	>0.05	Not significant
Duration of third stage				
Mean ± SD	6.58 ± 3.98 minutes	5.88 ± 3 minutes	>0.05	Not significant
Normal vaginal delivery	40 (80%)	42 (84%)	>0.05	Not significant
Operative vaginal delivery	3 (6%)	2 (4%)	>0.05	Not significant
Cesarean section	7 (14%)	6 (12%)	>0.05	Not significant
Apgar score 1 minute				
Range	4-9	4-9		
Mean ± SD	7.88 ± 0.93	7.38 ± 1.08	>0.05	Not significant
Apgar score 5 minutes				
Range	7-10	6-10		
Mean ± SD	9.62 ± 0.69	9.34 ± 0.96	>0.05	Not significant
Thick meconium	2 (4%)	4 (8%)	>0.05	Not significant
Thin meconium	11 (22%)	12 (24%)	>0.05	Not significant
Admissions to NICU	1 (2%)	4 (8%)	>0.05	Not significant

Table 4. Complications Seen in Both Groups

	Case	Control	P value	Interpretation
Nausea and vomiting	2 (4%)	3 (6%)	>0.05	Not significant
Headache	11 (22%)	2 (4%)	<0.05	Significant
Palpitation	—	—	—	—
Hyperstimulation	—	—	—	—
Tachysystole	—	—	—	—
Fetal tachycardia	0	2 (4%)	>0.05	—
Postpartum hemorrhage	4 (8%)	5 (10%)	>0.05	—

CONCLUSION

To summarize, it was found from the study that ISMN was more effective than placebo with respect to number of women going into spontaneous labor, improvement in cervical score, favorability for induction of labor, admission to delivery interval and reduced the number of doses of inpatient cervical ripening agent without increasing cesarean delivery rate and affecting neonatal outcomes.

However, following are the drawbacks of the study: 1) ISMN tablets intended for oral administration were administered vaginally. NO donors in vaginal paste or gel form may allow better drug absorption. 2) Study population is less. The definitive clinical efficacy needs to be evaluated in larger series of patients.

Use of NO donor, ISMN may have the major advantage that uterine contractions are not stimulated and may allow cervical ripening before induction of labor to be performed as an outpatient procedure. The use of NO donors for the induction of cervical ripening at term may prove to be a major therapeutic advance.

Acknowledgment

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REFERENCES

1. Alderton WK, Cooper CE, Knowles RG. Nitric oxide synthases: structure, function and inhibition. Biochem J. 2001;357:593-615.
2. Tschugguel W, Schneeberger C, Lass H, Stonek F, Zaghula MB, Czerwenka K, et al. Human cervical ripening is associated with an increase in cervical inducible nitric oxide synthase expression. Biol Reprod. 1999;60(6):1367-72.
3. Ledingham MA, Thomson AJ, Young A, Macara LM, Greer IA, Norman JE. Changes in the expression of nitric oxide synthase in the human uterine cervix during pregnancy and parturition. Mol Hum Reprod. 2000;6(11):1041-8.
4. Bao S, Rai J, Schreiber J. Brain nitric oxide synthase expression is enhanced in the human cervix in labor. J Soc Gynaecol Investig. 2001;8(3):158-64.
5. Thomson AJ, Lunan CB, Cameron AD, Cameron IT, Greer IA, Norman JE. Nitric oxide donors induce ripening of the human uterine cervix: a randomized controlled trial. Br J Obstet Gynaecol. 1997;104(9):1054-7.
6. Arteaga-Troncoso G, Villegas-Alvarado A, Belmont-Gomez A, Martinez-Herrera FJ, Villagrana-Zesati R, Guerra-Infante F. Intracervical application of the nitric oxide donor isosorbide dinitrate for induction of cervical ripening: a randomized controlled trial to determine clinical efficacy and safety prior to first trimester surgical evacuation of retained products of conception. BJOG. 2005;112(12):1615-9.
7. Rameez MF, Goonewardene IM. Nitric oxide donor isosorbide mononitrate for pre-induction cervical ripening at 41 weeks' gestation: a randomized controlled trial. J Obstet Gynaecol Res. 2007;33(4)452-6.

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A Case of Abruption of the Succenturiate Lobe of Placenta

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ABSTRACT

Succenturiate lobe of placenta is a morphological abnormality, in which there are one or multiple accessory lobes connected to the main part of the placenta by blood vessels. It has been known to be located on the lower segment and then present either as placenta previa or as a case of vasa previa, if vessels connecting the main placenta with the succenturiate placenta lie below the presenting part. Here, we present a rare case of antepartum hemorrhage resulting from the abruption of the succenturiate lobe of placenta.

Keywords: Abruptio placenta, succenturiate lobe, accidental hemorrhage

Antepartum hemorrhage, i.e., bleeding after the 20th week of pregnancy, occurs in 25% of all pregnancies and placental abruption accounts for approximately one-quarter of such cases.[1] Placental abruption and placenta previa are the two common causes of antepartum hemorrhage. The diagnosis of placental abruption is always clinical,[2,3] and the condition should be suspected in women who present with vaginal bleeding or abdominal pain or both. The succenturiate placenta is a morphological abnormality, in which there are one or multiple accessory lobes connected to the main part of the placenta by blood vessels.[4] The incidence is 16-28 cases per 10,000 pregnancies. Here, we report a case in which placental abruption occurred in the succenturiate lobe of the placenta.

CASE REPORT

Mrs SDC, 33-year-old, G_2P_1 with previous preterm delivery was on regular antenatal follow-up. She was admitted at 32 weeks of gestation with complaints of spotting for 3 days followed by fresh bleeding on the day of admission with a diagnosis of ? accidental hemorrhage. Ultrasound examination done at admission showed a single live intrauterine gestation at 31-32 weeks in cephalic presentation with adequate liquor. Placenta was anterior with no previa and with evidence of a small retroplacental clot. Her condition was stable and bleeding was minimal.

On general physical examination: Patient was conscious and of good built; weight 66 kg; no pallor/icterus/pedal edema; pulse rate - 98/min; blood pressure - 124/80 mmHg.

Examination of respiratory and cardiovascular systems revealed no abnormality.

Per abdominal examination: Uterus 30-week size, relaxed, fetus in cephalic presentation; fetal heart sound (FHS) - present and regular (150 beats/min).

Routine tests: Hemoglobin - 11 g/dL; human immunodeficiency virus/Venereal Disease Research Laboratory/hepatitis B virus surface antigen (HIV/VDRL/HbsAg) - NR; urine and stool - NAD.

Ultrasonography (USG): Single live intrauterine gestation at 31-32 weeks, liquor adequate, anterior placenta, evidence of a small retroplacental clot, cervix long with internal os closed. Diagnosis: G_2P_1 at 32 weeks of gestation with ? abruptio placenta.

As the patient's condition was stable, bleeding was minimal and in view of the preterm gestation, she was put on conservative management, with close watch on both fetal and maternal conditions. She received steroid prophylaxis for fetal lung maturity. There were

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small intermittent bouts of bleeding but the maternal and fetal condition remained stable.

Repeat ultrasound 2 weeks after admission showed a live fetus in cephalic presentation 34-35 weeks, with anterior placenta and a small retroplacental clot. The estimated fetal weight was 2.5 kg. A decision for induction of labor was taken since the estimated fetal weight was 2.5 kg and because of the facts that the patient was covered with steroids for fetal lung maturity and had intermittent bleeding. Labor was induced with prostaglandin tablets and followed by artificial rupture of membranes (ARM), which revealed blood-stained liquor. Further augmentation with slow oxytocin drip resulted in a vaginal delivery of a live baby girl of 2.6 kg. Placenta was delivered and revealed a succenturiate lobe (Figs. 1 and 2). There was a huge retroplacental clot occupying the whole of succenturiate lobe, while the rest of the placenta was normal.

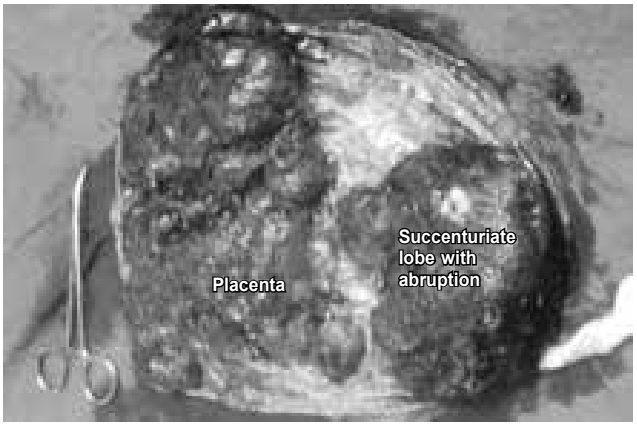

Figure 1. Postnatal picture showing fetal surface of the placenta and succenturiate lobe.

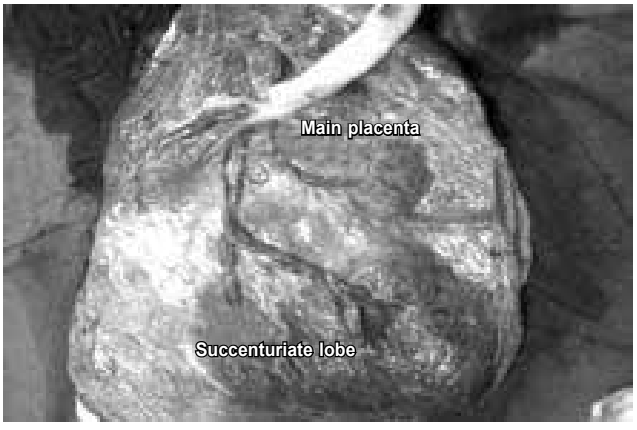

Figure 2. Postnatal picture showing maternal surface of the placenta and abruption of the succenturiate lobe.

DISCUSSION

Placental abruption is defined as the complete or partial separation of the placenta before delivery and is one of the leading causes of vaginal bleeding in the second-half of pregnancy.[1,2] Approximately 0.51% of the pregnancies are complicated by placental abruption.[2,5] It is one of the most important causes of maternal morbidity and perinatal mortality. Approximately 10% of all preterm births and up to one-third of all perinatal deaths are caused by placental abruption.[2,6] Placental abruption is suspected in all patients presenting with bleeding, uterine contractions and fetal distress.

Hemorrhage into the decidua basalis occurs as the placenta separates from the uterus, which usually manifests as vaginal bleeding. However, at times the hemorrhage may be concealed with no signs of vaginal bleeding. Bleeding, if it continues, may result in fetal and maternal distress and if not attended to appropriately can result in maternal and fetal death. Management depends on severity of abruption, period of gestation, fetal and maternal condition. In case of deteriorating maternal condition and fetal demise, pregnancy is terminated by attempting a vaginal delivery if no contraindications exist. Labor induced with amniotomy, usually progresses rapidly and may be further augmented with oxytocin drip.

Cesarean section is needed when labor does not progress well or the maternal condition becomes unstable. In case of a live fetus and a stable maternal condition, management is decided by the period of gestation. In term gestation, induction of labor is the best option. In preterm gestation, a policy of wait and watch, along with steroid injections for fetal lung maturity usually pays good returns. Close monitoring of both maternal and fetal condition is carried out to watch for fetal and maternal distress. Labor is induced at term or at the first signs of fetal or maternal distress.

Succenturiate placenta is usually a postnatal diagnosis but can also be suspected on an antenatal ultrasound.[4,7,8] Its antenatal recognition is important as vessels connecting the main placenta with the succenturiate placenta, if lying below the presenting part: Vasa previa may rupture during labor causing massive hemorrhage and fetal death. In addition, there is an increased risk of postpartum hemorrhage from retention of placental material.[4,7,8] A bilobate placenta is a similar anomaly and it is not clear from literature as to what is the exact difference, if any exists.[9] It appears that some authors use the term 'bilobate' when both segments of the placentas are almost equal in size and 'succenturiate' when there is a greater difference between the two segments. When

an outlying portion of the placenta has not maintained its vascular connections with decidua vera, the placenta is called placenta spuria. Succenturiate placentas are known to be located on the lower segment and the management then would be that as of placenta previa.

CONCLUSION

Our case was treated as a case of placental abruption and was managed conservatively till fetal maturity and then delivered by induction of labor at term. Succenturiate lobe with complete abruption of the lobe was noted on delivery of the placenta. This case is presented for the rare occurrence of placental abruption in the succenturiate lobe.

REFERENCES

1. Konje JC, Taylor DJ. Bleeding in late pregnancy. In: James DK, Steer PJ, Weiner CP, et al (Eds.). High Risk Pregnancy. 2nd Edition, Edinburgh, UK: WB Saunders Co; 2001 .pp. 111-28.
2. Oyelese Y, Ananth CV. Placental abruption. Obstet Gynecol. 2006;108(4):1005-16.
3. FayePetersen OM, Heller DS, Joshi VV (Eds.). Gross abnormalities of the placenta: lesions due to disturbances of maternal and of fetal blood flow. In: Handbook of Placental Pathology. 2nd Edition, Oxon, UK: Taylor & Francis; 2006. p. 2751.
4. Jeanty P, Kirkpatrick C, Verhoogen C, Struyven J. The succenturiate placenta. J Ultrasound Med. 1983;2:9-12.
5. Kyrklund-Blomberg NB, Gennser G, Cnattingius S. Placental abruption and perinatal death. Paediatr Perinat Epidemiol. 2001;15(3):290-7.
6. Ananth CV, Getahun D, Peltier MR, Smulian JC. Placental abruption in term and preterm gestations: evidence for heterogeneity in clinical pathways. Obstet Gynecol. 2006;107(4):785-92.
7. Hata K, Hata T, Aoki S, Takamori H, Takamiya O, Kitao M. Succenturiate placenta diagnosed by ultrasound. Gynecol Obstet Invest. 1988;25(4):273-6.
8. Nelson LH, Fishburne JI, Stearns BR. Ultrasonographic description of succenturiate placenta. Obstet Gynecol. 1977;49(1 Suppl):79-80.
9. Angtuaco TL, Boyd CM, Marks SR, Quirk JG, Galwas B. Sonographic diagnosis of the bilobate placenta. J Ultrasound Med. 1986;5(11):672-4.

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J Just a simple photographic illusion but can be used in mental counseling.

Every citizen of India should have the right to accessible, affordable, quality and safe heart care irrespective of his/her economical background

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"No one should die of heart disease just because he/she cannot afford it"

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.

Committee Members

Chief Patron

Raghu Kataria

Entrepreneur

President

Dr KK Aggarwal

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

Governing Council Members

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Harish Malik
Aarti Upadhyay
Raj Kumar Daga
Shalin Kataria
Anisha Kataria
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Rishab Soni

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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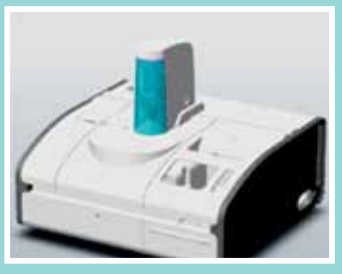

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Advantages of Subunit Influenza Vaccine: An Overall Perspective

RAJU SHAH*, SUHAS PRABHU†

ABSTRACT

Influenza, a contagious respiratory infection, is caused by influenza virus A, B and C in humans. Chills, fever, headache, myalgia, fatigue and respiratory discomfort are the most commonly observed symptoms, whereas progression of illness may result in bronchitis, pneumonia, secondary bacterial infections, acute respiratory distress, cardiovascular diseases and even death. Management of influenza involves high treatment costs and functional losses. Therefore, immunization against influenza is the best method to prevent it. Seasonal trivalent influenza vaccine (TIV) formulations, i.e., whole inactivated virus (WIV) vaccines, "detergent"-split vaccines (SIV) and subunit vaccines (SUV), use inactivated influenza antigens. There are live attenuated influenza viruses vaccines also available, which we will not be discussed in this article. Administration of WIV vaccines leads to an increased rate of and more severe adverse reactions; therefore, less reactogenic forms of influenza vaccine, SIV and SUV are preferably being used. The present review compares SUV and SIV in terms of tolerability, and reactogenicity. Furthermore, the immunizing and reactogenicity profile of SUV in high-risk subgroups of the populations (children, elderly, pregnant women, liver transplant patients, asthmatics, diabetics and nursing home residents) has also been discussed.

Keywords: Subunit, vaccine, influenza, split, trivalent, whole, immunogenicity, reactogenicity

Influenza is a contagious respiratory illness, usually observed in humans and is caused by influenza virus A, B, C (Table 1).[1,2] The clinical manifestation observed in individuals with seasonal influenza includes chills, fever, headache, myalgia, fatigue and respiratory discomfort characterized by a cough, sore throat and rhinitis.[3] Untreated or progressed form of influenza may result in severe complications such as bronchitis, pneumonia, secondary bacterial infections, acute respiratory distress and cardiovascular diseases; which if further left untreated, can lead to death. Moreover, elderly, children, immunocompromised patients and individuals with weakened immune system are more vulnerable to such infections and are thus considered as high-risk populations.[3-6] Infection due to highly pathogenic strains of influenza virus (some of the avian H5 subtypes) may also cause severe respiratory distress and multi-organ failure in infected humans.[7] Other symptoms observed in patients during the attack of H1N1 virus in 2009 included gastrointestinal and neurological (encephalopathy, focal neurological findings, aphasia, and abnormal electroencephalographic findings) complications.[8,9]

Table 1. Influenza Virus A-C

Types	Results	Types	Reservoirs
A	Epidemics, pandemics	Based on the antigenic differences between two surface glycoproteins: H and N. Till date, 18 H subtypes (H1-H18) and 11 N subtypes (N1-N11) have been identified	Animals, humans
B	Epidemics	Only single subtypes of H and N	Humans
C	Infects humans but causes little or no disease	Only single subtypes of H and N	Humans

H = Hemagglutinin; N = Neuraminidase.

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Global influenza epidemics are highly influenced by the seasonal factors where it is commonly observed during the winter in the northern and southern hemispheres.[10] Globally, in 2016, the annual attack rate of influenza infection was reported to be 5-10% and 20-30% in adults and children, respectively, with a total of about 2,50,000 to 5,00,000 annual deaths along with 3-5 million cases of influenza-related severe illness.[11-13]

Though influenza disease can be shortened using various drugs, the high inpatient and outpatient treatment costs of influenza pose a socioeconomic burden on individuals, families and society. Moreover, the productivity and functional losses also add on to the economic burden associated with the diseases.[14] Besides, the severity of influenza infection outcomes along with the complications associated with it may lead to hospitalization or even death. Therefore, vaccination against influenza infection is the best and the most cost-effective way to prevent the influenza infection.[1]

Numerous types of influenza vaccine formulations are available these days. Seasonal trivalent influenza vaccine (TIV) formulations use inactivated influenza antigens and are available as whole inactivated virus (WIV) vaccines, "detergent"-split vaccines (SIV) and subunit vaccines (SUV).[15,16] The present review compares SUV and SIV in terms of tolerability, and reactogenicity. Furthermore, the immunizing and reactogenicity profile of SUV in high-risk populations (children, elderly, pregnant women, liver transplant patients, asthmatics, diabetics and nursing home residents) has also been discussed.

GENERATIONS OF TRIVALENT INACTIVATED VACCINES: AN OVERVIEW

All generations of TIV (WIV, SIV, SUV) contain inactivated influenza viruses derived from two influenza A strains (H3N2 and H1N1) and one influenza B strain. The three major formulations differ in either structural organization or viral components (Fig. 1).[15,16]

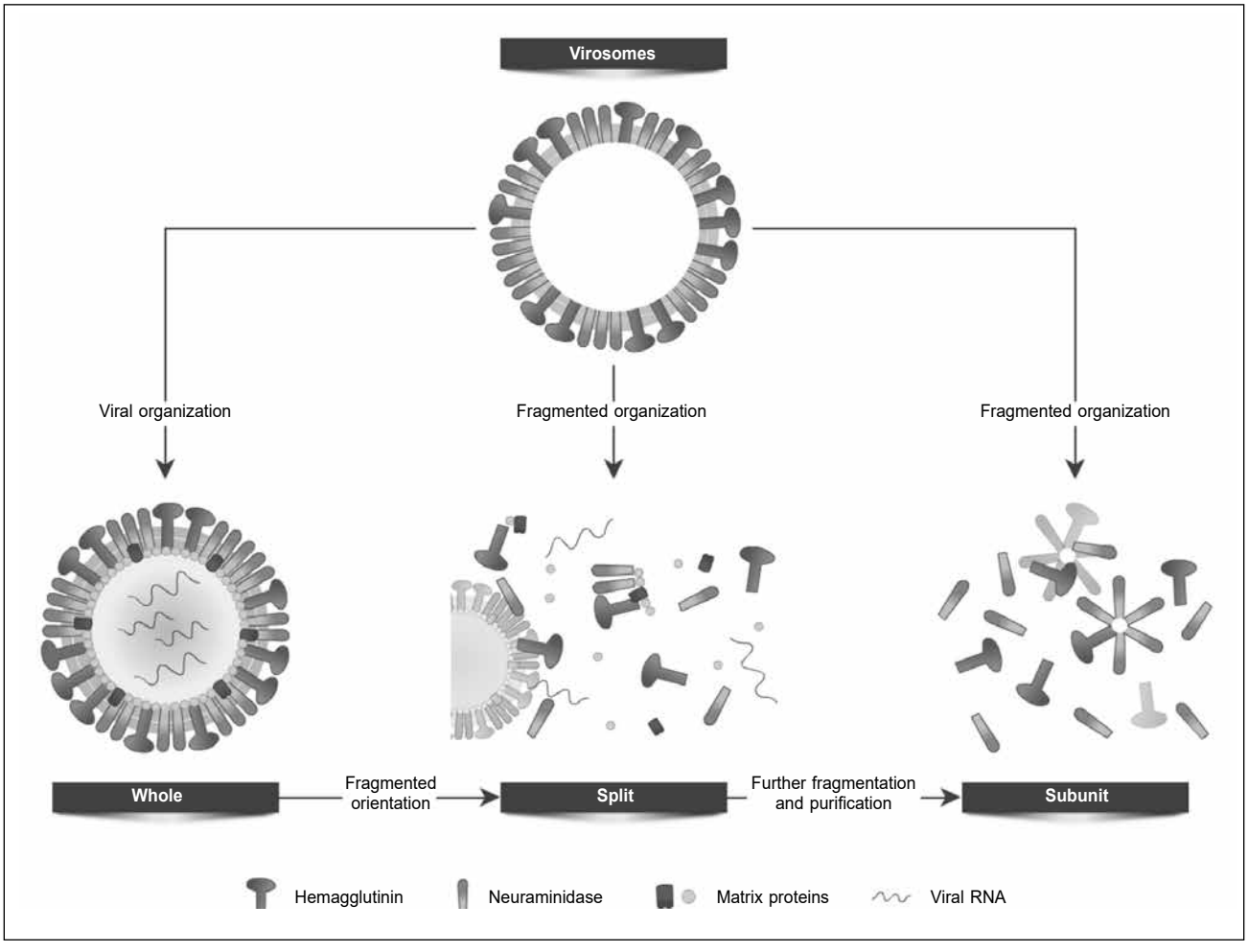

Figure 1. Structural difference in trivalent influenza vaccine formulations.

