Questions and guide to answers

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Q: Discuss the generation and adaptation of evidence-based clinical practice guidelines

A: Generation and adaptation of evidence-based clinical practice guidelines [1]

Clinical Practice Guidelines (CPGs) are systematically standardized and scientifically developed statements designed to help practitioners in decision making about appropriate healthcare for specific clinical conditions or healthcare issues. CPGs have evolved from opinion-based guidelines to consensus-based guidelines and finally to evidence-based guidelines in recent times.

Evidence-Based Clinical Practice Guidelines (EBCPGs) are based on systematic literature search, identification, and synthesis of the highest quality research to generate the best available scientific evidence. Valid scientific research is translated, after thorough critical appraisal and analysis of the risk of bias, into evidence of clinical effectiveness and is then transformed into recommendations for healthcare practitioners.

EBCPGs aim at:

(1) Improving patient outcomes.
(2) Improving healthcare practice for certain difficult conditions.
(3) Maximizing benefits of various therapeutic interventions and diagnostic modalities.
(4) Reducing variations in medical practice.

Methodology of Evidence-Based Clinical Practice Guidelines development

(1) It requires significant resources, an extended period of time, and a substantial number of experienced personnel.
(2) There are many reputable sources for high-quality EBCPGs that follow high standards in guideline generation, such as the National Institute for health and Clinical Excellence (NICE in the UK). Guidelines are published on the corresponding websites and can be downloaded for free to help their dissemination and implementation in practice.
(3) Development of EBCPGs follows a strict systematic and highly scientific methodology.

The methodology followed for guideline development includes:

(1) Topic selection.
(2) Development of multidisciplinary teams including clinicians from all concerned specialties, nurses, bioethicists, economic analysts, consumers (patients), and others.
(3) Determination of the purpose and scope of the guideline, including the presentations of the disease to be addressed, patient characteristics, and domains to be studied (diagnosis, prevention, treatment, etc.).
(4) Remodeling the various diagnostic and/or therapeutic modalities and transforming the guidelines into key PICO questions.
(5) Systematic literature review for every key question to obtain all published and unpublished research.
(6) Quality assessment of the retrieved studies and formation of evidence tables.
(7) Drafting and grading of recommendations.
(8) Consultation and peer reviewing.
(9) Finalization of the guideline and its publication and dissemination.
(10) Implementation of the guideline.
(11) Auditing, reviewing, and updating.

Adaptation of international Evidence-Based Clinical Practice Guidelines

Low-resources countries such as Egypt cannot replicate the above-mentioned methodology to produce their own guidelines.

As regards the utility of 'other's' guidelines in 'our' local community with unique circumstances, some of the recommendations can be used and applied as such and others need some form of modification to ensure their acceptability and applicability in everyday situations in our hospitals. In other words, the guidelines may need some form of adaptation.

Adaptation of guidelines is a systematic approach to modify guidelines produced in one cultural and organizational setting to be applicable in another context. Adaptation makes guidelines suitable to a particular country, region, or hospital circumstances.

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The ADAPTE collaboration is a group of researchers, guideline developers, and guideline implementers who have proposed a scientific process and methodology for the adaptation of guidelines.

The ADAPTE collaboration has proposed a framework and a systematic procedure for the adaptation of CPG.

References: 1 Abdelhamid A (2013). Adaptation of international evidence based clinical practice guidelines: the ADAPTE process. *Middle East Fertil Soc J* 2013; **18**: 123–126.

Q: Discuss brittle asthma

A: Brittle asthma is a type of asthma distinguishable from other forms by the presence of recurrent, severe attacks

Brittle asthma is one of the 'unstable' subtypes of 'difficult asthma', a term used to characterize the less than 5% of asthma cases that do not respond to maximal inhaled treatment, including high doses of corticosteroids combined with additional therapies such as long-acting β-2 agonists [1].

There are two subtypes: type 1 and type 2, depending on the stability of the patient's maximum speed of expiration or peak expiratory flow rate (PEFR). Type 1 is characterized by a sustained, chronic variability in PEFR (usually >40% diurnal variation in PEFR >50% of the time), whereas type 2 is distinguished by sudden unpredictable drops in PEFR wherein asthma symptoms are otherwise well controlled and the function of the lungs is not substantially impaired [2].

Symptoms

The cardinal symptoms of an asthma attack are shortness of breath (dyspnea), wheezing, and chest tightness.