Whole Influenza Vaccine

WIV is prepared from harvested allantoic fluid of hen's egg which is chemically inactivated with chemicals such as formalin or β-propiolactone or formaldehyde and subsequently concentrated and purified to remove the contaminants, i.e., non-viral proteins.[17] The procedure followed to prepare WIV does not destroy the viral envelope (Fig. 1).[18]

The WIV was introduced first among the other types, and was the most widely used TIV.[17] However, an association of WIV with painful local and systemic reactions has declined its use over a period of time. A recipient blinded study conducted by Al-Mazrou et al, 1991 compared the adverse drug reactions (ADRs) caused by WIV and SIV in 333 patients with influenza who received the vaccine for the first time. It was reported that WIV formulations caused more local and systemic adverse effects upon administration, as compared to SIV. Generalized aching was observed in 13% of the SIV recipients in comparison to 26% WIV recipients ($p < 0.01$). Moreover, SIV group reported fewer visible local reactions such as soreness (SIV vs. WIV; 68% vs. 78%), redness/swelling (SIV vs. WIV; 18% vs. 29%).[17]

The ADRs observed in patients taking WIV may be attributed to the presence of impurities in WIV in the form of egg proteins. Such studies also supported the restriction of WIV vaccines in the market and promoted the entry of SIV in the market.[19] SIV and SUV are being used since the 1970s.[20,21] Another study by Carle et al, 1988 comparing WIV (received by 49 subjects, males = 21, females = 28, average age: 70.20 ± 11.98 years) with SUV (received by 53 subjects, males = 23, females = 30, average age: 80.12 ± 7.25 years) reported a lower reactogenicity of SUV as compared to WIV, despite similar immunogenicity and sero-protection. Though, patients receiving WIV and SUV did not experience any systemic reactions (headache, malaise, fever), the proportion of patients experiencing local reactions (such as redness, swelling and pain at site of injection) was high in WIV group as compared to SUV group (SUV vs. WIV: 41.51% vs. 53.06%).[22] The immunogenicity demonstrated by WIV and SUV was comparable with reduced reactogenicity with SUV in comparison with WIV formulations.

Split Influenza Vaccine

SIV is prepared by following an additional step to the ones followed for WIV, i.e., treatment of vaccine with diethyl ether or detergent for the disruption of viral lipid envelope as well as for exposure to all viral proteins and subviral elements (Fig. 1). Though SIV contains complete viral protein content, the loss of organization of original viral particulates as well as viral single-stranded ribonucleic acid (ssRNA) which is required for the immunogenicity of the virus helps in the formulation of a lesser reactogenic vaccine as compared to WIV.[15,16] SIVs are more acceptable due to their adequate immunogenicity, lower reactogenicity and easy process of production.[23]

Subunit Influenza Vaccine

In SUV, the viral content is treated with diethyl ether or a detergent to separate hemagglutinin (H) and neuraminidase (N) surface proteins from the viral nucleocapsid and lipids. The H and N proteins are further purified by removing other viral components (Fig. 1).[24,25] Sometimes, adjuvants are also added to the antigens to attain adequate immunogenicity in the elderly.[26] A recent modification in SUV, a recombinant H protein SUV has been introduced. This contains a high dose of antigen, i.e., 45 μg per strain to attain adequate immunogenicity. However, high dose antigen results in high seroconversion rates among healthy adults (50-64 years)[27] and low seroconversion and efficacy rates in children (6-59 months).[28]

SUV has been considered to be the least reactogenic influenza vaccine as compared to the other types, till date.[29] A meta-analysis conducted in 1996 included 14 clinical studies which evaluated SUV and reported that 95% of the study population vaccinated with SUV experienced no or mild (clinically insignificant) adverse events (AEs), which lasted up to 2 days. It was also reported that among 1,800 subjects (females: 891; males: 909), 745 subjects experienced local symptoms (redness, swelling, itching, warmth, pain on contact, continuous pain, restricted arm movement), whereas, 378 subjects experienced systemic symptoms such as fever, increased sweating, headache, malaise, insomnia and inconvenience.

However, the percentage of patients who experienced each of the above mentioned local and systemic symptoms was not reported in the meta-analysis.[30]

KEY CLINICAL STUDIES COMPARING SUBUNIT INFLUENZA VACCINE WITH SPLIT INFLUENZA VACCINE

Several studies conducted in the past have compared SUV and SIV in terms of efficacy, immunogenicity, reactogenicity (common and expected AEs), and safety (relative freedom from harmful effect to

vaccine recipients, directly or indirectly). This section elaborates the literature comparing these two vaccines.

Many studies report SUV to be well-tolerated and associated with fewer AEs as compared to other vaccine types. A study comparing SUV (dosages: 700 and 2,100 International Units; IU) with SIV (800 IU/dose) and WIV (2,100 IU/dose) included 399 volunteers in the study and reported that SUV was well-tolerated as compared to WIV. SUV at both doses caused fewer AEs as compared to SIV and WIV.[31] A retrospective study, by Leeb et al, 2011, was conducted to compare the reactogenicity of SUV (Influvac®) with SIV (Fluvax®) among adults (≥18 years). Overall, 127 subjects received SUV and 156 received SIV. The study reported swelling (SIV vs. SUV; 18% vs. 7%, p = 0.009), muscle pain (SIV vs. SUV; 12% vs. 3%, p = 0.014) and use of anti-fever/pain medication after vaccination (SIV vs. SUV; 12% vs. 2%, p = 0.008) in both the groups. Moreover, SIV was considered to be a significant independent predictor of muscle pain and/or swelling (odds ratio, [OR] = 3.3, 95% confidence interval [CI] 1.5-7.4, p = 0.004).[32]

Another randomized, double-blind study compared the reactogenicity and serology of SUV and SIV in children (SUV: n = 249; SIV: n = 250; age 6-12 years). SIV-induced fever in a higher percentage of subjects (6.4%) as compared to SUV group (2.4%; p > 0.05). Blood samples collected from SUV group (n = 224) and SIV group (n = 223) demonstrated similar seroprotection (hemagglutination inhibition [HI] titer ≥1:40, SUV vs. SIV: H1N1, 99.6% vs. 100.0%; H3N2, 99.1% vs. 99.1%) and seroconversion rates (4-fold increase, SUV vs. SIV: H1N1, 95.1% vs. 97.8%; H3N2, 74.5% vs. 79.8%) with an increased geometric mean titer (GMT) (SUV vs. SIV: H1N1, 16.0 vs. 21.0; H3N2, 5.4 vs. 6.4) against the two A subtypes. A similar seroprotection rate (94.2% vs. 96.4%) and GMT increase (21.2 vs. 18.2) against the influenza B strain were also produced by both vaccines, showing that both vaccines were well-tolerated and presented effective immune response.[33]

Overall, SUV presents better safety as compared to SIV. SUV is also associated with a lower likelihood of local reactions among adults as compared to SIV.[32] This can be further supported by a meta-analysis (conducted in 1998), which included 22 randomized controlled trials (RCTs) describing 5,416 observations (local reactions: 2,858; systemic reactions: 2,990) with subjects of all age groups (children to elderly). The analysis compared SUV with SIV and WIV; and reported SUV to be superior than SIV and WIV in terms of lower reactogenicity.[34]

CLINICAL STUDIES ON SUBUNIT INFLUENZA VACCINE IN DIFFERENT SUBPOPULATIONS

van de Witte et al, 2012 reviewed 30 years of clinical experience with Influvac, which is an SUV. It was reported to be safe and clinically effective for all age groups (≥6 months of age).[35] Many other clinical trials have been conducted to assess the safety and immunogenecity of SUVs in different subpopulations such as children, elderly, pregnant women, etc.

Children

Children are at a higher risk of being infected with influenza virus as compared to elderly.[36,37] Moreover, school children play an important role in transmitting influenza infection.[38] The safety, immunogenicity and efficacy of influenza vaccines in children have demonstrated TIVs as well-tolerated vaccines in children.[39]

A randomized phase III trial was conducted on 205 healthy, unprimed children (aged 6 to <36 months) to evaluate the immunogenicity, safety and tolerability of a single 0.5 mL dose of the seasonal virosomal SUV, where 102 received one single 0.5 mL dose and 103 received the standard two 0.25 mL doses in a gap of 4 weeks. Both the doses enhanced the immune response against all three vaccine strains. Moreover, immunogenicity was maintained 7 months after the first vaccination with both the doses. Overall, the vaccine was found to be well-tolerated, where a single dose of 0.5 mL demonstrated long-term immunogenicity in terms of efficacy and safety in unprimed children, that too against all the influenza virus strains.[40]

A randomized endpoint-blinded, parallel group trial was conducted to evaluate the immunogenicity and safety of two SUVs, Influvac and Agrippal, in healthy children (aged 3-12 years), adults (aged 18-60 years) and elderly (aged 60 years or more). Both, Influvac and Agrippal, induced high antihemagglutinin antibody titers in all the age groups. All the groups presented seroprotection and seroconversion rates of >85% and >70%, respectively for both vaccines and against all the three virus strains. Both vaccines were well-tolerated, immunogenic and safe for a population of all age groups.[41]

Grippol®, an SUV bound with polyoxidonium, received by the school children (aged 6-18 years) demonstrated low reactogenicity, high safety and adequate prophylactic effectiveness with no adverse effects. Moreover, the complaint of high morbidity rate due to

respiratory complications also decreased as compared to that of the control group (by 2.4 times).[42]

The efficacy of inactivated TIVs in 2,723 children aged 6-59 months at increased risk of severe disease was compared with children with no such risk by Blyth et al, 2016. It was reported that vaccine was found to be ≥70% efficacious in young children with and without risk factors for severe disease.[43]

An open, randomized, multicenter study compared the immunogenicity and safety of a single-dose regimen and a two-dose regimen of a trivalent virosome influenza vaccine (Inflexal Berna V) with those of an SUV (Influvac) in 11 young children (1-6 years old) and 53 older children and adolescents (>6 years old) with cystic fibrosis. The study reported that both the vaccines met all requirements, in terms of seroconversion, seroprotection and GMT, for influenza vaccine efficacy in all treatment groups. However, the rate of systemic ADRs reporting (mainly cough, fatigue, coryza or a headache) was less for SUV (71%) as compared to the other vaccine (84%).[44]

Another study assessing the humoral response of SUV in children (previously vaccinated with SUV [n = 25]; never vaccinated [n = 20]) with acute lymphoblastic leukemia also demonstrated high immunogenicity of SUV in patients with acute lymphoblastic leukemia. Previously vaccinated subjects exhibited a 13.2- and 21.1-fold increase in antibodies, respectively against H1N1; 10.8- and 20.5-fold increase, respectively against H3N2 and 9.2- and 15.6-fold increase, respectively, against influenza type B, at 3 weeks and 6 months post-vaccination. Children vaccinated for the first time showed a 8.3-fold increase in antibodies after three weeks of vaccination and 23.4-fold increase in antibodies after 6 months of vaccination against H1N1. An increase of 7.9- and 16.3-fold in antibodies was observed against H3N2 after 3 weeks and 6 months of vaccination, respectively, while, 5.5- and 14.4-fold increase against influenza type B. Moreover, none of the children vaccinated with influenza vaccine was observed with infection. The vaccine was found to be well-tolerated with no reported ADRs.[45]

Elderly

The influenza disease burden is high in elderly patients which is assumed to be a result of impaired immune system in this age group. Many countries generally recommend vaccination against influenza for the elderly, chronically ill and residents of health care facilities to prevent the occurrence of influenza in susceptible patients.[46]

Adjuvanted vaccines are reported to induce a stronger immune response in the elderly (>65 years old) population.[47,48] A study conducted to compare conventional SUV, MF59-adjuvanted and intradermal (ID) influenza vaccines in terms of safety and immunogenicity enrolled 335 healthy elderly volunteers who randomly received one of three seasonal TIVs. All the TIVs attained satisfactory protection against A/H1N1 and A/H3N2 strains but not for the B strain. ID vaccine demonstrated noninferior results as compared to the SUV, whereas MF59-adjuvanted vaccine exhibited superior results.[49] A randomized, observer-blind, three-arm, parallel group, multicenter trial including 386 elderly subjects compared immunogenicity and safety of a conventional SUV, MF59-adjuvanted SUV and a virosomal SUV. All the vaccines had similar immunogenicity and were found to be safe and well-tolerated. However, conventional SUV was found to be less reactogenic as compared to the MF59-adjuvanted vaccine in the elderly population.[50]

Another randomized, controlled evaluator-blinded study comparing ID, MF59-adjuvanted and SUV formulations of equal potency and strain composition on 887 non-frail adults, annually TIV-immunized (≥65 years old) reported redness at the site of injection in the following order: ID (75%) > MF59-adjuvanted (13%) > SUV (13%); whereas pain was observed as MF59-adjuvanted (38%) > ID (29%) > SUV (20%). Seroprotection rates of MF59-adjuvanted vaccine were highest, and all the vaccines were well-tolerated.[51]

Patients with Cardiovascular Diseases

According to the Centers for Disease Control and Prevention (CDC), patients with cardiovascular disorders are considered as high-risk population group for developing complications related to influenza infection. The inpatient record for influenza during 2015-2016 reports heart disease (such as heart attacks and stroke) as the most commonly occurring chronic condition affecting 41% of total influenza-infected hospitalized adults. Therefore, vaccination against influenza is highly recommended in patients with cardiovascular disorders.[52]

A randomized prospective double-blind placebo-controlled Influenza Vaccination in Prevention From Acute Coronary Events in Coronary Artery Disease (FLUCAD) study was conducted to compare humoral response in patients with coronary artery disease

receiving SUV (n = 325) and placebo (n = 333). The post-vaccination antibody titers were significantly higher (4.9- to 5.7-fold for antihemagglutinin; 3.5- to 4.2-fold for neuraminidase antibodies) and post-vaccination protection rates ranged from 56.4% to 60.3% and response rates from 62.8% to 68%. Moreover, immunoglobulin G and M levels were high in patients receiving the vaccine.[53]

Diabetics

Patients with diabetes are vulnerable to influenza and are prone to influenza-related complications resulting due to impaired immune system. Vaccination against influenza is therefore highly recommended in this subgroup of patients.[54,55] Type 2 diabetes subjects (n = 105) were compared with nondiabetic controls (n = 108) in a randomized controlled study to evaluate the long-term immunogenicity and safety of SUV (intramuscular). The vaccine achieved adequate seroprotection after 1 month except for the A/H1N1 influenza virus strain, which was lower in the elderly diabetic group than that in the elderly nondiabetic group (diabetic group vs. nondiabetic group [p value], A/H1N1: 69.5% vs. 76.9% [0.227], A/H3N2: 99.0% vs. 98.1% [0.578], B: 56.2 vs. 60.2 [0.555]). The post 6-month seroconversion (diabetic group vs. nondiabetic group [p value], A/H1N1: 26.7% vs. 19.4% [0.211], A/H3N2: 34.3 vs. 29.6 [0.466], B: 32.4% vs. 24.1 [0.178]) and GMT levels (mean titer diabetic group vs. mean titer non-diabetic group [95% confidence interval or CI], A/H1N1: 33.3 [27.5-38.0] vs. 34.8 [29.7-40.8], A/H3N2: 161.1 [127.1-204.2] vs. 159.0 [128.9-196.0], B: 22.7 [19.6-26.2] vs. 18.6 [16.2-21.5]) were well-tolerated in both the groups. Moreover, the ADRs observed post-vaccination were mild-to-moderate with its reduced incidence in the diabetic group. The study reported the association of long-term immunogenicity with age and pre-vaccination titer, instead of diabetes status.[56] Another study comparing the cytotoxic T-cell and humoral immune response of an influenza A-H1N1 SUV among 27 subjects (patients with type 1 diabetes mellitus [T1DM]: 14; healthy subjects: 13) reported poor cytotoxic T-cell response to vaccination in both the groups.[55] A pilot study conducted to evaluate inactivated TIV in juvenile diabetics and matched healthy controls reported no difference in both groups in terms of the humoral immune response.[57]

Another study evaluating the effect of SUV in combination with pneumococcal vaccination in children and adolescents (group vaccinated with pneumococcal vaccine: 100 out of which 28% were vaccinated with SUV also; unvaccinated group = 30; age: 2-18 years) with T1DM who were on intensified insulin treatment did not report any activation of autoimmune process or increase in levels of autoantibodies to n-DNA, d-DNA and pancreatic tissue in group receiving vaccination. In addition, there was no disease progression observed in the subjects, while the immune system of the vaccinated patients was found to be positively influenced by a tendency to shift towards normalization.[58]

Liver Transplant Patients

Like other subgroups of the population at risk, patients with liver transplant also warrant immunization against influenza vaccine. However, the response of recipients receiving immunosuppressive therapy is controversial. A study assessing efficacy of first and second vaccination using SUV in 61 immunocompromised adult liver transplant recipients, 35 liver cirrhosis patients and 45 healthy spouses of these patients reported a significant rise in GMT of all three antigens after one vaccination (H3N2, ranges, controls: 194-375, cirrhosis: 207-531, liver transplant 53-103; $p < 0.001$; H1N1, ranges, controls: 292-655, cirrhosis: 484-1303, liver transplant: 132-278, $p < 0.001$; B, ranges, controls: 65-166, cirrhosis: 61-199; liver transplant: 37-83, $p = 0.058$), without further significant increase in patients with cirrhosis (ranges: H3N2: 215-533, H1N1: 461-1,219, B: 73-204) and control subjects (ranges: H3N2: 181-354, H1N1: 291-630, B: 119-246) after second vaccination. Patients with liver transplant were observed with a rise in GMT after the second vaccination. The overall antibody response to all three influenza virus strains was lower in the liver transplant recipients as compared to control group. Despite immunosuppressive therapy, liver transplant recipients were effectively vaccinated using SUV.[59]

Pregnant Women

The CDC recommends vaccination against influenza infection for pregnant women due to the likelihood of getting infected because of weakened immune system and risk of pregnancy complications associated with influenza. Vaccination may be done anytime during pregnancy.[60] Studies have suggested a reduction in preterm birth and low birth weight in babies with mother getting vaccinated during pregnancy.[61,62] A recent meta-analysis conducted by Nunes et al, 2016, included five studies to assess the effect of vaccination in pregnant women. The study reported an association between maternal influenza vaccination and decreased risk of preterm birth (odds ratio [OR]: 0.87; 95% CI: 0.77-0.98) and low birth weight (OR: 0.74; 95%

CI: 0.61-0.88).[63] Pregnant women (second trimester) immunized against influenza A (H1N1) using SUV were evaluated to assess alterations in immune response and possible risk of antenatal development of the fetus in post-vaccination period. Mild local reactions were observed in 13% cases during vaccination, whereas 26.1% subjects presented general systemic reactions such as weakness, dizziness and headaches. The SUV demonstrated comparable reactogenicity with the control group and was considered safe to be used in pregnant women.[64]

Nursing Home Residents

A cohort study comparing the SUV vaccinated 10,739 elderly (older than 65 years; patients receiving one dose: 2,027; patients receiving two doses: 8,712) nursing home residents and 11,723 control subjects during an influenza A (H3N2) epidemic in 1998 to 1999 reported decrease in the number of cases diagnosed with influenza infection among the vaccinated group. Out of 950 cases diagnosed clinically with influenza infection, only 256 infected cases, 32 hospital admissions and one death were observed in vaccinated group as compared to the unvaccinated controls with 694 infected cases, 150 hospital admissions and five deaths. An equal efficacy was observed in patients receiving one or two doses of vaccine with no serious adverse reactions.[65]

Asthma Patients

Asthmatic patients infected with influenza virus may present worsened symptoms and other complications. Vaccination of asthma patients is recommended by physicians as well as the CDC. In a study, a total of 95 children (male: 52; female: 43; age range: 7 months to 12 years) suffering from moderate-to-severe asthma received SUV (Aggripal, IV). No sign of fever was observed till 48 hours after vaccination. Only three children (age: 7-30 months) showed signs of local side effects such as pain, restricted movement) at the site of injection for 8-12 hours. Overall, no side effects were observed till 2 months following the vaccination along with no worsening effect on asthma.[66]

Another study conducted on 14 asthmatic patients (12 men; 2 women; age range: 24-65 years) to assess the efficacy of SUV (Influvac, subcutaneous) reported SUV as well-tolerated vaccine in patients with asthma and was found to be immunogenic. No local or systemic side effects were observed following vaccination. Moreover, no change in the asthma symptoms was observed.[67]

CONCLUSION

Influenza virus infects individuals of all age groups and is associated with a diverse clinical presentation. Influenza is associated with several complications, which can be adverse to a considerable extent. Vaccination against influenza infection is therefore highly recommended. All the TIVs, i.e., WIV, SIV and SUV have been considered immunogenic; however, SUV presents better tolerability and lower reactogenicity as compared to other vaccine types. In addition, SUV has demonstrated high immunizing and favorable safety profile in clinical studies conducted on high-risk subgroups of population which include children, elderly, pregnant, liver transplant patients, asthmatics, diabetics and nursing home residents.

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REFERENCES

1. Seasonal Influenza: Flu Basics. Available at: https://www.cdc.gov/flu/about/disease/. Accessed on 18th July, 2017.
2. King AMQ, Lefkowitz EJ, Adams MJ, Carstens EB (Eds.). Virus Taxonomy - Ninth Report of the International Committee on Taxonomy of Viruses. London, United Kingdom: Elsevier/Academic Press; 2011.
3. Soema PC, Kompier R, Amorij JP, Kersten GF. Current and next generation influenza vaccines: Formulation and production strategies. Eur J Pharm Biopharm. 2015;94:251-63.
4. Kunisaki KM, Janoff EN. Influenza in immunosuppressed populations: a review of infection frequency, morbidity, mortality, and vaccine responses. Lancet Infect Dis. 2009;9(8):493-504.
5. McElhaney JE, Zhou X, Talbot HK, Soethout E, Bleackley RC, Granville DJ, et al. The unmet need in the elderly: how immunosenescence, CMV infection, co-morbidities and frailty are a challenge for the development of more effective influenza vaccines. Vaccine. 2012;30(12):2060-7.
6. Fraaij PL, Heikkinen T. Seasonal influenza: the burden of disease in children. Vaccine. 2011;29(43):7524-8.
7. Hui DS. Review of clinical symptoms and spectrum in humans with influenza A/H5N1 infection. Respirology. 2008;13 Suppl 1:S10-3.
8. Writing Committee of the WHO Consultation on Clinical Aspects of Pandemic (H1N1) 2009 Influenza, Bautista E, Chotpitayasunondh T, Gao Z, Harper SA, Shaw M, Uyeki TM, et al. Clinical aspects of pandemic 2009 influenza A (H1N1) virus infection. N Engl J Med. 2010; 362(18):1708-19.

9. Ekstrand JJ, Herbener A, Rawlings J, Turney B, Ampofo K, Korgenski EK, et al. Heightened neurologic complications in children with pandemic H1N1 influenza. Ann Neurol. 2010;68(5):762-6.
10. Neumann G, Noda T, Kawaoka Y. Emergence and pandemic potential of swine-origin H1N1 influenza virus. Nature. 2009;459(7249):931-9.
11. World Health Organization. Influenza seasonal. Available at: http://www.who.int/mediacentre/factsheets/fs211/en/. Accessed on 18th July, 2017.
12. Biologicals: Influenza. Available at: http://www.who.int/biologicals/vaccines/influenza/en/. Accessed on 18th July, 2017.
13. Medina RA, García-Sastre A. Influenza A viruses: new research developments. Nat Rev Microbiol. 2011; 9(8):590-603.
14. Molinari NA, Ortega-Sanchez IR, Messonnier ML, Thompson WW, Wortley PM, Weintraub E, et al. The annual impact of seasonal influenza in the US: measuring disease burden and costs. Vaccine. 2007;25(27):5086-96.
15. Duxbury AE, Hampson AW, Sievers JG. Antibody response in humans to deoxycholate-treated influenza virus vaccine. J Immunol. 1968;101(1):62-7.
16. Laver WG, Webster RG. Preparation and immunogenicity of an influenza virus hemagglutinin and neuraminidase subunit vaccine. Virology. 1976 ;69(2):511-22.
17. Al-Mazrou A, Scheifele DW, Soong T, Bjornson G. Comparison of adverse reactions to whole-virion and split-virion influenza vaccines in hospital personnel. CMAJ. 1991;145(3):213-8.
18. Goldstein MA, Tauraso NM. Effect of formalin, beta-propiolactone, merthiolate, and ultraviolet light upon influenza virus infectivity chicken cell agglutination, hemagglutination, and antigenicity. Appl Microbiol. 1970;19(2):290-4.
19. van Boxtel RA, Verdijk P, de Boer OJ, van Riet E, Mensinga TT, Luytjes W. Safety and immunogenicity of influenza whole inactivated virus vaccines: A phase I randomized clinical trial. Hum Vaccin Immunother. 2015;11(4):983-90.
20. Parkman PD, Hopps HE, Rastogi SC, Meyer HM Jr. Summary of clinical trials of influenza virus vaccines in adults. J Infect Dis. 1977;136 Suppl:S722-30.
21. Gross PA, Ennis FA, Gaerlan PF, Denson LJ, Denning CR, Schiffman D. A controlled double-blind comparison of reactogenicity, immunogenicity, and protective efficacy of whole-virus and split-product influenza vaccines in children. J Infect Dis. 1977;136(5):623-32.
22. Carle F, Bolgiani M, Zanon P, Moiraghi Ruggenini A, Zotti C. Immunoprophylaxis for influenza: comparison of a subunit and a whole virion vaccine. Boll Ist Sieroter Milan. 1988;67(2):105-15.
23. Ansaldi F, de Florentiis D, Durando P, Icardi G. Fluzone® Intradermal vaccine: a promising new chance to increase the acceptability of influenza vaccination in adults. Expert Rev Vaccines. 2012;11(1):17-25.
24. Bachmayer H, Liehl E, Schmidt G. Preparation and properties of a novel influenza subunit vaccine. Postgrad Med J. 1976;52(608):360-7.
25. Brady MI, Furminger IG. A surface antigen influenza vaccine. 2. Pyrogenicity and antigenicity. J Hyg (Lond). 1976;77(2):173-80.
26. Squarcione S, Sgricia S, Biasio LR, Perinetti E. Comparison of the reactogenicity and immunogenicity of a split and a subunit-adjuvanted influenza vaccine in elderly subjects. Vaccine. 2003;21(11-12):1268-74.
27. Baxter R, Patriarca PA, Ensor K, Izikson R, Goldenthal KL, Cox MM. Evaluation of the safety, reactogenicity and immunogenicity of FluBlok® trivalent recombinant baculovirus-expressed hemagglutinin influenza vaccine administered intramuscularly to healthy adults 50-64 years of age. Vaccine. 2011;29(12):2272-8.
28. King JC Jr, Cox MM, Reisinger K, Hedrick J, Graham I, Patriarca P. Evaluation of the safety, reactogenicity and immunogenicity of FluBlok® trivalent recombinant baculovirus-expressed hemagglutinin influenza vaccine administered intramuscularly to healthy children aged 6-59 months. Vaccine. 2009;27(47):6589-94.
29. Potter CW, Jennings R, McLaren C, Edey D, Stuart-Harris CH, Brady M. A new surface-antigen-adsorbed influenza virus vaccine. II. Studies in a volunteer group. J Hyg (Lond). 1975;75(3):353-62.
30. Beyer WE, Palache AM, Kerstens R, Masurel N. Gender differences in local and systemic reactions to inactivated influenza vaccine, established by a meta-analysis of fourteen independent studies. Eur J Clin Microbiol Infect Dis. 1996;15(1):65-70.
31. Kunz C, Hofmann H, Bachmayer H, Liehl E, Moritz A, Schmidt G. A new influenza subunit vaccine: reactogenicity and antigenicity in comparison to split and whole virus vaccines (author's transl). Infection. 1976; 4(2):73-9.
32. Leeb A, Carcione D, Richmond PC, Jacoby P, Effler PV. Reactogenicity of two 2010 trivalent inactivated influenza vaccine formulations in adults. Vaccine. 2011; 29(45):7920-4.
33. Dong PM, Li YQ, Zheng TZ, Jia YP, Li F, Han TW, et al. Comparative study on safety and immunogenicity between influenza subunit vaccine and split vaccine. Zhonghua Liu Xing Bing Xue Za Zhi. 2003;24(7):570-3.
34. Beyer WE, Palache AM, Osterhaus AD. Comparison of serology and reactogenicity between influenza subunit vaccines and whole virus or split vaccines: a review and meta-analysis of the literature. Clin Drug Investig. 1998;15(1):1-12.
35. van de Witte S, Nauta J, Giezeman-Smits K, de Voogd J. Trivalent inactivated subunit influenza vaccine Influvac®: 30-year experience of safety and immunogenicity. Trials Vaccinol. 2012;1:42-8.

36. Heikkinen T, Silvennoinen H, Peltola V, Ziegler T, Vainionpaa R, Vuorinen T, et al. Burden of influenza in children in the community. J Infect Dis. 2004; 190(8):1369-73.
37. Izurieta HS, Thompson WW, Kramarz P, Shay DK, Davis RL, DeStefano F, et al. Influenza and the rates of hospitalization for respiratory disease among infants and young children. N Engl J Med. 2000;342(4):232-9.
38. Neuzil KM, Hohlbein C, Zhu Y. Illness among schoolchildren during influenza season: effect on school absenteeism, parental absenteeism from work, and secondary illness in families. Arch Pediatr Adolesc Med. 2002;156(10):986-91.
39. Neuzil KM, Edwards KM. Influenza vaccines in children. Semin Pediatr Infect Dis. 2002;13(3):174-81.
40. Esposito S, Marchisio P, Montinaro V, Bianchini S, Weverling GJ, Pariani E, et al. The immunogenicity and safety of a single 0.5 mL dose of virosomal subunit influenza vaccine administered to unprimed children aged ≥6 to <36 months: data from a randomized, Phase III study. Vaccine. 2012;30(49):7005-12.
41. Zhu FC, Zhou W, Pan H, Lu L, Gerez L, Nauta J, et al. Safety and immunogenicity of two subunit influenza vaccines in healthy children, adults and the elderly: a randomized controlled trial in China. Vaccine. 2008;26(35):4579-84.
42. El'shina GA, Gorbunov MA, Bektimirov TA, Lonskaia NI, Pavlova LI, Nikul'shin AA, et al. The evaluation of the reactogenicity, harmlessness and prophylactic efficacy of Grippol trivalent polymer-subunit influenza vaccine administered to schoolchildren. Zh Mikrobiol Epidemiol Immunobiol. 2000;(2):50-4.
43. Blyth CC, Jacoby P, Effler PV, Kelly H, Smith DW, Borland ML, et al; WAIVE Study Team. Influenza vaccine effectiveness and uptake in children at risk of severe disease. Pediatr Infect Dis J. 2016;35(3):309-15.
44. Schaad UB, Bühlmann U, Burger R, Ruedeberg A, Wilder-Smith A, Rutishauser M, et al. Comparison of immunogenicity and safety of a virosome influenza vaccine with those of a subunit influenza vaccine in pediatric patients with cystic fibrosis. Antimicrob Agents Chemother. 2000;44(5):1163-7.
45. Brydak LB, Rokicka-Milewska R, Machała M, Jackowska T, Sikorska-Fic B. Immunogenicity of subunit trivalent influenza vaccine in children with acute lymphoblastic leukemia. Pediatr Infect Dis J. 1998;17(2):125-9.
46. Wong SS, Webby RJ. Traditional and new influenza vaccines. Clin Microbiol Rev. 2013;26(3):476-92.
47. Gasparini R, Pozzi T, Montomoli E, Fragapane E, Senatore F, Minutello M, et al. Increased immunogenicity of the MF59-adjuvanted influenza vaccine compared to a conventional subunit vaccine in elderly subjects. Eur J Epidemiol. 2001;17(2):135-40.
48. Frey S, Poland G, Percell S, Podda A. Comparison of the safety, tolerability, and immunogenicity of a MF59-adjuvanted influenza vaccine and a non-adjuvanted influenza vaccine in non-elderly adults. Vaccine. 2003;21(27-30):4234-7.
49. Seo YB, Choi WS, Lee J, Song JY, Cheong HJ, Kim WJ. Comparison of the immunogenicity and safety of the conventional subunit, MF59-adjuvanted, and intradermal influenza vaccines in the elderly. Clin Vaccine Immunol. 2014;21(7):989-96.
50. de Bruijn I, Meyer I, Gerez L, Nauta J, Giezeman K, Palache B. Antibody induction by virosomal, MF59-adjuvanted, or conventional influenza vaccines in the elderly. Vaccine. 2007;26(1):119-27.
51. Scheifele DW, McNeil SA, Ward BJ, Dionne M, Cooper C, Coleman B, et al; PHAC/CIHR Influenza Research Network. Safety, immunogenicity, and tolerability of three influenza vaccines in older adults: results of a randomized, controlled comparison. Hum Vaccin Immunother. 2013;9(11):2460-73.
52. Centers for Disease Control and Prevention: Influenza. Available at: https://www.cdc.gov/flu/heartdisease/. Accessed on 12th June, 2017.
53. Brydak LB, Romanowska M, Nowak I, Ciszewski A, Bilińska ZT. Antibody response to influenza vaccine in coronary artery disease: a substudy of the FLUCAD study. Med Sci Monit. 2009;15(7):PH85-91.
54. Diepersloot RJ, Bouter KP, Beyer WE, Hoekstra JB, Masurel N. Humoral immune response and delayed type hypersensitivity to influenza vaccine in patients with diabetes mellitus. Diabetologia. 1987;30(6):397-401.
55. Diepersloot RJ, Bouter KP, van Beek R, Lucas CJ, Masurel N, Erkelens DW. Cytotoxic T-cell response to influenza A subunit vaccine in patients with type 1 diabetes mellitus. Neth J Med. 1989;35(1-2):68-75.
56. Seo YB, Baek JH, Lee J, Song JY, Lee JS, Cheong HJ, et al. Long-term immunogenicity and safety of a conventional influenza vaccine in patients with type 2 diabetes. Clin Vaccine Immunol. 2015;22(11):1160-5.
57. el-Madhun AS, Cox RJ, Seime A, Søvik O, Haaheim LR. Systemic and local immune responses after parenteral influenza vaccination in juvenile diabetic patients and healthy controls: results from a pilot study. Vaccine. 1998;16(2-3):156-60.
58. Kostinov MP, Skochilova TV, Vorob'eva VA, Tarasova AA, Korovkina TI, Lukachev IV, et al. Autoantibodies after vaccination against pneumococcal and influenza infections in children and adolescents with type I diabetes mellitus. Zh Mikrobiol Epidemiol Immunobiol. 2009;(2):53-7.
59. Soesman NM, Rimmelzwaan GF, Nieuwkoop NJ, Beyer WE, Tilanus HW, Kemmeren MH, et al. Efficacy of influenza vaccination in adult liver transplant recipients. J Med Virol. 2000;61(1):85-93.
60. Centers for Disease Control and Prevention: Influenza. Available at: https://www.cdc.gov/flu/protect/vaccine/qa_vacpregnant.htm. Accessed on 12th June, 2017.
61. Fell DB, Sprague AE, Liu N, Yasseen AS 3rd, Wen SW, Smith G, et al; Better Outcomes Registry & Network (BORN)

Ontario. H1N1 influenza vaccination during pregnancy and fetal and neonatal outcomes. Am J Public Health. 2012;102(6):e33-40.

62. Richards JL, Hansen C, Bredfeldt C, Bednarczyk RA, Steinhoff MC, Adjaye-Gbewonyo D, et al. Neonatal outcomes after antenatal influenza immunization during the 2009 H1N1 influenza pandemic: impact on preterm birth, birth weight, and small for gestational age birth. Clin Infect Dis. 2013;56(9):1216-22.
63. Nunes MC, Aqil AR, Omer SB, Madhi SA. The effects of influenza vaccination during pregnancy on birth outcomes: a systematic review and meta-analysis. Am J Perinatol. 2016;33(11):1104-14.
64. Cherdantsev AP, Kostinov MP, Kuselman AI, Voznesenskaia NV. Vaccination against influenza A (H1N1) in pregnancy. Zh Mikrobiol Epidemiol Immunobiol. 2011;(4):46-50.
65. Deguchi Y, Nishimura K. Efficacy of influenza vaccine in elderly persons in welfare nursing homes: reduction in risks of mortality and morbidity during an influenza A (H3N2) epidemic. J Gerontol A Biol Sci Med Sci. 2001;56(6):M391-4.
66. Ghirga G, Ghirga P, Rodinò P, Presti A. Safety of the subunit influenza vaccine in asthmatic children. Vaccine. 1991;9(12):913-4.
67. Albazzaz MK, Harvey JE, Grilli EA, Caul EO, Roome AP. Subunit influenza vaccination in adults with asthma: effect on clinical state, airway reactivity, and antibody response. Br Med J (Clin Res Ed). 1987; 294(6581):1196-7.

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Moisturizers: False Claims and Allergic Ingredients

JAYAKAR THOMAS

It will not be wrong to mention that modern cosmetic and skin care products are mostly safe today and the chances of adverse reactions to them are very rare in spite of the fact that a large number of people are using these products over a lifetime. However, with an ever-rising need of intensifying the biological activity and therapeutic efficacy of these cosmetic products, it will not be possible to avoid the risk of side effects increasing in the future. Hence, it becomes important for dermatologists to familiarize themselves with all possible untoward reactions to cosmetics.

WHAT ARE ADVERSE REACTIONS IN SKIN CARE PRODUCTS?

Adverse reactions encompass an extreme variant of sensitive skin known as "cosmetic intolerance syndrome" which describes those individuals who are no longer able to tolerate a wide range of cosmetic products. However, "true" allergic reactions to cosmetics occur much less commonly than irritant reactions. These reactions are more serious in nature, difficult to treat and need to completely avoid the agent causing it. Damaged eczematous skin is at an increased risk to develop such allergies.[1]

WHAT ARE CONSUMERS LOOKING FOR AND WHAT IS THE DERMATOLOGISTS TAKE?

Considering moisturizer use to be critical for the prevention and treatment of numerous dermatological conditions, patients frequently request the dermatologist for product recommendations. A cohort study showed that among the commonly available moisturizing products available in the market, they varied by price and marketing claims and the lotions were the most popular choice. Out of the 174 products listed in the study, only a few best-selling moisturizers were free of potential allergens.[2] The cohort study revealed that the most popular product lotions was followed by creams, oils, butter and lastly ointments.[2]

While recommending moisturizers to patients with skin conditions that benefit from over-the-counter moisturizer use, dermatologists should base their recommendations on the broad availability and affordability of the product with a low risk of potential allergenicity.[2] It is important for the dermatologists to balance consumer preference, price and allergenicity in their recommendations, in view of dearth of readily available comparison data on moisturizing efficacy of these products.[2] It is also important for the dermatologists to discuss with parents and patients that baby moisturizing products can differ in allergenicity and irritancy.[3]

ALLERGENS PRESENT IN MOISTURIZERS

The cohort study involving publicly available data of the top 100 best-selling whole-body moisturizing products at 3 major online retailers revealed that in the total study sample, only 12% of the best-selling moisturizing products were free of the North American Contact Dermatitis Group (NACDG) allergens. The 3 most common allergens found in these products included fragrance mix, paraben mix and tocopherol.[2]

Recently, it has been seen in a study that alkyl glucoside is present in various leave-on cosmetic products such as sunscreens and facial moisturizers. Alkyl glucosides are contact allergens which were recently named as the 2017 "Allergen of the Year" by the American Contact Dermatitis Society (ACDS) partially due to the increasing prevalence of positive patch-test reactions. It has been found that among the 20 best-selling facial moisturizers, almost 10% contain alkyl glucoside in their ingredients.[4]

Another new contact allergen, caprylhydroxamic acid has also been found to cause an epidemic of allergic contact dermatitis in patients using moisturizers containing this preservative.[5]

LABELING ISSUES

It has been seen that products labeled with claims such as, "dermatologist recommended" and "phthalate free" are sold at a higher median price as compared

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to the ones without such claims. It was also seen that products, which claimed to be "fragrance-free" had at least 1 fragrance cross reactor or botanical ingredient.[2]

One of the major concerns in this regard is the use of misleading labeling in various skin care products for babies. Parents consider baby products to be safe and gentle for their babies but it has been seen that many baby moisturizers contain various fragrance factors such as organic calendula, sweet almond oil, and sunflower oil; many baby products also contain lanolin.[3] A study published in 2016 conducted a systematic review of patch test in children and adolescents and revealed that top 5 most common allergens in children were nickel, thimerosal, cobalt, fragrance and lanolin.[6]

REFERENCES

1. Wolf R, Wolf D, Tuzun B, Tüzun Y. Cosmetics and contact dermatitis. Dermatol Ther. 2001;14(3):181-7.
2. Xu S, Kwa M, Lohman ME. Consumer preferences, product characteristics, and potentially allergenic ingredients in best-selling moisturizers. JAMA Dermatol. 2017;153(11):1099-105.
3. Hamann CR, Thyssen JP. Allergen concerns and popular skin care products. JAMA Dermatol. 2018; 154(1):114-5.
4. Boozalis E, Patel S. "Allergen of the year" alkyl glucoside is an ingredient in top-selling sunscreens and facial moisturizers. J Am Acad Dermatol. 2017 Oct 14. [Epub ahead of print]
5. Ackermann L, Virtanen H, Korhonen L, Laukkanen A, Huilaja L, Riekki R, et al. An epidemic of allergic contact dermatitis caused by a new allergen, caprylhydroxamic acid, in moisturizers. Contact Dermatitis. 2017; 77(3):159-62.
6. Rodrigues DF, Goulart EM. Patch-test results in children and adolescents: systematic review of a 15-year period. An Bras Dermatol. 2016;91(1):64-72.

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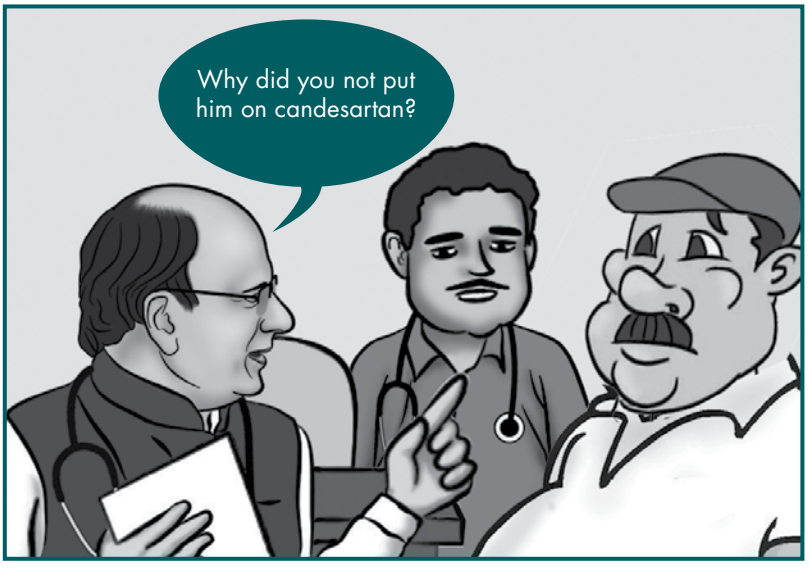
Make sure

DURING MEDICAL PRACTICE

SITUATION: A hypertensive patient with impaired glucose tolerance was started on enalapril for hypertension.



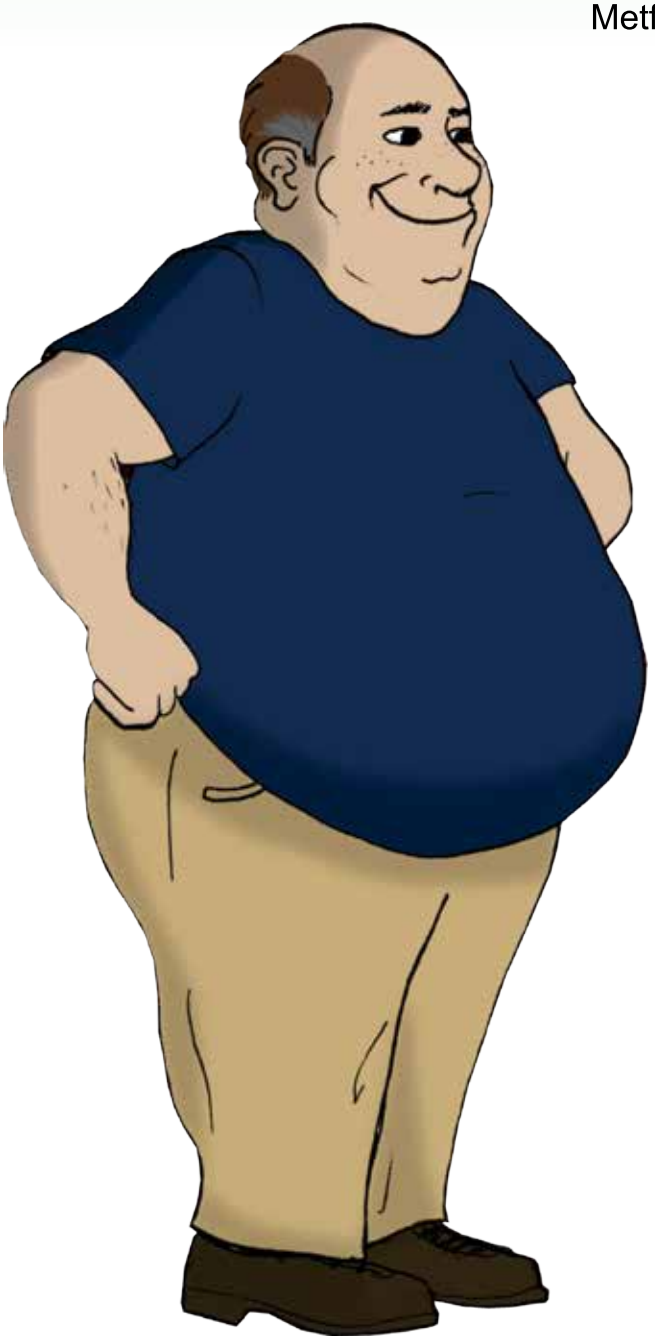
LESSON: Make sure to remember that patients initiated on candesartan treatment had a lower risk of new-onset type 2 diabetes and lower rates of drug discontinuation compared with patients initiated on enalapril.

J Hum Hypertens. 2014;28(11):663-9.

In Obese T2DM Patients

Rx Voliphage™ M 0.2 mg / 0.3 mg

Metformin SR 500 mg + Voglibose 0.2 / 0.3 mg Tablets



Superior Glycaemic Control In Obese T2DM

2018

DIABÉTIX
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Maharashtra Plastic and Thermocol Products (Manufacture, Usage, Sale, Transport, Handling and Storage) Notification, 2018

ENVIRONMENT DEPARTMENT
15th Floor, New Administrative Building
Madam Cama Road, Mantralaya,
Mumbai 400 032, dated 23rd March, 2018
NOTIFICATION
No. Plastic-2018/C.R. No. 24/TC-4.

WHEREAS, concerns about usage and disposal of plastic are diverse and include accumulation of waste in landfills, water bodies and in natural habitats, physical problems for wild animals resulting from ingestion or entanglement in plastic, the leaching of chemicals from plastic products and the potential for plastics to transfer chemicals to wildlife and humans are increasing.

AND WHEREAS, because of non-biodegradable plastic waste handling of municipal solid waste becomes difficult and incurs more financial burden and also due to burning such waste in open environment causes various diseases in humans and animals. AND WHEREAS, it is observed that non-biodegradable garbage is responsible for clogging drains and nallas causing flood in urban settlement leading to loss of lives and damage to properties and infrastructure.

AND WHEREAS, plastic waste and microplastic cause danger to marine and freshwater bio-diversity and also hamper ecosystem services due to spreading of such waste in and around ecosystems, on tourists places, beaches and on agriculture and forest areas.

AND WHEREAS, non-biodegradable plastic waste and microplastic are having negative impacts on fish diversity and fisheries activity. AND WHEREAS, non-biodegradable waste is posing problems in effective implementation of Clean India Mission.

AND WHEREAS, detailed stake-holders consultations and deliberations with the field level officials were undertaken, and public notices were also published in leading newspapers.

AND WHEREAS, despite the ban on plastic bags of less than 50 micron through Maharashtra Plastic Carry Bags (Manufacture and Usage) Rules, 2006, there is increase in the non-biodegradable plastic garbage waste causing damage to environment and health.

Therefore, in exercise of the powers conferred by Clause (1) & (2) of Section 4 of the Maharashtra Non-Biodegradable Garbage (Control) Act, 2006, the Government of Maharashtra hereby authorises regulations for manufacture, usage, sale, storage, transport of the products made from plastic and thermocol, etc. which generates non-biodegradable waste.

1. Short Title and Commencement:
   1) This may be called the Maharashtra Plastic and Thermocol Products (Manufacture, Usage, Sale, Transport, Handling and Storage) Notification, 2018.
   2) This Notification shall come into force with effect from the date of their publication in the Maharashtra Government Gazette.
2. Definitions:
   1) "Act" means the Maharashtra Non-Biodegradable Garbage (Control) Act, 2006.
   2) "Plastic" means material; which contains as an essential ingredient a high polymer such as polyethylene terephthalate, high-density polyethylene, vinyl, low-density polyethylene, polypropylene, polystyrene resins, polystyrene (thermacol), non-oven polypropylene, multi-layered co-extruder, polypropylene, poly-terephthalate, polyamides, polymethyl methacrylate, plastic micro beads, etc.
   3) "Compostable Plastic" means plastic that undergoes degradation by biological processes during composting to yield CO_2, water, inorganic compounds and biomass at a rate consistent with other known compostable materials, excluding environmental petro-based plastic, and does not leave visible, distinguishable or toxic residue, and which shall confirm to the Indian Standard: IS 17088:2008 titled as Specifications for Compostable Plastics, as amended from time to time.
   4) "Plastic sheets" means sheet made of plastic.

5) "Plastic waste" means any plastic discarded after use or after their intended use is over.

6) "Recycling" means the process of transforming segregated plastic waste into a new product or raw material for producing a new products.

7) "Producer/Manufacturer" means person engaged in manufacture or import of plastic bags or multilayered packaging or containers or plastic sheets or like, and includes industries or individuals using plastic sheets or like or covers made up of plastic sheets or sheets or also manufacture products made from plastic or used plastic for packaging or wrapping the commodity.

8) "Commodity" means tangible items that may be brought or sold and includes all marketable goods or wares.

9) "Plastic bags" means bags made from plastic material, used for the purpose of carrying or dispensing commodities which have handle or without handle and also includes bags made from non-woven polypropylene and constitute or form an integral part of the packaging at manufacturing stage or is an integral part of manufacturing.

10) "PET and PETE bottles" means bottles made up of polyethylene terephthalate (PET) and polyethylene terephthalate esters (PETE) used for packaging or storing liquid or semi-liquid food, including water.

11) "Commodities made from thermocol" means any commodity or product made from thermocol.

12) "Form" means form attached with these regulations.

13) "Product" means anything or object or item made from plastic or thermocol.

3. Following activities will be regulated in the whole State of Maharashtra in exercise of the powers conferred by Section 2(h), Sub-section 1 and 2 of Section 4 of the Maharashtra Non-Biodegradable Garbage (Control) Act, 2006.

1. 1) The ban in the whole State of Maharashtra for manufacture, usage, transport, distribution, wholesale and retail sale and storage, import of the plastic bags with handle and without handle, and the disposable products manufactured from plastic and thermocol (polystyrene) such as single use disposable dish, cups, plates, glasses, fork, bowl, container, disposable dish/bowl used for packaging food in hotels, spoon, straw, non-woven polypropylene bags, cups/pouches to store liquid, packaging with plastic to wrap or store the products, packaging of food items and food grain material, etc.

2) These regulations are applicable to every person, body of person, government and non-government organization, educational institution, sport complex, clubs, cinema halls and theaters, marriage/celebration halls, industrial units, commercial institutions, offices, pilgrimage organizers, pilgrimages and religious places, hotels, dhabas, shopkeepers, malls, vendors or sellers, traders, manufacturers, caterer, wholesalers, retailers, stockiest, businessmen, hawkers, salesmen, transporters, market, producers, stalls, tourist places, forest and reserved forest, eco-sensitive areas, all sea beaches, all public places, bus stands, railway stations in the State of Maharashtra.

3) There will be ban in whole state for use of plastic and thermocol for decoration purpose.

2. Use, sale, storage and manufacture of PET or PETE bottles made up of high quality food grade virgin Bisphenol-A free material having liquid holding capacity not less than 0.5 liters and printed on it with predefined buy back price shall be allowed subject to compliance of the following.

PET or PETE bottle manufacturers, producers, sellers and traders under "Extended Producers and Sellers/Traders Responsibility" will develop "Buy Back Depository Mechanism" with a predefined buy back price printed specifically on such PET or PETE bottles and also set up Collection and Recycling units of adequate capacity and number to collect and recycle such PET or PETE bottles within 3 months from the date of publication of this notification. Traders/sellers will buy back such used PET/PETE bottles with predefined buy back price printed on such bottles.

PET/PETE bottles having liquid holding capacity 1 liter or more and of 0.5 liter will

be printed on the body of the bottle with predefined buy back price of Rs. 1/- and Rs. 2/, respectively. However, there will be ban on usage, purchase, sale, distribution and storage of PET/PETE bottles having liquid holding capacity less than 0.5 liters in the State.

3. These regulations shall not be applicable to the following items:
   i. Plastic bags or plastic used for packaging of medicines;
   ii. Only compostable plastic bags or material used for plant nurseries, horticulture, agriculture, handling of solid waste. However, bags/sheets utilized for this purpose shall be prominently printed on it with "Use exclusively for this specific purpose only". The manufacturers or seller of compostable plastic carry bags shall obtain a certificate from the Central Pollution Control Board before marketing or selling for this purpose.
   iii. To manufacture plastic and plastic bags for export purpose only, in the Special Economic Zone and export oriented units, etc.
   iv. The plastic cover/plastic to wrap the material at the manufacturing stage or is an integral part of manufacturing. Guidelines to recycle or reuse such plastic should be printed prominently on the cover and material.
   v. Food grade virgin plastic bags not less than 50 micron thickness used for packaging of milk. However, on such plastic bags used for this purpose, should be clearly printed with the price for buy back which should not be less than Rs. 0.50 to develop buy back system for recycling. To develop collection mechanism and ensure proper recycling of such used bags, milk dairies, retail sellers and traders will buy back such used milk bags with predefined buy back price printed on it. Milk dairies, retail sellers and traders will ensure that such buy back mechanism and collection and recycling system shall establish within 3 months from the date of publication of this regulation. However, Milk Dairy and distributors shall make efforts to develop alternative system with glass bottles or any other environmental friendly material for distribution of milk.

4. The following officers are authorized and empowered for the implementation and to take necessary legal action under powers conferred u/s 12 of the provisions of the Maharashtra Non-biodegradable (Control) Act, 2006, as per their jurisdiction:
   1. 1) Municipal Commissioners, Deputy Municipal Commissioners, Shops & Establishment Officers and Inspectors, Sanitary Inspector, Health Inspector, Health Officer, Ward Officers or any other Officer nominated by the Municipal Commissioner as well as Chief Officers of all Municipal Councils and any other Officer nominated by the Chief Officer are authorized to implement the provisions of the said Regulations in their respective jurisdiction.
      2) District Collector, Deputy Collector, Sub-Divisional Officer, Tahasildar, Talathi and any other officer nominated by Collector, are authorized to implement the provisions of the said Regulations in their respective jurisdiction.
      3) Chief Executive Officer, Zilla Parishad; Block Development Officer, Health Officer, Development Officer, District Education Officer, Block Education Officer and Gram Sevak are authorized to implement the provisions of the said Regulations in their respective jurisdiction.
      4) Member Secretary, Regional Officer, Sub-Regional Officer and Field Officer of Maharashtra Pollution Control Board, Scientist-I & II and Director, Environment Department, Government of Maharashtra.
      5) Director, Health Services; Deputy Director, Health Services; Health Officers.
      6) Director, Primary and Secondary Education Board.
      7) All Tourism Police, Police Inspector, Police Sub-Inspector, Motor Vehicle Inspector, Traffic Police, Joint Managing Director, Maharashtra Tourism Development Corporation or any other officer authorized by Managing Director, Maharashtra Tourism Development Corporation.

8) Deputy Commissioner (Supply), District Supply Officer

9) Commissioner State Tax and all State Tax Officers.

10) Range Forest Officer or any other officer authorized by Deputy Conservator of Forest.

2. 1) For implementation of these regulations, the person at village or city level, interested persons, group of people, welfare organizations, industrial association and members of all local bodies, etc. shall register any offence with the concerned authorized officer, notified in these regulations for this purpose.

2) The said registered person, group of people, welfare organizations, industrial association shall help the officers authorized under the said regulations, for providing information of violation of these regulations and assist such officers to impose fine, to confiscate the material made from plastic and thermocol and assist in registering the offence.

5. Maharashtra Pollution Control Board shall impose the condition on manufacturers indicating that recycling price and buy back price should be prominently printed on PET/PETE bottles and plastic bags permissible under these regulations while issuing consent to establish, consent to operate/renewal and also to initiate actions on non-complying units or industries under appropriate act.

6. Separate order for levying recycling fees from manufacturers at manufacturing stage and recycling fees at selling point at local body level will be issued in consultation with Directorate of Goods and Services Taxes and with approval of the Empowered committee.

7. Time frame for implementation of these regulation:

Sr. No.	Stake Holder	Implementation period	
		Activity	**Time frame**
1.	Manufacturer/Producer	Manufacturing and sale of banned items.	From date of notification.
		Disposal of existing stock of banned items by: 1) Sale outside the state 2) Sale to authorized recycler or industry.	One month from the date of notification.
2.	Sellers, Retailers, Traders	Ban on sale	From the date of notification
		Disposal of existing stock by: 1) Sale outside the state 2) Sale to authorized recycler or industry 3) Handed over to Local Body for Scientific disposal or recycling; and plastic waste generated under buy back scheme to be handed over to authorized recyclers or to the such mechanism developed for the same.	One month from the date of notification.
3.	Users	Use of banned items.	From the date of notification.
		Disposal of existing plastic banned items with the individual users by 1) Handed over to Local Body for Scientific disposal or recycling 2) Sale to authorized recycler or industry.	One month from the date of notification.
4.	Local Body	To arrange the collection, transportation of banned plastic items or plastic waste of existing stock for recycling to authorized recyclers or industries or scientific disposal.	One month from the date of notification.

8. Empowered Committee, constituted under the chairmanship of Minister (Environment) shall monitor the implementation of these regulations and will regularly review the incorporation of additional items which generate non-biodegradable garbage including use of PET or PETE bottles to be banned in the state. This committee will also help in resolving any difficulty faced by implementing authorities during implementation and if required also carry out any amendment in these regulations with an aim to reduce the volume of non-biodegradable garbage generation in the State.
9. Expert Committee shall be constituted under these regulations which will suggest the recommendations including amendment required, if any in the regulations to the Empowered Committee for effective implementation of the regulations and solutions to reduce the non-biodegradable garbage.
10. Implementing Authorities, shall submit quarterly report in the Form-A to the State Government.

By order and in the name of the Governor of Maharashtra,

SATISH GAVAI
Additional Chief Secretary (Environment)

FORM-A

(1) Period of Report: From _____to_____

(2) Name and Address of Enforcing Agency:

(3) Name of the Officers Incharge of enforcement of the aforesaid Rules:

(4) Telephone/Cell No. (Office):

(5) E-mail ID:

(6) No. of cases registered in the jurisdiction for violation:

Jurisdiction	Compounding		3rd Offence	No. of cases filed in the Court	No. of cases sub-judiced	Amount of fine collected	Remarks
	1st Offence	2nd Offence					0

1. _____

Sub-Total

2. _____

Sub-Total

Grand Total ----------

(7) Details of special drives undertaken for effective implementation of the Rules:

(8) List of first time offenders and second time offenders.

(9) Details of public awareness programs conducted by Enforcing Agency in their jurisdiction.

(10) Any other relevant information.

(Signature of the Reporting Authority)

IN THE HIGH COURT OF JUDICATURE AT BOMBAY CRIMINAL APPELLATE JURISDICTION CRIMINAL ANTICIPATORY BAIL APPLICATION NO. 513 OF 2018

1 Deepa Sanjeev Pawaskar.

2 Sanjeev Anant Pawaskar. .. Applicants.

V/s.

The State of Maharashtra. .. Respondent.

Mr. Shirish Gupte, Sr. Counsel a/w. Mr. A.P. Mundargi, Senior Counsel I/b. Mr. Jayant J. Bardeskar, advocate for applicants.

Mr. Deepak Thakare a/w. Ms. Veera Shinde, APP for State.

Mr. Prashant Thombare a/w. Mr. Sandeep Agne, advocate for intervenor.

Mr. S.M. Varale, API, Ratnagiri City Police Station.

CORAM : SMT. SADHANA S. JADHAV, J.

RESERVED ON : JUNE 13, 2018.

PRONOUNCED ON : JULY 25, 2018.

P. C.:

1. Heard the learned Counsel for the applicants and the learned APP for State.

2. This is an application under Section 438 of the Code of Criminal Procedure, 1908. The applicants herein are apprehending their arrest in Crime No. 71 of 2018 registered with Ratnagiri City Police Station for offence punishable under Section 304 read with Section 34 of Indian Penal Code.

3. The applicant No. 1 happens to be the wife of applicant No. 2. The applicants are medical practitioners. The qualification of the applicants is M.D. (Gynecology).

4. **Issue for consideration: Prescription without diagnosis and hence resulting into death of the patient amounts to criminal negligence on the part of the doctors.**

5. The whole thrust of the applicants in the present case is that the act of the applicants would fall under Section 304A of the Indian Penal Code or under Section 304 of the Indian Penal Code and therefore, this Court is considering the issue.

6. It is the case of the prosecution that on 7th March, 2018 Pranav Pramod Polekar was constrained to lodge a report at the police station. The first informant informed the police that Dnyanada was his wife. Dnyanada was hail and hearty. That in the month of June, 2017 preliminary diagnosis indicated symptoms of having conceived and therefore, they had visited the hospital of Dr. Pawaskar. Dr. Sanjiv Pawaskar (applicant No. 2) had examined Dnyanada and had confirmed that she was pregnant. Dnyanada was registered with Dr. Pawaskar. Dnyanada used to visit the hospital regularly for routine check-up. She had taken the medicine prescribed by Dr. Pawaskar. He was informed that due date is approximately 18/2/2018.

7. On 5/2/2018, she had started having labor pains and therefore, they had rushed to Dr. Pawaskar Hospital. The doctor and his wife were present. She was admitted in the hospital. Initially, the family members were informed that she would have normal delivery. On 6/2/2018, she was advised to undergo sonography test at Gurukrupa Sonography Center. Upon seeing the sonography report, the doctors were of the opinion that she should undergo cesarean operation. On 6/2/2018, she had undergone **cesarean** operation. Dr. Ketkar was the anesthesist. Dnyanada had given birth to a female child. The baby was admitted in Gajanan Bal Rugnalay of Dr. Vijay Suryagandh. On 6/2/2018, Dnyanada appeared to be normal. The first informant had deposited Rs. 25,000/- towards medical fees. On 8/2/2018, baby was also

discharged and on 9/2/2018 at 5 p.m. Dnyanada was discharged from Dr. Pawaskar Hospital. At the time of discharge, doctors were not available. The staff had also not informed the family members or the patient about the postoperative care.

8. On 10/2/2018, Dnyanada was vomiting throughout the day. Her relatives had called upon Dr. Deepa Pawaskar. She had asked them to call her from medical shop. The doctor had given instructions to the medical shop owner and accordingly, he had given them tablets which she had taken. On the same day, in the evening Dnyanada had fever and she continued vomiting and therefore, she was taken to the hospital of Dr. Deepa Pawaskar at 8.30 p.m. In their presence, the staff nurse had called upon Dr. Deepa Pawaskar. She was advised to admit the patient. The staff had informed that the doctors are not available in the hospital. **The first informant had asked as to whether she should be taken to another hospital.** However, he was informed that it was not necessary and that the patient would be admitted for 1 day and on the next day, she would be discharged.
9. Dnyanada was being treated by two nurses, who were administering medicines on the telephonic instructions of Dr. Deepa Pawaskar. The condition of the patient was deteriorating and the relatives, out of anxiety were accordingly informing the staff nurse. The relatives were insisting upon shifting the patient to another hospital. However, the staff nurse upon instructions of the applicant No. 1 had informed the relatives that they need not panic and that they are in touch with Dr. Deepa Pawaskar and she has guided them telephonically. At about 10.15 p.m. Dr. Girish Karmarkar had been to the hospital. He had patiently heard about the complaints of the patient. Dr. Karmarkar had prescribed the tablet-Trazine H, which the first informant got from National Medical Shop as advised by Dr. Karmarkar.
10. On 11/2/2018 at about 3.45 a.m. his sister Mrunali, who was with the patient, had asked the first informant to rush to the hospital. They realized that tip of nose and lips of Dnyanada had turned black. Dr. Girish Karmarkar did not visit again nor enquired about the patient. The first informant had realized that the health of the patient had deteriorated to a large extent. He had to quarrel with the staff and thereafter, at 4 a.m. the staff had called upon Dr. Pawaskar. Upon his instructions, Dr. Ketkar had visited hospital at 4.30 a.m. Dr. Ketkar had enquired as to why the head of the patient was lowered. Upon objectionable query made by Dr. Ketkar, the staff had informed that the head was lowered at the instructions of Dr. Karmarkar. By then Dnyanada was getting fits. Dr. Ketkar felt need of putting her on oxygen. Dr. Ketkar had diagnosed poor prognosis and therefore, needed to be shifted to Parkar Hospital. Dr. Ketkar was not able to tell the relatives of as to what had happened to her. He informed Dr. Pawaskar that he is shifting the patient to Parkar Hospital. There was no ambulance with Dr. Pawaskar. To save time, Dr. Ketkar had to take the patient in his own car. She was admitted in the ICU of Parkar Hospital. She was kept on ventilator and at 7 a.m. the doctor had informed that Dnyanada had expired. The first informant had specifically stated that it was due to negligence by the present applicants that he had lost his wife. On the basis of the said report, an offence was registered. Investigation was set in motion.
11. The dead body of Dnyanada was sent for autopsy. The post-mortem notes indicated that the cause of death was due to pulmonary embolism. Thereafter, it was sent for histopathological test. The findings recorded in the histopathological test are as follows:

    Brain: Congestion.

    Heart: No specific lesion.

    Lungs: Pulmonary thromboembolism and bone marrow embolism in medium-sized blood vessels.

    Intra-alveolar hemorrhages and focal pulmonary edema.

    Liver: Focal fatty change, portal triaditis.

    Spleen, kidney: Congestion.

    Uterus with bilateral adnexae: Postpartum changes.

    LSCS suture site: Acute nonspecific inflammation.
12. The case papers of Dr. Pawaskar Hospital, Dr. Parkar's Hospital along with medical reports were referred to the District Civil Surgeon and his opinion was sought vide report dated 3/3/2018. His opinion was as follows:

    (i) Since Dnyanada Polekar had undergone cesarean operation and was readmitted on the very next day, it was incumbent upon the hospital to have examined the patient by the gynecologist before admission.

(ii) The patient was admitted on the telephonic instructions of Dr. Deepa Pawaskar.

(iii) Dr. Deepa Pawaskar is responsible for the health condition of the patient.

(iv) Dr Deepa Pawaskar should have referred the patient to a specialist immediately. Her negligence is apparent on the face of the record.

(v) The health condition was not monitored properly from 10/2/2018 8.30 p.m. to 11/2/2018 5.40 a.m. and therefore, negligence is apparent.

13. The second report given by the District Civil Surgeon to the Investigating Officer dated 13th March, 2018 reads as follows:

The statement of the staff nurses was recorded by the Investigating Officer and was placed before the District Civil Surgeon along with medical reports, upon which, medical analysis was as follows:

(i) Smt. Shital Thick had examined the patient at the time of readmission. Her educational qualification is 12th standard and passed A.N.M. Another staff nurse was Smt. Anuradha Sharad Rasal whose educational qualification is S.S.C. After the patient was admitted at 8.30 p.m., she was not examined by any medical officer. Dr. Girish Karmarkar had prescribed Trazin H. There was no preliminary assessment of the ailment and therefore, the treatment was not proper. The patient ought to have undergone pathological test such as X-ray and sonographic test. The condition of the patient ought to have been monitored every half an hour. The relatives of the patient were not informed immediately about the poor prognosis.

(ii) **The absence of Dr. Deepa Pawaskar was pre-planned and therefore, the patient ought not to have been admitted in her absence. Except checking pulse and blood pressure, no other tests were performed on the patient.**

(iii) The complications were not noticed immediately for want of proper medical officer.

(iv) Civil Surgeon has assigned reasons for pulmonary embolism and the symptoms which were found in patient Dnyanada, which are as follows:

(1) Restlessness

(2) Leg pain

(3) Breathlessness

(4) Pedal edema

(5) Cold extremities

(6) Pulse 132/min (on monitor)

(7) RR 32/min (on monitor).

(v) There is no record to show that there was any effort to refer the re-admitted patient to another doctor in the absence of Deepa Pawaskar and she continued to prescribe medicine telephonically. There was no resident medical officer or any other doctor to look after the patient in the absence of Mr. and Mrs. Pawaskar. In fact, the said trip was prescheduled.

14. In the course of investigation, the Investigating Officer had recorded the statements of staff of Dr. Pawaskar Hospital. Sarika Dakare has stated that she has passed her 12th standard. That the doctors had prepared the discharge card of the patient 1 day before, as they were to go out of station. Co-nurse Harshada Kanade had handed over the discharge papers, birth certificate to the patient at the time of discharge. On 9/2/2018 from 2 p.m. to 8 p.m., no doctor was available in the hospital. They had been asked by the doctors to discharge the patient on 9/2/2018 at 5 p.m. At that time, doctors were not available in the hospital. She has further stated that as per the telephonic instructions of Dr. Deepa Pawaskar, the patient was re-admitted. Saline was given. Saline could not be given on left hand as it was swollen.

15 The statement of one Anuradha Rasal was recorded. She is also studied up to 10th standard. She was an untrained nurse. On 7/2/2018, when she attended her duty at 8 p.m., she was informed by the co-nurse Manali Vasave that the applicants are leaving for Pune for conference on 8/2/2018 and that they have kept discharge papers of Dynanada Polekar ready and in case there is new patient, they should call upon Dr. Girish Karmarkar. On 10/2/2018, Dynanada was readmitted. On telephonic instructions of Dr. Deepa Pawaskar, case papers were prepared as per her instructions. The newborn baby was not with the mother when she was re-admitted. She was admitted in room No. 3. She was given dextrose injection through saline. Another injection was R-din. Dompan tablet and Aciloc was given and as per the instructions of Dr. Karmarkar, Trazine H was given. The patient had complaint of nausea, headache, giddiness,

tremendous, unbearable pain in her legs, loose motions. However, the said symptoms were not mentioned in the case papers. There was abdominal inflammation, swelling on her legs and lips had turned black. Her condition deteriorated between 4 and 4.30 a.m. The patient was panting for breath and complained of severe pain in her legs. At 4.30 a.m. Dr. Ketkar arrived and had shifted her at Parkar Hospital. She has specifically stated that there was no stretcher and therefore, she had to be taken up to the car in a plastic sheet. The relatives were made to hold plastic sheet. Similar are the statements of the other staff nurses.

16. Learned Senior Counsel for the applicants in the course of argument has submitted that the applicants at the most be prosecuted under Section 304A of the Indian Penal Code and not under Section 304 of the Indian Penal Code. What is placed on record to substantiate his argument is the Literature in respect of Pulmonary Embolism. Introduction itself reads as follows:

    "*The pathophysiology of pulmonary embolism. Although pulmonary embolism can arise from anywhere in the body, most commonly it arises from the calf veins.*"

    The literature further shows:

    "*In patients who survive a pulmonary embolism, recurrent embolism and death can be prevented with prompt diagnosis and therapy. Unfortunately, the diagnosis is often missed because patients with pulmonary embolism present with nonspecific signs and symptoms.*"

17. In the present case, it is more than clear that the patient had shown specific signs of embolism as she had fever, her calf was aching terribly. There was swelling on the abdominal, which was apparent. She had severe headache and fever. All these symptoms are noted by the District Civil Surgeon.

18. The learned APP has submitted that the sonographic report of the patient dated 6/2/2018 itself showed that "Umbilical artery show reduced diastolic flow with increased S/D ratio s/o fetoplacental insufficiency." In these circumstances, the patient had undergone cesarean. All the medical case papers of 10th and 11th show that the medicines were administered on the oral instructions of Dr. Mrs. Pawaskar.

19. Learned APP has further submitted that in the course of investigation, the applicants had tried to tamper with the evidence and the same cannot be disclosed till filing of the charge-sheet. The medical Board has also opined that it is a case of negligence, more particularly, because the visit to Pune on 9/2/2018 was pre-scheduled. The discharge card was prepared by the Doctors without examining the patient at the time of discharge. The statement of Dr. Karmarkar shows that 1 day Dr. Mr. and Mrs. Pawaskar had casually met him on road and requested him to attend patient, if necessary in their absence. That he was never requested by Dr. Pawaskar telephonically to examine the patient Dynanada. It was at the request of nurse that he had been to examine Dynanada on humanitarian ground and by virtue of professional courtesy. In his statement, he has given symptoms of pulmonary embolism, which can be diagnosed immediately and could have been treated.

20. It is pertinent to note that on 9/3/2018 when the investigation was in progress, the Indian Medical Association, Ratnagiri Branch wrote a letter of protest to the District Collector and the Superintendent of Police, threatening to go on strike for prosecuting Dr. Pawaskar couple for offence punishable under Section 304 of the Indian Penal Code. They have also warned that they would not hesitate to go on strike in all cities and at the State level or even at the National level. They had threatened of keeping the hospital closed in Ratnagiri. The letters were sent to the Chief Minister of Maharashtra, District Civil Surgeon, District Information Officer and the Superintendent of Police. **It is unfortunate that all private hospitals in Ratnagiri actually remained closed for 2 days and the patients were forced to rush to Civil Hospital**.

21. The medical board has observed that there were clots in inferior vena cava. Inferior vein returns blood to the heart from the lower part of the body. It is a vein which carries de-oxygenated blood from lower half of the body to the artium of the heart. The said vein runs beyond abdominal cavity.

22. The learned APP submits that in the eventuality, there was proper diagnosis at the time of readmission, Dynanada would have been saved. According to the learned APP, it is criminal negligence, more particularly, because the first informant had specifically asked as to whether he should admit his wife in some other hospital and as per the instructions of Dr. Deepa Pawaskar, the patient was readmitted being oblivious of the fact that the patient needed readmission within 24 hours of discharge. It is clear that the patient was not examined by the doctor at the time of

discharge. This Court had perused the discharge certificate which is signed by the applicants. It was post dated discharge certificate as it was prepared on 7/2/2018, since the doctors had left for Pune on 8th in the morning, the date on the discharge card is 9/2/2018.

23. The learned Senior Counsel vehemently submits that this would be a case of 304(A) and not 304 of the Indian Penal Code. Section 304A reads thus:

304A. Causing death by negligence—Whoever causes the death of any person by doing any rash or negligent act not amounting to culpable homicide, shall be punished with imprisonment of either description for a term which may extend to 2 years, or with fine, or with both.

It is submitted that in no way, it can be said that this was a criminal negligence.

24. To appreciate the submissions of the learned Senior Counsel one has to see the definition of "negligence'" as per Black's Law Dictionary. The word "negligence" is defined in Black's Law Dictionary as follows:

"*Failure to exercise the standard of care that a reasonably prudent person would have exercised in similar situation; any conduct that falls below the legal standard established to protect others against unreasonable risk of harm, except for conduct that is intentionally, want only, or willfully disregardful of others' rights. The term denotes culpable carelessness.*"

The Criminal Negligence is defined as "*Gross negligence so extreme that it is punishable as a crime.*" Whereas Culpable Negligence is *an intentional conduct which the actor may not intend to be harmful but which ordinary and reasonably prudent man would recognize as involving a strong probability of injury to others*. This would be a case of culpable neglect which is defined as censurable or blameworthy neglect: neglect i.e., less than gross carelessness, but more than failure to use ordinary care.

25. Doctors failure to exercise the degree of care and skill that a physician or surgeon of the medical specialty would use under similar circumstances would amount to malpractice. An error in diagnosis could be negligence and covered under Section 304A of the Indian Penal Code. **But this is a case of prescription without diagnosis and therefore, culpable negligence.** The element of criminality is introduced not only by a guilty mind but by the practitioner having run a risk of doing something with recklessness and indifference to the consequences. It should be added that this negligence or rashness is gross in nature.

26. When a doctor fails in his duty, does it not tantamount to criminal negligence? The Courts cannot ignore the ethical nature of the medical law by liberally extending legal protection to the medical professionals. The ethical issues raised by failure to assist a person in need arises from positive duties. According to this Court, the breach of these duties could fall within the realm of a criminal law of negligence.

27. The learned Senior Counsel submits that it is a case of civil law and the doctors could be made to pay compensation. It is submitted that at the most it is a negligence under Section 304A and not criminal negligence. Therefore, according to the learned Senior Counsel, the scope of the present case cannot be enhanced to make out a case of criminal negligence.

28. At this stage, a line of distinction needs to be withdrawn. As is held above, in case there was an error in diagnosis, it would be a civil liability. But in the present case:

(i) the patient was directed to be admitted in the absence of the doctors;

(ii) the medicines were administered on telephonic instructions without even enquiring about the symptoms or nature of the pain suffered by the patient;

(iii) there was no resident medical officer;

(iv) no alternative arrangement was made;

(v) In fact, Dr. Karmarkar was also called by the staff when the health of the patient started deteriorating. The applicants had not even bothered to ask Dr. Karmarkar about the treatment given by him or the condition of the patient.

(vi) All these when the complainant wanted to admit his wife in another hospital.

29. The question is whether all this is a civil liability? Whether the compensation can buy a child her mother and beloved wife to a husband.

30. To add to all this, the applicants had indulged into pressure tactics through Indian Medical Association, Ratnagiri Branch by putting other vulnerable patients into peril. Initially, the report of the Civil Surgeon clearly indicated that the

applicants were responsible for the cause of death. However, subsequently, all the doctors had mellowed down in support of the applicants. There is no element of deterrence to medical fraternity. Negligence becomes actionable on account of the injury resulting from the act or omission to commit the act amounting to negligence i.e., criminal negligence. The initially essential components are breached out and the resultant damage.

31. The medical professionals have been put on pedestal near mortals especially destitute patient and their families suffer because of lack of knowledge and over imposition of technologies in law.

32. The time has come for weeding out careless and negligent persons in the medical profession. Segregation of reckless and negligent doctor in the profession will go a great way in restoring the honor and prestige of large number of doctors and hospital who are devoted to the profession and scrupulously follow the ethics and principles of the noble profession. Recklessness and negligence are tricky road to travel. There is gross negligence from the point of standard of care. **Prescription without diagnosis would amount to culpable negligence. This issue is decided in the affirmative.**

33. According to the learned Senior Counsel, the offence would at the most be under Section 304A of the Indian Penal Code. The learned Counsel has drawn attention of this Court to the observations of the Hon'ble Apex Court in the case of **Jacob Mathew v/s. State of Punjab and anr. reported in (2005) 6 SCC 1**, wherein it is held that:

"*Indiscriminate prosecution of medical professionals for criminal negligence is counter-productive and does no service or good to the society*."

"*A medical practitioner faced with an emergency ordinarily tries his best to redeem the patient out of his suffering. He does not gain anything by acting with negligence or by omitting to do an act. Obviously, therefore, it will be for the complainant to clearly make out a case of negligence before a medical practitioner is charged with or proceeded against criminally*."

"*A doctor who administers a medicine known to or used in a particular branch of medical profession impliedly declares that he has knowledge of that branch of science and if he does not, in fact, possess that knowledge, he is prima facie acting with rashness or negligence*."

In the aforesaid Judgment, the Hon'ble Apex Court has also held as follows:

"*To prosecute a medical professional for negligence under criminal law it must be shown that the accused did something or failed to do something which in the given facts and circumstances no medical professional in his ordinary senses and prudence would have done or failed to do. The hazard taken by the accused doctor should be of such a nature that the injury which resulted was most likely imminent*."

The Hon'ble Apex Court has discussed the observations of Sir Lawrence Jenkins in **Emperor v. Omkar Rampratap (1902) 4 Bom. LR 679** as follows:

"*To impose criminal liability under Section 304-A, Indian Penal Code, it is necessary that the death should have been the direct result of a rash and negligent act of the accused, and that act must be the proximate and efficient cause without the intervention of another's negligence. It must be the causa causans; it is not enough that it may have been the causa sine qua non*."

It is also observed by the Hon'ble Apex Court that:

"*An error of judgment on the part of a professional is not negligence per se. Higher the acuteness in emergency and higher the complication, more are the chances of error of judgment*."

It is pertinent to note that present case is not a case of error of judgment but of pure neglect and taking the patient for granted.

34. The next Judgment relied by the learned Senior Counsel is in the case of **P.B. Desasi v/s. State of Maharashtra reported in (2013) 15 SCC 481**, wherein the Hon'ble Apex Court has observed that:

"*An omission is sometimes called a negative act, but this seems dangerous practice, for it too easily permits an omission to be substituted for an act without requiring the special requirement for omission liability such as legal duty and the physical capacity to perform the act*."

In that case, the Court was considering the purport of section 338 of the Indian Penal Code. The Hon'ble Apex Court had held that:

"*The solution to the issue of punishing what is described loosely, and possibly inaccurately, as negligence is to make a clear distinction between negligence and recklessness and to reserve criminal punishment for the latter. If the conduct in question involves elements of recklessness, then it is punishable and should not be described as merely negligent*."

35. In the present case, the gynecologist should have been aware that a person who was discharged after cesarean operation had to be admitted within 24 hours. There was no reason for not referring the patient to another doctor. This was the commercial aspect of looking at the profession and retaining the patient in the absence of the doctor and then claiming that it is an error of judgment and that she has died due to pulmonary embolism for which the doctors cannot be held responsible. Firstly, the doctors had not thoroughly examined the patient at the time of discharge or else some diagnosis could have been made at that stage itself.

36. The learned Senior Counsel has also placed reliance on the Judgment of the Apex Court in the case of **Mahadev Prasad Kaushik v/s. State of U.P. reported in (2009) ALL MR (Cri.) 1864 (SC).** The facts of the case are at variance. In that case, the complainant had alleged that the treatment was given by the appellant who administered three injections to Buddha Ram and within half an hour, Buddha Ram died. That could be a case of an error of judgment. In case of **Mahadev Prasad Kaushik(cited supra)**, it was an appeal filed against the conviction recorded by the High Court. There was material evidence before the Court. In the present case, the material shows that the applicants were influential so much that the doctors had gone on strike and closed the private hospital for a week.

37. The other cases relied upon by the learned Senior Counsel are in respect of the complaints decided by the Consumer Protection Forum.

38. In the case of **A.S.V. Narayanan Rao v/s. Ratnamala and anr. Reported in (2013) 10 SCC 741,** the Hon'ble Apex Court has placed reliance upon the Judgment of the Apex Court in the case of **Jacob Mathew (cited supra)** and has held that for an act to amount to criminal negligence, the degree of negligence should be much higher i.e., gross or of a very high degree. The word "gross" has not been used in Section 304-A of the Indian Penal Code, yet it is settled that in criminal law negligence or recklessness, to be so held, must be of such a high degree as to be "gross".

39. It is in the aforesaid observations that this Court is not inclined to exercise the discretion under Section 438 of the Code of Criminal Procedure, 1973 in favor of the applicants.

40. These observations are restricted to the application under Section 438 of the Code of Criminal Procedure, 1973 and the same shall not be taken into consideration in any other proceedings.

41. The application being sans merits stands rejected and disposed of accordingly.

42. However, operation of this order is stayed till 2/8/2018.

[SMT. SADHANA S. JADHAV, J]

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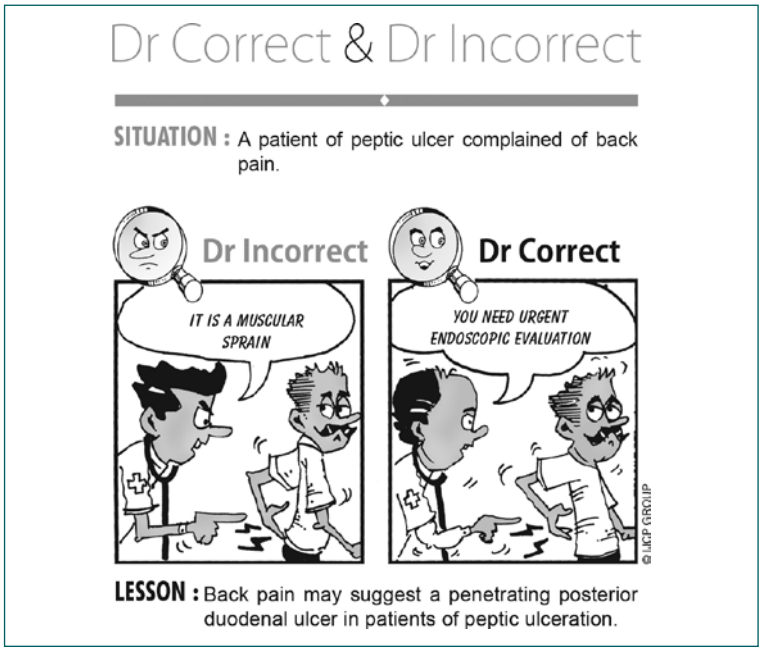

India Live 2018

WHAT ARE THE TECHNIQUES THAT CAN BE USED TO WIRE DIFFICULT SIDE BRANCHES?

Dr Praveen Chandra, Gurugram

Successful wiring of a side branch or bifurcation is a significant step in some complex percutaneous coronary interventions (PCIs). Some anatomical subsets can be particularly challenging. Branch vessels arising at a retroflexed steep angle from the main vessel and those that arise from a stented segment pose major challenges. Some techniques that may help access difficult side branches include reverse hook, balloon backstop, twin-pass catheter and deflecting tip guidewire.

HOW FAR ARE WE IN THE FIELD OF BIODEGRADABLE VASCULAR SCAFFOLDS?

Dr Sanjeeb Roy, Jaipur

Bioresorbable vascular scaffolds (BVS) are a promising new therapeutic option in Interventional Cardiology. Outcomes from the GHOST-EU registry showed acceptable rates of target lesion failure (TLF) at 6 months with BVS. Technical success was achieved in 99.7% of cases. There was TLF rate of 4.4% at 6 months, and the incidence of definite/probable scaffold thrombosis was 1.5% at 30 days and 2.1% at 6 months. This was higher than that observed with second-generation drug-eluting stent (DES). Strut size is an important factor that affects healing response after metal stent implantation. Data suggest that thick metal struts have delayed re-endothelialization and elicit more neointimal proliferation than a thinner strut design.

Currently, bioabsorbable scaffolds require a large strut thickness to provide sufficient radial support and prevent acute and late elastic recoil. BVS have been designed to provide mechanical support and drug delivery similar to the DES, followed by complete resorption over several years. Trials have demonstrated clinical noninferiority of the BVS compared with contemporary DES; however, outcomes such as higher rates of scaffold thrombosis are concerning. Physicians should follow a conservative approach with careful patient and lesion selection and follow meticulous implantation techniques that involve frequent intracoronary imaging for sizing, and pre- and post-dilation.

IN CONVERSATION WITH DR DAVINDER SINGH CHADHA

Dr Davinder Singh Chadha, Bangalore

Which factors should be considered while selecting a stent?

The factors to be considered while selecting an appropriate stent include duration of dual antiplatelet therapy, size matrix, stent deliverability, longitudinal stent deformation and type of polymer used for the delivery of the drug while selecting a DES.

Which bifurcation lesions are most appropriate for a two-stent strategy?

A two-stent strategy may be needed in true bifurcation lesion, where both main vessel and side branch have more than 50% stenosis with large plaque burden (Medina: 1-1-1, 1-0-1 and 0-1-1); large side branch (>2.5 mm diameter); important side branch that you do not want to lose; diffusely diseased side branch (>20 mm diseased segment); bifurcation with a take-off angle that would be difficult to rewire.

DIFFUSE DISEASE, TANDEM LESIONS (FFR/iFR)

Dr Prashant Jagtap, Nagpur

Complex coronary disease requires differentiation between diffuse and focal disease. Instantaneous wave free ratio (iFR) and iFR co-registration appears to be particularly useful for serial or diffuse disease assessment. Hyperemic flow (fractional flow reserve [FFR]): The proximal lesion limits the maximum blood flow into the distal lesion, while the distal lesion limits the maximum blood flow across the proximal lesion. When one lesion is removed, the FFR value of the remaining lesion is changed. Baseline flow (iFR): The microvasculature maintains the baseline distal flow. When a lesion is removed, flow does not change substantially. The iFR value of remaining lesion remains constant. Currently, there is insufficient data regarding long-term prognosis in iFR-guided revascularization.

WHICH PROCEDURE IS BETTER FOR UNPROTECTED LMCA DISEASE - STENTING OR BYPASS SURGERY?

Dr Subhash Chandra, New Delhi

Left main coronary artery (LMCA) stenosis refers to the reduction in the luminal diameter of LMCA by more

than 50%. LMCA stenosis is associated with higher mortality, and it is a strong independent predictor of mortality and morbidity in patients with coronary artery disease (CAD). With an average diameter of >3 mm, LMCA is theoretically suitable for stenting. However, the complex anatomy of LMCA may be associated with periprocedural complications and restenosis. Additionally, most LMCA lesions are at distal site presenting as bifurcation or trifurcation lesions, which is challenging for PCI. Complete revascularization by coronary artery bypass graft (CABG) is still the gold standard for treating unprotected LMCA stenosis; however, intravascular ultrasound (IVUS)-guided PCI is a reasonable alternative nowadays.

With improvements in the design in PCI devices such as DES and pharmacological treatment, increasing evidence now shows that PCI is a safe and effective revascularization strategy for patients with unprotected LMCA stenosis and multivessel CAD. SYNTAX study is the first large-scale randomized trial comparing the long-term outcomes after LMCA stenting with first-generation DES to CABG in patients with unprotected LMCA stenosis. No significant difference was found between PCI and CABG in mortality and major adverse cardiac and cerebrovascular event (MACCE) in patients with unprotected LMCA stenosis in low/intermediate SYNTAX score (<33). Target lesion revascularization (TLR) rate was higher in PCI group. However, CABG provided better long-term outcome including survival rate in patients with high SYNTAX score (≥33). Data suggest that stenting at LMCA can secure the upstream coronary artery flow and provide adequate perfusion to the large territory of left coronary artery system. Results from PRECOMBAT and EXCEL are also consistent with the results of LMCA stenosis cohort in SYNTAX study. The EXCEL trial revealed that among patients with LMCA disease and low or intermediate SYNTAX scores by site assessment, PCI with everolimus-eluting stents was noninferior to CABG in terms of the rate of the composite endpoint of death, stroke or myocardial infarction (MI) at 3 years.

PCI seems promising! Current guidelines also recommend PCI as an alternative to surgical revascularization in certain left main CAD groups.

HEMODYNAMIC SUPPORT DURING PCI - ECMO/LVAD

Dr Venkat Goyal, Mumbai

Issues in the implantation of durable ventricular assist devices (VADs) - ***Proper patient selection:*** recognizing the patient who is too sick, with end-organ damage; recognizing the patient who is too debilitated or malnourished; recognizing the patient who needs biventricular support. ***Timing of surgery:*** especially important in the elderly 'destination' patient.

Which mechanical support should we use as a first-line option: The one you have experience with; start simple and think about the appropriate setting for the patient; before you transfer the patient, get all the details of medical and social history; ask for help. Intra-aortic balloon pump (IABP) should be used when the hemodynamic reserve is mildly decreased. Impella or Tandem Heart should be used when the hemodynamic reserve is low.

A DIALOGUE WITH DR RONY MATHEW

Dr Rony Mathew, Kerala

What is the burden of cardiovascular diseases in India?

Cardiovascular diseases (CVDs) have now become the leading cause of mortality in India. A quarter of all mortality is attributable to CVD. The Global Burden of Disease study estimate of age-standardized CVD death rate of 272 per 1,00,000 population in India is higher than the global average of 235 per 1,00,000 population.

The disease is also changing its trend with the changing times and has become more complex. It is therefore sometimes challenging for the physicians to take a decision on the treatment approach.

How do technologies help in CVD?

Interventional technologies for the heart have brought revolutionary changes in the way diseases are diagnosed and treated. In clinical practice, the decision to proceed with stenting/surgery and check the correct stent placement becomes particularly challenging when it comes to multivessel CAD, calcified blockages, long blockages, dissection and with blockages restricting 30-70% of the blood flow.

New technologies like optical coherence tomography (OCT) help in planning of interventional strategies and optimization before and after the stent deployment, particularly with complex diseases.

This new age imaging tool helps determine and improve patient outcomes by reducing the geographic misses, stent mal-apposition, under-expansion, etc., which may result in better long-term clinical results.

TETE-A-TETE WITH DR BALBIR SINGH

Dr Balbir Singh, Gurugram

How does OCT help in interventional cardiology?

OCT, with its high resolution, can provide complete information about the vessel that cannot be obtained with other modalities. OCT provides high quality detailed 3D views of the inside of coronary arteries to help assess the anatomical characteristics of the vessel and blockage. OCT produces clear, easy-to-understand views of vessel anatomy and composition of the blockage that can be helpful in determining and optimizing treatment strategy. It uses near-infrared light to provide almost histological/microscopic/fine tissue resolution of the coronary artery. These images can be acquired in less than 3 seconds and the overall procedure can be done in a few minutes. As a result, OCT can overcome many limitations of angiography as it offers 3D images which are 20x higher resolution than angiography and 10x higher resolution than the currently available ultrasound-based imaging tools. Physicians can navigate through the artery and visualize the blockage and stent to the minutest of detail to ensure optimal stent deployment.

What is the significance of OCT for the patient?

OCT is an imaging procedure that provides significant benefits in the assessment of CAD and stent implantation and follow-up. It is being used to validate stent placement, vessel injury and proper deployment of stent. OCT provides useful real-time information beyond that obtained by angiography alone, and impacts directly on physician decision-making. It improves clinical outcomes and ultimately the patient's well-being. Every patient has a different clinical need and OCT helps customize the treatment strategy basis the individualistic requirements. It saves the patients from undergoing incomplete/unnecessary procedures/surgeries and its associated risks. Thus, it also provides the patients with economic benefits.

WHAT IS THE CURRENT STATUS OF OCT, FOLLOWING THE ILUMIEN III FINDINGS?

Dr Robert Van Geuns, Netherlands

The comparison of OCT, IVUS and angiography has yielded mixed results in terms of choosing the best imaging modality to guide stent placement in PCI. OCT has been found noninferior to IVUS. Yet some questions remain to be answered before physicians can completely adopt newer, high-resolution intravascular imaging. The superior resolution of OCT is able to detect malapposition and major dissection that are missed by IVUS and thus could potentially impact clinical outcomes. In ILUMIEN III, 450 patients undergoing PCI were randomized to OCT, IVUS or angiographic guidance. For the primary endpoint of final median minimum stent area, OCT guidance was noninferior to IVUS, but not superior. Additionally, it was not superior to angiography-guided stent placement either. Minimum and mean stent expansion were significantly greater with OCT-guided PCI than angiography-guided PCI, but similar to IVUS-guided PCI. Procedural success was also higher with OCT than with angiography. OCT could be of most benefit when the true patient and true lesion complexity that can benefit from this technology are identified.

IS DURABLE POLYMER DES BETTER THAN BIODEGRADABLE POLYMER DES?

Dr Chuck Simonton, USA

The polymer on the surface of the stent plays an important role as it comes in direct contact with the blood stream and artery wall when the stent is implanted. Recent data shows that the fluoro-copolymer on DES has documented anti-inflammatory and antithrombotic properties and has demonstrated fast healing response post stent implantation. Pre-clinical data with fluorinated copolymer has shown less thrombus than bare metal stents (BMS) surface. Biodegradable polymer DES (BP-DES) converts to BMS post drug-elution but, in clinical and pre-clinical trials, durable polymer DES have proven to be safer than BMS. BP-DES has still not been able to demonstrate superiority of safety and efficacy vs. current generation durable polymer DES in randomized clinical trials.

WHICH OF THE TWO DES - DURABLE POLYMER OR BIODEGRADABLE POLYMER - ARE PREFERRED IN PATIENTS WITH COMORBIDITIES AND COMPLEX LESIONS?

Dr Krishna Sudhir, USA

Whereas durable polymer DES have been studied in thousands of patients with comorbidities like diabetes, high bleeding risk, etc., along with complex lesions like chronic total occlusion (CTO), left main, etc., BP-DES has not been able to demonstrate superiority to durable polymer DES. BP-DES is also yet to prove superiority of safety and efficacy in complex lesions/patients. BP-DES technology is yet to show conclusive clinical evidence in terms of its safety and efficacy benefits to patients in comparison to existing durable polymer technology.

WHAT IS THE SIGNIFICANCE OF OCT IN BIFURCATION STENTING?

Dr Junya Shite, Japan

Intravascular OCT provides high-resolution images of the pathoanatomy, thrombus, wires and stent positions during PCI for bifurcation lesions. The information provided by OCT may prove crucial in improving PCI results and clinical outcomes after complex bifurcation treatment. Increasing amount of evidence confirms the feasibility of OCT in bifurcations, and specific steps where OCT may be advantageous in guiding bifurcation PCI have been identified. For instance, immediate automated online detection of the lumen area after pullback helps in rapid assessment of the vessel morphology and minimum lumen area. OCT with online 3D reconstruction helps obtain a 3D visualization of the lesion, such as stent cell figure, stent link position and Guidewire recross point, and plan an appropriate strategy accordingly. 3D images may provide a unique tool during complex intervention in bifurcation, and improve stenting results.

LEFT MAIN ISR

Prof. Dr Fazila-Tun-Nesa Malik, Bangladesh

To prevent left main in-stent restenosis (ISR): Proper sizing of stent is mandatory; proper imaging and physiological assessment can help decide whether PCI is required or not, and also helps optimize outcome; in case of ostial left main, overhang of stent should be avoided; in case of double stent strategy, final kissing is mandatory; POT and Re-POT should be done when required; proper control of diabetes and hypertension is essential; long-term dual antiplatelet therapy (DAPT) and high intensity statin should be considered in complex cases. **In case of left main ISR:** Proper assessment of situation by imaging is mandatory; in case of isolated ISR, drug-eluting balloons may be an option; in case of re-do PCI, proper preparation of bed is essential (NC balloon, cutting balloon, scoring balloon); newer generation DES should be chosen with proper sizing, good radial strength, radio-opacity, side branch accessibility and deliverability.

TISSUE PROLAPSE - INSIGHT FROM OCT

Dr DS Chadha, Bangalore

Tissue prolapse (TP) is a commonly noted finding on OCT in patients undergoing angioplasty. Thin-cap fibroatheroma (TCFA) is the most important predisposing factor for the occurrence of TP. The pattern of TP and plaque volume determine its clinical significance. Recent studies have shown that the outcomes of TP may not be benign, as was reported in earlier studies. Rarity of the clinical events and common occurrence of this entity will make it difficult to design an adequately powered study to determine its significance.

STEMI BEYOND 48 HOURS

Dr Rajesh Vijayvergia, Chandigarh

Benefits of early reperfusion therapy - **<12 hrs:** Increased myocardial salvage, improved LV function and better survival; **12-24 hrs:** Mortality and combined endpoint of death, MI, stroke is significantly less with PCI than conservative approach; **12-48 hrs:** PCI vs. conservative approach - infarct size significantly reduced with PCI. **PCI after 48 hrs** (OAT trial) - Rates of primary endpoint (death, reinfarction and heart failure), fatal and nonfatal MI, death and Class IV heart failure (HF) were similar in PCI and medicine therapy groups. The 7-year rate of PCI of infarct-related artery (IRA) during follow-up was 11.1% vs. 14.7% in PCI vs. medical therapy arm. **Recommendation for delayed PCI -** Cardiogenic shock or acute severe HF; intermediate- or high-risk findings on predischarge noninvasive ischemia testing; spontaneous or easily provoked myocardial ischemia; patients with evidence of failed reperfusion or reocclusion after fibrinolytic therapy (as soon as possible); stable patients after successful fibrinolysis, ideally between 3 and 24 hrs; stable patients >24 hrs after successful fibrinolysis; delayed PCI of a totally occluded infarct artery >24 hrs after STEMI in stable patients.

CURRENT STATUS OF LEFT MAIN STENTING: POST EXCEL AND NOBLE

Dr Christoph K Naber, Germany

CABG remains the standard of care in anatomically complex left main disease with high SYNTAX scores. PCI is an excellent alternative in patients with low-intermediate SYNTAX scores, where the risk for surgery is high, or if patients have shorter life expectancy. PCI, as a revascularization strategy, comes with improved short-term outcomes but at the cost of increased rates of repeat revascularization. New recommendations should be patient-centered and based on early and long-term trade-offs of each procedure.

IS IT SPONTANEOUS CORONARY ARTERY DISSECTION? OCT GIVES THE ANSWER

Dr G Sengottuvelu, Chennai

With availability of sophisticated imaging such as OCT, we can identify the mechanism of acute coronary syndrome (ACS). We have shown plaque formation, rupture and calcific nodule and etiology of ACS. Spontaneous coronary artery dissection (SCAD) is an uncommon condition and is one of the important causes of ACS. Angiography is not a very good investigation to confirm the diagnosis of SCAD. Angiographic differentiation includes organized thrombus, calcific nodule, etc. OCT, though has to be done carefully without extension of intramural hematoma, gives very valuable information in conforming diagnosis. It delineates the location of entry point and the extent of intramural hematoma and appropriate management can be planned.

LEFT MAIN BIFURCATION STENTING AND LESSONS FROM DKCRUSH 5

Dr Viveka Kumar, New Delhi

Left main PCI should be attempted by experienced operators at high volume centers. While DK Crush is the preferred dedicated two-stent strategy for true bifurcation lesions, single stent strategy may be used in cases with insignificant left circumflex ostial disease.

FFR/iFR - OPTIMAL ACQUISITION AND INTERPRETATION

Dr Justin Davies, London

Revascularization performed based on angiography alone is no better than medical therapy. In a large French multicenter registry, FFR guidance reduced PCIs by 6%, but changed the treatment for 45% of patients. Making good iFR/FFR measurements: Proper preparation - Calibration and equalization; Guide catheter selection - No side holes/damping; IC nitrate - 200-300 μg; Proper normalization - No damping; Adequate hyperemia - 140 μg/kg/min IV adeno; Maintenance of good quality signal - Drift check at the end. Different grades of stenosis impact on different phases of the pressure waveform. Always look at the shape of the pressure waveform.

GLOBAL AGING AND ITS IMPACT ON CVD BURDEN AND TREATMENT

Dr Ian Meredith, USA

Global proportion of young children has always outnumbered elderly; however, that is about to change. Aging inflection is driven by several factors: Improvement in public health; improved medical management of acute and chronic diseases resulting in greater longevity; falling fertility rates. By 2050, Asia will represent >60% of the global older population. Life expectancy has and will continue to increase globally. Chronic noncommunicable diseases (NCDs) are increasing and are leading causes of death. NCDs are leading causes of death in those aged >65 years. Patients aged ≥65 years are more likely to have multiple chronic conditions. 21st century global NCD health priorities and expectations include: CVD, hypertension, diabetes, obesity, cancer, dementia, depression/anxiety, degenerative/inflammatory arthritis, inflammatory bowel disease, alcohol and illicit drug use. A comprehensive research agenda is needed to address challenges relating to care of this 'high-need, high cost' population. Highest ranked research topics related to healthcare of elderly include: Health-related quality-of-life (QoL) in older adults; assessment tools (symptom burden, QoL); disability; tools to improve clinical decision making; interactions between medications, disease processes and health outcomes; implementation of novel (and scalable) models of care; role of caregivers; shared decision-making to enhance care planning; association between clusters of chronic conditions and clinical, financial and social outcomes. Leverage digital health technologies to create optimal solutions for aging populations. Simple, accessible solutions require access to a broad set of technologies. Don't accept convention. Challenge and change it.

OCT - IS IT EVIDENCE SUPPORTED?

Dr Jabir A, Cochin

In a recent systematic review and Bayesian network meta-analysis of 31 studies and 17,882 patients, PCI using either IVUS or OCT was associated with a consistent reduction in major adverse cardiac events (MACE) and CV mortality. Coronary angiography was rated as the worst strategy in rank probability analysis. **ILUMIEN I trial** - Based on pre-PCI OCT, the procedure was altered in 55% of patients by selecting different stent lengths (shorter in 25%, longer in 43%). Post-PCI OCT findings, such as malapposition, stent underexpansion and edge dissection, led to further optimization in 25%. Physician decision-making was affected by OCT imaging prior to PCI and post-PCI. **ILUMIEN III trial** - OCT-guided PCI using a specific reference segment external elastic lamina-based stent optimization strategy was safe and resulted in similar minimum stent area to that of IVUS-guided PCI. The

final median minimum stent area was 5·79 mm^2 (IQR 4.54-7.34) with OCT guidance, 5.89 mm^2 (4.67-7.80) with IVUS guidance and 5.49 mm^2 (4.39-6.59) with angiography guidance. OCT is an invaluable, proven, powerful visual tool to guide PCI. It provides excellent imaging, allowing exquisite assessment of the vessel wall and structure closest to histology in the cath lab.

LARGE THROMBUS - INTRACORONARY LYSIS

Dr Jayagopal PB, Kerala

Intracoronary thrombolysis has a role in the current era of primary PCI in certain subsets like patients with huge thrombus burden who present early; young patients who have mostly thrombus; patients with ectatic coronaries and large vessels. Tenecteplase is preferable because of ease of administration. In a series of STEMI patients with large thrombus burden treated successfully with low dose intracoronary thrombolysis, there was prompt and early ST resolution. There was improvement in TIMI flow and myocardial blush grade postlysis in all patients. Majority had recanalized infarct-related coronary artery thus obviating the need for stenting. It is worthwhile to do OCT in these patients.

CONQUER THE COMPLEX WITH DES - LATEST CLINICAL UPDATES

Dr Praveen Chandra, Gurugram

Complex PCI is on the rise. Expectations from an ideal stent - Good deliverability; good scaffolding; high radial strength with minimum recoil; good visibility; minimal foreshortening; side branch accessibility; appropriate metal to artery ratio; biocompatibility; optimal stent delivery system; variety of size and lengths; drug and polymer. EXCEL trial: In full 3-year data set, PCI with everolimus-eluting stent (EES) successfully met primary endpoint to show noninferiority to CABG in left main patients. EES outcomes were comparable to CABG in different patient populations, anatomies and lesion types. PCI with EES demonstrated lower rates of clinically significant depression at 1 month and 1 year. SENIOR trial: Among elderly patients (≥75 years; had stable angina, silent ischemia or an ACS; and at least one coronary artery with a stenosis of at least 70%) who have PCI, a DES and short duration of DAPT were better than BMS and a similar duration of DAPT with respect to the occurrence of all-cause mortality, MI, stroke and ischemia-driven target lesion revascularization (TLR). ABSORB trials at TCT: *Key messages* - Optimal implantation technique is associated with positive outcomes; long-term data suggests the potential benefits of a fully resorbed scaffold.

VALVE-IN-VALVE

Dr AB Gopalamurugan, Chennai

The Good: No major confusion on valve sizing; clear fluoroscopic landing zone (exceptions exist). **The Bad:** High risk of coronary occlusion in aortic tricuspid valve-in-valve (VIV); high risk of embolization/stroke; mitral and tricuspid VIV require specific work-up and expertise. **The Ugly:** Needs specific training in imaging; needs hybrid team; needs proctoring support for planning and initial experience building.

WHAT CAUSES CORONARY ARTERY ANEURYSMS AFTER DES IMPLANTATION?

Dr Upendra Kaul, New Delhi

Coronary aneurysms have been reported from 3 to 4 years following DES implantation. DES inhibit neointimal growth by eluting the drug locally, delay re-endothelialization and influence the remodeling process and lead to late incomplete stent apposition. Coronary aneurysms can develop as a result of exaggerated positive remodeling of the vessel wall. In some patients, this has been linked to bacterial arteritis or other predisposing factors such as Kawasaki disease. DES stents may also aggravate inflammation and elicit hypersensitivity reactions resulting in aneurysm formation. Mechanical factors, such as residual dissections, arterial wall injury due to oversized balloons and stents, high-pressure inflations and atherectomies, complicated procedures, contained perforations, or even vessel ruptures are all associated with early aneurysm formation following PCI.

DO YOU THINK OCT IS GOING TO CHANGE THE PRACTICE OF PCI?

Dr PC Rath, Hyderabad

OCT is changing the way we see coronary lesion pathophysiology. OCT allows for better visualization of lumen, plaque, thrombus, as well as stent apposition and dissection post-PCI. OCT can provide clinically useful and clinically actionable information about suboptimal stent deployment despite satisfactory angiographic images after PCI. It can show important residual pathology post-PCI that can change stent management strategies. OCT has distinct advantages in certain areas. With its high resolution, OCT is considered to be superior to IVUS for the assessment of the dissection, zones of incomplete stent apposition, tissue prolapse following PCI. Thrombus is poorly seen on IVUS; however, it is well visualized by OCT. OCT is very helpful in assessing stent apposition with overlapping stents.

WHAT IS THE IMPORTANCE OF OCT IN SAPHENOUS VEIN GRAFT ATHEROSCLEROSIS?

Dr Ajit Mullasari, Chennai

Left internal mammary grafts have high long-term patency rates; however, in current CABG practice a vast majority of patients also require saphenous vein grafts (SVG) as bypass conduits. SVG occlusion following surgery remains a significant limitation of CABG. OCT, but not IVUS, identifies clear features of atherosclerosis, including circumferential fibrous neointima, TCFA and adherent thrombus. High resolution imaging techniques such as OCT may provide significant insights into the causes of vein graft failure. OCT of culprit lesions of old SVGs in patients with ACS can show fibrofatty composition, relatively thin fibrous cap, plaque rupture, and thrombus, which correlate with the clinical spectrum of ACS.

The VEST study suggested that OCT is useful for characterizing luminal features of SVGs that are not clearly seen using IVUS. OCT was also helpful in identifying differences in SVGs with and without external stent support. Supported grafts were found to have a more uniform lumen than unsupported ones. This represents a significant finding since lumen irregularities are associated with suboptimal flow patterns that could lead to endothelial dysfunction and the development of significant atherosclerotic disease.

TETE-A-TETE WITH DR SANJAY MEHROTRA

Dr Sanjay Mehrotra, Bangalore

How do new vessel closure technologies help?

Vessel closure devices (VCDs) are novel devices that perform closure of opening of the artery after the angioplasty procedure. The main goal of a VCD is to provide immediate stoppage of bleeding of the artery and reduce access site complications. It reduces time for patient movement, hospital discharge and is more comfortable for the patient as compared to manual compression. Suture mediated closure (SMC) is a technique where a device delivers one or two stitches to the femoral artery that physically closes the access site after angiography/angioplasty. The SMC is a simple technique involving a single operator with no re-access restrictions and ability to confirm the hemostasis on the table.

What are the benefits of vessel closure technologies for the patients?

With the newer technologies, there is no pain of compression unlike manual pressure and patients are able to sit up in bed soon after the procedure as there are minimal leg restrictions. It results in early leg movement where patients may be able to get out of bed and be discharged sooner from the hospital. Overall, with SMC, patient can go back home faster, with less chances of complications. VCDs also allow us to do procedures which require large sheaths, for example Transcatheter aortic valve replacement or implantation (TAVRS/TAVI) and endovascular procedure completely percutaneous, where one may have to expose the artery surgically to do such procedure. There are of course some limitations which one should be aware of in using these devices and limit situations where those are likely to fail.

WHAT IS THE ROLE OF OCT IN CHRONIC TOTAL OCCLUSION?

Dr Samuel Mathew, Chennai

PCI of chronic total occlusions (CTOs) is a challenging coronary intervention, and is associated with lower success rates, increased restenosis and reocclusion compared with non-CTO procedures. Patients with CTOs are often referred for CABG surgery. Angiography provides a two-dimensional image of contrast-filled lumen, and does not allow an accurate assessment of the plaque. OCT, on the contrary, allows high resolution imaging that can improve the understanding of the vascular response after stenting of chronically occluded vessels.

The ACE-CTO study accrued angiographic and clinical outcomes from 100 patients undergoing CTO PCI with the EES. OCT was performed 8-month post stenting in 62 patients. In all, 44,450 struts in 6,047 frames were analyzed. Of these, 9.3% were malapposed and 2.8% were uncovered. Fifty-five of 62 patients (88.7%, 95% confidence interval (CI) 78.5-98.4%) had at least one malapposed stent strut and 50 patients (80.7%, 95% CI 69.2-88.6%) had at least one uncovered stent strut. There has been advancement in the use of optical coherence reflectometry in CTOs. This is an FL fiber optic guidance system to navigate through CTOs. It is able to differentiate the tissue characteristics of arterial tissue including the calcified or noncalcified plaque and atherosclerotic lesions from arterial wall.

At follow-up in patients undergoing further angiography for ISR concerns, or because of other ongoing symptoms, OCT is an extremely useful modality to determine the vessel healing response to stent implantation.

IJCP SUTRA 217: People who travel to areas with high risk of leptospirosis, should avoid swimming in fresh water ponds, drink only sealed water, clean and cover any open wounds.

News and Views

Most Black Adults have High Blood Pressure Before Age 55

Approximately 75% of black men and women are likely to develop high blood pressure (BP) by the age of 55, compared to 55% of white men and 40% of white women in the same age range, according to new research published July 11, 2018 in *Journal of the American Heart Association*. Higher body weight was associated with an increased risk for high BP, regardless of race or gender, and those who adhered to the Dietary Approaches to Stop Hypertension (DASH)-style diet, both blacks and whites, were at lower risk for hypertension.

US FDA Approves Emergency Use of Freeze-dried Plasma for the Military

The US Food and Drug Administration (FDA) has granted authorization for emergency use of pathogen-reduced leukocyte-depleted freeze-dried plasma to help treat military members in the battlefield.

Higher BP may be Linked to Brain Disease and Alzheimer's

Older people who have higher BP may have more signs of brain disease, specifically brain lesions, according to a study published in the July 11, 2018, online issue of the journal *Neurology*. An association between higher BP and more markers of Alzheimer's disease, tangles in the brain.

New Zealand Scientists Preform the First-ever 3D Color X-ray on a Human

Scientists from New Zealand have performed the first-ever 3-D color X-ray on a human, using a color medical scanner using the particle-based Medipix3 technology provided by the CERN physics lab. Medipix works like a camera detecting and counting individual subatomic particles as they collide with pixels while its shutter is open. The small pixels and accurate energy resolution allow high-resolution and high-contrast pictures that no other imaging tool can achieve, according to Phil Butler, who developed this technique. According to the CERN, the images very clearly show the difference between bone, muscle and cartilage, but also the position and size of cancerous tumors, for example. The colors represent different energy levels of the X-ray photons as recorded by the detector and so identify different components of body parts such as fat, water, calcium and disease markers … (*ET Healthworld/CERN*)

Risk of Transmission of HIV Through Breastmilk is Low in Women on Effective ART

The risk of human immunodeficiency virus (HIV) transmission through breastfeeding by mothers on effective antiretroviral treatment (ART) is not non-existent, but is very low in high-income settings. The study is reported June 27, 2018 in *The Lancet HIV* online.

Athletes More Prone to Depression and Anxiety Post-concussion

Athletes who have attention-deficit hyperactivity disorder (ADHD) may be at greater risk for experiencing persistent anxiety and depression after a concussion versus people who do not have ADHD, according to findings of a study presented at the American Academy of Neurology's Sports Concussion Conference in Indianapolis.

A New CDC Website on ME/CFS for Healthcare Providers

The Centers for Disease Control and Prevention (CDC) has released an updated website "https://www.cdc.gov/me-cfs/index.html" about myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) specifically for healthcare providers. The website includes information on diagnosis, clinical course and management of people who have been diagnosed with ME/CFS.

FDA Approves Tecovirimat as Treatment of Smallpox

The US FDA has approved tecovirimat, the first drug with an indication for treatment of smallpox. Although, small pox was declared as eradicated in 1980 by the World Health Organization (WHO), there have been long-standing concerns that smallpox could be used as a bioweapon.

Direct Oral Anticoagulants Linked with Higher Bleeding Risk in CKD Patients

Compared with warfarin use, direct oral anticoagulant use was linked with a 23% higher risk of bleeding in patients with chronic kidney disease (CKD), according to the results of a study published July 12, 2018 in the

Clinical Journal of the American Society of Nephrology (CJASN). But, no difference was observed between the two treatment groups in terms of benefits from prevention of ischemic stroke.

Asian Indians Increase their Risk of Developing Diabetes by Adopting Poor Lifestyle Habits

Adopting American habits by Asian Indians who had been living in the United States was found to be bad for cardiometabolic health, suggests a study presented June 22, 2018 at the recent American Diabetes Association 2018 Scientific Sessions in Orlando, Florida. The study subjects with an unhealthy diet had poor A1c levels and those who led a sedentary lifestyle had poor high-density lipoprotein cholesterol (HDL-C) levels.

Once-weekly Ciprofloxacin Comparable to Daily Norfloxacin for Preventing Spontaneous Bacterial Peritonitis

Once-weekly ciprofloxacin was as effective as norfloxacin 400 mg daily for the prevention of spontaneous bacterial peritonitis in patients with cirrhosis and ascites suggesting its benefits as a more convenient and cost-effective treatment option. Systolic BP (SBP) developed in 4 patients (4/55) and in 3 patients (3/57) in each group, respectively.

Portugal on Fast Track to Achieve HIV Targets Ahead of 2020 Deadline

The Portuguese Minister of Health has announced that Portugal has achieved 2 of the 3 '90-90-90' HIV targets set by the Joint United Nations Programme on HIV/AIDS (UNAIDS) for 2020. Portuguese Minister of Health Dr Adalberto Campos Fernandes announced on 5 July 2018 that Portugal has achieved 2 of the 3 HIV targets set the UNAIDS, known as the 90-90-90 targets. This puts the country on track to reach all 3 targets ahead of the 2020 deadline. This announcement is based on data from 2016:

- 91.7% of people living with HIV are diagnosed
- 86.8% of people diagnosed are on treatment
- 90.3% of people on treatment achieve HIV viral load suppression.

"Portugal has become one of the pioneer countries in the WHO European Region in moving towards ending AIDS by 2030," says Dr Masoud Dara, Coordinator for Communicable Diseases at WHO/Europe. "Its success is built on a thorough implementation of evidence-based measures, high-level commitment and a true whole-of-government and whole-of-society approach in line with the Sustainable Development Goals." (*Source: WHO Europe, July 11, 2018*).

Early Introduction of Solids Improves Sleep Quality in Infants

A secondary analysis of the Enquiring About Tolerance study shows that the early introduction of solids into the diet at 5 months was associated with longer sleep duration, less frequent waking at night in infants. Also, parents of these babies also reported fewer serious sleep problems. The study is published online July 9, 2018 in *JAMA Pediatrics*.

FDA Warns of Imposters Sending Consumers Fake Warning Letters

The US FDA is warning consumers about criminals forging FDA warning letters to target individuals who tried to purchase medicines online or over the phone. Based on the agency's experience with criminals posing as FDA employees, the FDA is concerned that these fake warning letters are linked to an international extortion scam. The FDA generally does not issue warning letters to individuals who purchase medicines online.

Hemodynamic Valve Deterioration of Surgically Implanted Aortic Valve Increases Mortality Risk

Hemodynamic valve deterioration (HVD) of surgically implanted aortic bioprostheses on Doppler echocardiography is independently associated with a marked increase in the risk of valve reintervention or mortality, according to a study published online July 9, 2018 in the *Journal of the American College of Cardiology*. Leaflet calcification, insulin resistance and dysmetabolic profile were predictors of HVD.

Enzalutamide FDA-approved for Nonmetastatic Prostate Cancer

The US FDA has approved enzalutamide for the treatment of men with castration-resistant prostate cancer.

Down Syndrome Patients may have Corneal Features Similar to Keratoconus

In a multicenter observational study published online June 21, 2018 in *JAMA Ophthalmology*, around 71% of patients with Down syndrome showed characteristics compatible with keratoconus. They were found to have steeper and thinner corneas and more corneal aberrations than those without genetic alterations and normal corneas.

17 Picked Nipah Virus from 1st Victim: Kerala Govt. Report

Thiruvananthapuram, July 15 (PTI): A detailed study by the Kerala government in the recent outbreak of Nipah virus has suggested that 17 of the 19 infected people might have contracted the deadly virus from the first victim, a 26-year-old Mohammed Sabith, who died on May 5. He was among the 17 people who lost their lives after they contracted the virus. Two people had recovered.

As per available records, it has been found that Sabith contracted the Nipah virus from fruit bats and 17 others—including three from his family i.e., father, younger brother and a paternal aunt - got infected from him, government sources said.

Besides, the virus from him is also suspected to have infected four other people at the Peramabra Taluk Hospital, Kohzikode, where he was first brought, the sources in the state surveillance department of the Kerala Health Services said, adding that 10 others in the Kozhikode Medical College Hospital, where he was taken for a CT scan in the radiology department, also picked the virus from him.

One patient was infected by another man at the Perambra Hospital, they said. It is suspected that Sabith, an electrician, had contracted the virus from fruit bats, however, it is not clear the circumstances under which he got infected. Sabith had returned from the gulf 8 months before he died.

Sabith first took treatment as an 'outpatient' at the Perambra Hospital for high fever and body pain on May 2. On May 3, he was admitted at the hospital, and it is suspected that four people on night duty including Sister Lini Puthussery, who attended to him, picked the virus from him. As his condition worsened on May 4, Sabith was shifted to the Medical College Hospital for a CT scan, where he died on May 5. Ten people got infected at the medical college on the single day he was there, the sources said.

Though Sabith's blood samples were not tested for Nipah, as per records, it has been concluded that he had contracted Nipah virus, the sources said. His younger brother was admitted to the hospital with similar symptoms and tests revealed that he was Nipah positive. He died shortly after, followed by their 60-year-old father and a paternal aunt who had come to help them. It was suspected that the brothers might have contracted the virus when they got into a bat-infested well in their newly bought property. However, the bats in the well were found to be insect-eating ones, the sources said.

As a precautionary measure, a contact list of nearly 3,000 people with whom the infected persons had been in touch was prepared and they were put under quarantine. Nipah test was also conducted on them, the sources said.

The exhaustive report on the Nipah outbreak has been sent to the central surveillance department, the sources said…. (*PTI*)

C. difficile Infection Rates Higher in Intermediate Levels of Hospital Occupancy

A study published online first June 27, 2018 in the *Journal of Hospital Medicine* has found an inverse association of *Clostridium difficile* infection with hospital occupancy. Higher hospital occupancy rates were not related to higher risk of acquiring hospital-acquired *C. difficile* infection. Unexpectedly, *C. difficile* infection rates were 3-folds higher for intermediate hospital occupancy.

Prevalence of Depression is Higher in Pregnant Women Today

In the Avon Longitudinal Study of Parents and Children examining the prevalence of prenatal depression among two generations of pregnant mothers, 25% of the current generation of mothers included in the study, whose pregnancies occurred between 2012 and 2016 suffered high levels of depressive symptoms versus only 17% in the generation of their mothers in the study, whose pregnancies occurred between 1990 and 1992. These findings are published July 13, 2018 in *JAMA Network Open*.

Healthy Diet Associated with Fewer Asthma Symptoms and Better Asthma Control

According to a study published online in the *European Respiratory Journal*, eating a healthy diet rich in vegetables, fruits and whole grains reduced asthma symptoms by 30% in men and 20% in women, compared to a diet high in red meat, salt and sugar.

Exposure to Environmental Tobacco Smoke Increases Risk of Habitual Snoring in Children

Exposure to environmental tobacco smoke, in particularly prenatal tobacco smoke exposure and maternal smoking, is associated with an increased risk of habitual snoring, suggests a meta-analysis of 24 studies involving more than 80,000 children published online June 15 in the *Journal of Epidemiology & Community Health*.

Classic MS is Preceded by a Prodrome, says Study

A study published in *Multiple Sclerosis Journal* says that multiple sclerosis (MS) can be preceded by a prodrome comprising of symptoms like blurred vision or numbness or weakness in the limbs, pain or sleep problems which are not the classic manifestations of the disease. They are therefore more likely to consult a neurologist or a psychiatrist for these symptoms.

WMA Condemns Complicity of Doctors in Iranian Executions

The complicity of state-affiliated doctors in Iran in facilitating the execution of young prisoners in the country has been condemned by the World Medical Association (WMA).

This follows the execution last month of a 19-year-old Abolfazl Chezani Sharahi who was sentenced to death in 2014. The WMA says his sentence was issued based on an official medical opinion by the Legal Medicine Organization in Iran, stating that he was mentally "mature" at the age of 14 when the crime of which he was convicted took place.

In a letter jointly addressed to the Office of the Supreme Leader, Ayatollah Sayed 'Ali Khamenei, to President Hassan Rouhani and to the Head of the Judiciary Ayatollah Sadegh Larijani, the WMA President Dr Yoshitake Yokokura and WMA Chair Dr Ardis Hoven say this involvement of physicians is in direct violation of international law and their duties as physicians, and is both unethical and illegal.

The WMA leaders write: "Further, physicians have a clear duty to avoid any involvement in torture and other cruel, inhuman or degrading punishment, including the death penalty. This is specified in the World Medical Association's policies and the International Code of Medical Ethics. Doctors who provide "maturity" assessments that are then used by courts to issue death sentences, as do physicians affiliated with the Legal Medicine Organization, are facilitating the execution of individuals."

In their letter, the WMA leaders say that according to Amnesty International, Abolfazl Chezani Sharahi was the fourth individual since the beginning of 2018 to be executed after being convicted of crime committed when under the age of 18 and that there are at least 85 other juvenile offenders who currently remain on death row based on medical maturity assessments.

"Iran has ratified the Convention on the Rights of the Child, which absolutely prohibits the use of the death penalty against people who were below the age of 18 at the time of the crime they are convicted of committing. We urge Iran's authorities to amend the Islamic Penal Code so as to comply with international human rights laws by abolishing the use of the death penalty for crimes committed by people below the age of 18 in all circumstances." "Further, physicians have a clear duty to avoid any involvement in torture and other cruel, inhuman or degrading punishment, including the death penalty."

The letter concludes: "The WMA calls for Iranian authorities to acknowledge a physician's duty to do no harm and to guarantee that physicians are complying with the fundamental principles of medical ethics by prohibiting physician involvement in sentencing individuals to the death penalty or in the preparation, facilitation or participation in executions."

In a further letter to Dr Iradj Fazel, President of the Iranian Medical Council, the WMA calls on the Council to publicly acknowledge a physician's duty to do no harm and to condemn firmly the medical maturity assessments provided by the Legal Medicine Organization.

"The WMA urges the Iranian Medical Council to speak out in support of the fundamental principles of medical ethics, and to investigate and sanction any breach of these principles by association members." (*WMA, July 16, 2018*)

A Positive Fecal Occult Blood Test Associated with Increased Risk of All-cause Mortality

A study published online in the journal *Gut* suggests that fecal hemoglobin is not just associated with death from colorectal cancer, it is also associated with greater all-cause mortality. A positive fecal occult blood test was also associated with a 58% increased risk of death from all causes other than bowel cancer.

Mobile Apps may Overdiagnose Mental Health Conditions

Mobile apps that offer advice on managing mental health may overdiagnose mental health conditions by "medicalizing" normal ups and downs of life, suggests a study published in the July/August 2018 issue of the *Annals of Family Medicine*.

Childhood Infections may Adversely Affect Long-term School Performance

Severe infections leading to hospitalizations during childhood are associated with lower school achievement

in adolescence, as per a study published in the July 2018 issue of *The Pediatric Infectious Disease Journal*. Analysis of data of 598,553 children born in Denmark between 1987 and 1997 showed that children with five or more infections requiring hospitalization had a 38% reduction in the odds of completing ninth grade.

Periconception Glycemic Control in Women with Type 1 Diabetes Increases Risk of Birth Defects

Among live-born infants of mothers with type 1 diabetes, increasingly worse glycemic control in the 3 months before or after estimated conception was associated with a progressively increased risk of major cardiac defects, says a study published July 5, 2018 in the *BMJ*.

US FDA Recalls Several Medicines Containing Valsartan Following Detection of an Impurity

The US FDA is alerting healthcare professionals and patients of a voluntary recall of several drug products containing the active ingredient valsartan, used to treat high BP and heart failure. This recall is due to an impurity, N-nitrosodimethylamine (NDMA), which was found in the recalled products. However, not all products containing valsartan are being recalled.

CDC is Investigating a Multistate Cyclosporiasis Outbreak in the US Linked to McDonald's Salads

CDC, the US FDA and state and local public health partners are investigating a multistate outbreak of Cyclospora infections associated with consumption of McDonald's salads. Reported cases come from 7 states: Illinois (29), Iowa (16), Minnesota (3), Missouri (7) Nebraska (2), South Dakota (2) and Wisconsin (2). The Wisconsin case-patient dined at a McDonald's in Illinois. The first illness was reported May 20, 2018 and the most recent illness was reported July 10, 2018. This investigation is ongoing, says the CDC.

CDC laboratory testing identified the strain as *Cyclospora cayetanensis*, a single-celled parasite that causes cyclosporiasis, an intestinal infection.

- Unlike other foodborne pathogens, Cyclospora is not transmitted directly from one person to another (e.g., by ill food handlers). Infection is acquired by consuming food or water contaminated with the parasite.
- The incubation period is 7 days (2 days to ≥2 weeks).
- Symptoms include diarrhea (most common), weight loss, loss of appetite, bloating, increased gas, nausea, fatigue, vomiting, fever and abdominal cramps.

(*CDC, July 13, 2018*)

Soccer Headers may be Linked to Balance Problems

Greater exposure to repetitive subconcussive head impacts is associated with vestibular dysfunction and balance impairments during walking. These findings from a study of soccer players presented at the American Academy of Neurology's Sports Concussion Conference in Indianapolis therefore suggest that soccer players who head the ball more often may be more likely to have balance problems than players who do not head the ball as often.

AAP Releases Choosing Wisely List of Appropriate Nephrology Tests for Children

As part of the Choosing Wisely campaign, the American Academy of Pediatrics (AAP) Section on Nephrology and the American Society of Pediatric Nephrology (ASPN) have jointly released a list of specific nephrology tests and procedures that are commonly ordered but not always necessary when treating children for kidney-related conditions. These recommendations include:

- Do not order routine screening urine analyses in healthy, asymptomatic pediatric patients as part of routine well child care.
- Do not initiate a work-up for hematuria or proteinuria before repeating an abnormal urine dipstick analysis.
- Avoid ordering follow-up urine cultures after treatment for an uncomplicated urinary tract infection in patients that show evidence of clinical resolution of infection.
- Do not initiate an outpatient hypertension work-up in asymptomatic pediatric patients prior to repeating the BP measurement.
- Do not place central lines or peripherally inserted central lines in pediatric patients with advanced (Stage 3-5) chronic kidney disease (CKD)/end-stage renal disease (ESRD) without consultation with pediatric nephrology due to goals to avoid adverse events, preserve long-term vascular access and avoid unnecessary and costly procedures.

Broadly Acting Antibodies Identified in Patients Who Survived the Lethal Ebola Virus Disease

Researchers have identified broadly neutralizing antibodies in the blood of patients who have survived the lethal Ebola virus disease. In animal studies, two of these antibodies provided substantial protection against disease caused by *Zaire ebolavirus*, *Bundibugyo*

ebolavirus and *Sudan ebolavirus*, the three species known to cause fatal human illness.

These antibodies bind to an essential virus protein, called glycoprotein or GP, from *Zaire*, *Bundibugyo* and *Sudan ebolavirus* species, and prevented the viruses from entering host cells.

Study Links Nitrate-cured Meats Linked to Manic Episodes

Among those with a history of psychiatric disorders, people who reported a history of eating of dried meats cured with nitrates was strongly and independently associated with current mania, a major symptom of bipolar disorder, according to a prospective cohort study published July 18, 2018 in *Molecular Psychiatry*. This association was not seen for other meat or fish products.

High Trough Levels of Infliximab Improve IBD Control

Maintaining higher trough levels of infliximab, more than 7 μg/mL provide better control of inflammation in hard-to-treat patients of inflammatory bowel disease (IBD) without increasing infection risk, according to a new research published online July 10, 2018 in the *Scandinavian Journal of Gastroenterology*. The median fecal calprotectin and median C-reactive protein (CRP) levels were lower in patients with high trough levels.

Record Number of Infants Vaccinated in 2017

A record 123 million infants were immunized globally in 2017 with at least one dose of the diphtheria-tetanus-pertussis (DTP) vaccine, according to data released by the WHO and UNICEF. The data shows that:

- Nine out of every 10 infants received at least one dose of DTP vaccine in 2017.
- An additional 4.6 million infants were vaccinated globally in 2017 with three doses of the DTP vaccine compared to 2010.
- One hundred sixty-seven countries included a second dose of measles vaccine as part of their routine vaccination schedule.
- One hundred sixty-two countries now use rubella vaccines and global coverage against rubella has increased from 35% in 2010 to 52%.
- Human papillomavirus (HPV) vaccine was introduced in 80 countries to help protect women against cervical cancer.
- Additional vaccines are being included into the immunization schedule, such as new formulations of meningitis and polio vaccines.

Despite these successes, almost 20 million infants did not receive the benefits of full immunization in 2017, as they were not vaccinated with three doses of the DTP vaccine… (*Source: UNICEF, July 16, 2018*)

Being Physically Active Reduces Risk of Heart Attack Even in Presence of Pollution

According to new research published in the *Journal of the American Heart Association*, physical activity reduced the risk of first and recurrent heart attack even in areas with moderate-to-high levels of traffic pollution. Higher levels of nitrogen dioxide (NO_2) were associated with more heart attacks, but the risk was lower among those who were physically active.

Urgent Care Clinics Prescribe the Most Antibiotics

Patients treated in urgent care clinics are far more likely than those treated in other ambulatory care settings to be prescribed antibiotics for conditions that do not require them, as per a study published July 16, 2018 in *JAMA Internal Medicine*. Around 46% of urgent care patients with an antibiotic-inappropriate respiratory diagnosis such as allergies, influenza or the common cold received an antibiotic prescription versus 24.6% of those treated in emergency room, 17.0% in medical offices and 14.4% in retail clinics.

Immunotherapy Improves Survival in Melanoma Patients with Brain Metastasis

Use of checkpoint inhibitors in melanoma patients with brain metastases was associated with a 1.4-fold increase in median overall survival and an increase in the rate of 4-year survival from 11.1% to 28.1%. These findings were published online July 12, 2018 in *Cancer Immunology Research*.

Avoid Acid-suppression for Extraesophageal Symptoms in the Absence of Typical Reflux Symptoms

As per new guideline on pediatric gastroesophageal reflux, acid-suppression therapy in patients with typical reflux symptoms should be limited to 4-8 weeks. Acid suppression should be avoided for cough, wheezing or asthma in the absence of typical reflux symptoms. In infants, a trial of hypoallergenic formula or maternal elimination for breast fed infants is recommended before use of acid suppression. The guideline is published online June 28, 2018 in *JAMA Otolaryngology-Head and Neck Surgery*.

What are the Principles of Vidur Niti?

KK AGGARWAL

The best description of the causes and treatment of insomnia comes from Vidura Niti a dialogue between Vidura and Dhritarashtra.

In the text, King Dhritarashtra said: "*O Vidura, Sanjaya has come back. He has gone away after rebuking me. Tomorrow he will deliver, in the midst of the court, Ajatashatru's message. I have not been able today to ascertain what the message is of the Kuru hero. Therefore, my body is burning, and that has produced sleeplessness. Tell us what may be good for a person that is sleepless and burning.*"

"My body is burning, and that has produced sleeplessness" is a typical description of anxiety and related sleeplessness, true even today.

Vidura said: "*Sleeplessness overtakes thief, a lustful person, him that has lost all his wealth, him that has failed to achieve success, and him also that is weak and has been attacked by a strong person.*"

He therefore described five basic reasons for insomnia and even in today's science they are true. No new cause has been added in this list of stress-induced insomnia.

The situations are:

- A thief
- A lustful person
- A person who has lost all his wealth
- A person who has failed to achieve success
- A person who is weak and has been attacked by a strong person.

Ayurveda describes sleep disorders as an aggravation of *Vata* and *Pitta dosha*. The number one cause of the same is mental tension; suppressed feelings and acute bitterness. The above five situations again hold true to this effect.

Apart in Allopathy other causes of insomnia mentioned are constipation; dyspepsia; excessive intake of tea, coffee and alcohol and environmental factors - excessive cold, heat or change of environment. They are in most of the situations the effect and not the cause of insomnia.

The treatment of insomnia involves either suppressing the emotions with drugs or root level eradication of stress with proper counseling. Bhagavad Gita, Chanakya Niti and Vidur Niti are high level counseling books of ancient era and provide texts and sutras even true today.

Bhagavad Gita was a counseling when Arjuna went in an acute anxiety state and was not being able to decide whether or not he should fight with his near ones. He said: my legs are trembling, my bows are leaving me, by body is shaking, what should I do". The principles of Gita today are incorporated as the principles of any counseling.

Chanakya gave principles of how to manage conflicts and win over others. One of his main teachings was that money earned by unfair means can only last for 8 years.

Another answer to insomnia is learning meditation as described in Patanjali Yoga Sutra or Yoga Vashistha. It is based on the principle of concentrating on the present, which shifts the inner environment from sympathetic to parasympathetic mode. Twenty minutes of meditation morning and evening provides the same biochemical benefit as gathered from 7 hours of deep sleep.

Here are some other sutras of Vidura Niti:

- Do not inhabit a country where you are not respected, cannot earn your livelihood, have no friends or cannot acquire knowledge. (1.8)
- Do not reveal what you have thought upon doing, but by wise counsel keep it secret, being determined to carry it into execution. (2.7)
- Consider again and again the following: the right time, the right friends, the right place, the right means of income, the right ways of spending and from whom you derive your power. (4.18)
- A wise man should not reveal his loss of wealth, the vexation of his mind, the misconduct of his own wife, base words spoken by others and disgrace that has befallen him. (7.1)

(Disclaimer: The views expressed in this write up are my own)

Group Editor-in-Chief, IJCP Group

INSPIRATIONAL STORY

Be Content About Your Life

Wonder if any of you ever had the feeling that life is bad, real bad…and you wish you were in another situation. Do you find that life seems to make things difficult for you, work sucks, life sucks and everything seems to go wrong?

It was not until yesterday that I totally changed my views about life; after a conversation with one of my friends.

He told me despite taking two jobs, and bringing back barely above 1 K per month, he is happy as he is. I wonder how he can be as happy as he is now, considering that he has to skimp his life with the low pay to support a pair of old-age parents, in-laws, wife, 2 daughters and the many bills of a household.

He explained that it was through one incident that he saw in India……

That happened a few years ago when he was really feeling low and was touring India after a major setback. He said that right in front of his very eyes, he saw an Indian mother chopped off her child's right hand with a chopper. The helplessness in the mother's eyes, the scream of the pain from the innocent 4 years old child haunted him until today. You may ask why did the mother do so, has the child been naughty, was the child's hand infected?

No, it was done for two simple words—to beg. The desperate mother deliberately caused the child to be handicapped so that the child can go out to the streets to beg. I cannot accept how this could happen, but it really did, just in another part of the world which I don't see.

Taken aback by the scene, he dropped a small piece of bread he was eating half-way. And almost instantly, flock of 5 or 6 children swamp towards this small piece of bread which was then covered with sand, robbing of bits from one another. The natural reaction of hunger. Stricken by the happenings, he instructed his guide to drive him to the nearest bakery. He arrived at two bakeries and bought every single loaf of bread he found in the bakeries.

The owner is dumb folded, but willing sold everything. He spent less than $100 to obtain about 400 loaves of bread (this is less than $0.25/per loaf) and spend another $100 to get daily necessities. Off he went in the truck full of bread into the streets. As he distributed the bread and necessities to the children (mostly handicapped) and a few adults, he received cheers and bows from these unfortunate. For the first time in life he wonders how people can give up their dignity for a loaf of bread, which cost less than $0.25. He began to ask himself how fortunate he is as a Singaporean. How fortunate he is to be able to have a complete body, have a job, have a family, have the chance to complain what food is nice what isn't, have the chance to be clothed, have the many things that these people in front of him are deprived of…..

Now I begin to think and feel it, too. Was my life really that bad?

Perhaps….no, it should not be bad at all….

What about you? May be the next time you think you are, think about the child who lost one hand to beg on the streets.

■■■■

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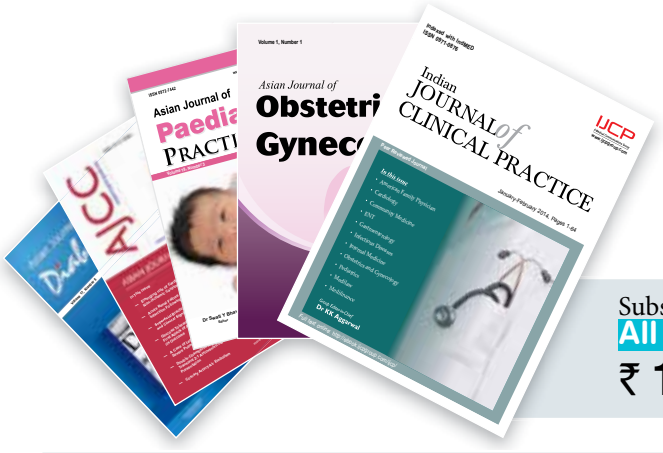

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Lighter Side of Medicine

HUMOR

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.

PRICE YOU PAY FOR BEING GOOD

Three men were waiting to go to heaven. St Peter was at the gate and said, "However good you were to your wife that is the vehicle you will get in heaven".

The first guy comes up to the gate and says, "I never, ever cheated on my wife and I love her". So St. Peter gives him a Rolls Royce.

The next man comes up and says, "I cheated on my wife a little but I still love her." He gets a mustang and drives off into heaven.

The next guy came up and said, "I cheated on my wife a lot". He gets a scooter.

Next day the guy that got the scooter was riding along and he saw the guy who owned the Rolls Royce crying.

He asked, "Why are you crying you have such a nice car?!" and the man sobbed, "My wife just went by on roller skates".

THE CAPTAIN

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."

BITE MY EYE

A man walks into a bar has a few drinks and asks what his tab was. The bartender replies that it is 20 dollars plus tip. The guy says, "I'll bet you my tab double or nothing that I can bite my eye." The bartender accepts the bet, and the guy pulls out his glass eye and bites it.

He has a few more drinks and asks for his bill again. The bartender reports that his bill now is 30 dollars plus tip. He bets the bartender he can bite his other eye. The bartender accepts knowing the man can't possibly have two glass eyes.

The guy then proceeds to take out his false teeth and bite his other eye.

WHAT IT MEANS

Five years old Becky answered the door when the Census taker came by.

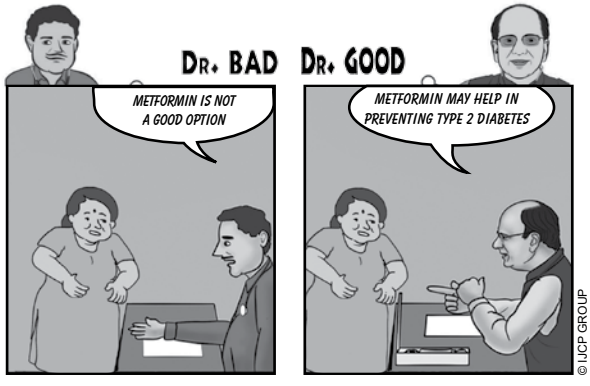
She told the Census taker that her daddy was a doctor and wasn't home, because he was performing an appendectomy.

"My," said the census taker, "that sure is a big word for such a little girl. Do you know what it means?"

"Sure! Fifteen hundred bucks and that doesn't even include the anesthesiologist!"

Dr. Good and Dr. Bad

SITUATION: A 48-year-old female with prediabetes (BMI: 37 kg/m^2) was prescribed metformin therapy for preventing type 2 diabetes.



LESSON: The ADA recommends the use of metformin for preventing type 2 diabetes in people with prediabetes, particularly those with BMI ≥35 kg/m^2, age <60 years, increasing HbA1c levels despite lifestyle intervention and females with prior gestational diabetes mellitus.

Diabetes Care. 2017;40(Suppl 1):S44-S47.

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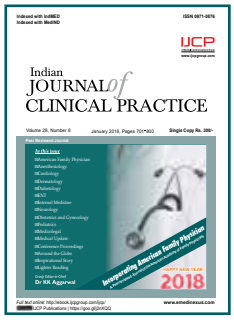

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Padma Shri Awardee
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- The statistical universe i.e., the population from which the sample for the study is selected.
- Method of selecting the sample (cases, subjects, etc. from the statistical universe).
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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.
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Paintal AS. Impulses in vagal afferent fibres from specific pulmonary deflation receptors. The response of those receptors to phenylguanide, potato S-hydroxytryptamine and their role in respiratory and cardiovascular reflexes. Q. J. Expt. Physiol. 1955;40:89-111.

Books

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

Articles in Books

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

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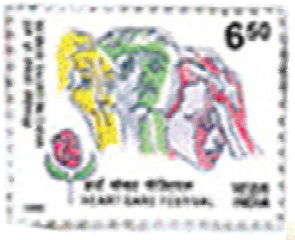

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