The condition is rare. Though found in all ages, it is most commonly found in individuals between the ages of 18 and 55 years; it is present in both sexes, though type 1 has been diagnosed in three times as many women as men. Hospitalization is more frequent for type 1 than type 2 [2].

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Q: Discuss osteopenia

A: Osteopenia

Osteopenia is a condition in which the bone mineral density is lower than normal. It is considered to be a precursor to osteoporosis. However, not every person diagnosed with osteopenia will develop osteoporosis. More specifically, osteopenia is defined as a bone mineral density *T*-score between −1.0 and −2.5 [1].

Diagnosis

Scans of bones anywhere in the body can be performed with radiographs, known as dual X-ray absorptiometry. Scans can also be performed with portable scanners using ultrasound, and portable X-ray machines can measure density in the heel [1].

Causes

Similar to osteoporosis, osteopenia occurs more frequently in postmenopausal women as a result of the loss of estrogen. It can also be exacerbated by lifestyle factors such as lack of exercise, excess consumption of alcohol, smoking, or prolonged use of glucocorticoid medications. It can result from exposure to radiation [1].

Osteopenia occurs more frequently in participants in non-weight-bearing sports such as bicycling or swimming than in participants in weight-bearing sports such as running, as bone-loading exercise tends to protect or possibly increase bone mineral density [2].

In particular, the condition is often observed in young female athletes. Female athletes tend to have lower body weight, lower fat percentage, and higher incidence of asthma than their less active peers. A chronic negative energy balance can suppress estrogen levels and decrease bone mineral density.

It is also a sign of normal aging, in contrast to osteoporosis, which is observed during pathological aging [3].

Osteopenia is also a common effect of celiac disease, even among patients who are otherwise asymptomatic [2].

Treatment [1]

Candidates for therapy include those at highest risk of osteoporotic bone fracture based on bone mineral density and clinical risk factors. Therapy should be considered for postmenopausal women and for men older than 50 years of age if any one of the following is present.

(1) Prior hip or vertebral fracture.
(2) *T*-score of −2.5 at the femoral neck or spine, excluding secondary causes.
(3) *T*-score between −1.0 and −2.5 at the femoral neck or spine and a 10-year probability of a hip fracture of at least 3% or a 10-year probability of a major osteoporotic fracture of at least 20%.
(4) The clinicians' judgment in combination with patient preference indicating treatment for individuals with 10-year fracture probabilities above or below these levels.

Notably, the first two conditions identify individuals with osteoporosis. The third condition corresponds to individuals with osteopenia, namely those with *T*-scores between −1.0 and −2.5.

The commonly used drugs include bisphosphonates such as alendronate, risedronate, and ibandronate; selective estrogen receptor modulators such as raloxifene; estrogen; calcitonin; and teriparatide.

Strontium ranelate is found to build bone both by slowing the work of osteoclasts and stimulating osteoblasts. Other (natural) forms of available strontium include strontium lactate, strontium gluconate, strontium carbonate, and strontium citrate. The food sources include spices (especially basil), seafood, whole grains, root and leafy vegetables, and legumes. Strontium should not be taken with calcium supplements so as to improve absorption [4].

References: 1 WHO Scientific Group on the Prevention and Management of Osteoporosis. *Prevention and management of osteoporosis: report of a WHO scientific group.* Geneva, Switzerland: WHO; 2003.
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4 Alonso-Coello P, García-Franco AL, Guyatt G, Moynihan R. Drugs for pre-osteoporosis: prevention or disease mongering?. *BMJ* 2008; **336**: 126–129.

Q: What are the types of mutations?

A: Types of mutations

By effect on structure

(1) Small-scale mutations, that affect a small gene in one or a few nucleotides, including:
  (a) Point mutations: are often caused by chemicals or malfunctioning of DNA replication [1]. These changes are classified as transitions [exchange of a purine for a purine (A↔G) or a pyrimidine for a pyrimidine (C↔T)] or transversions [exchanges of a purine for a pyrimidine or a pyrimidine for a purine (C/T↔A/G)] [2]. Point mutations may be classified into three types:
    (i) Silent mutations: which code for the same (or a sufficiently similar) amino acid.
    (ii) Missense mutations: which code for a different amino acid.
    (iii) Nonsense mutations: which code for a stop and can truncate the protein.
    (iv) Neutral mutations: which are mutations that occur in an amino acid codon and result in the generation of a different, but chemically similar, amino acid. The similarity between the two is such that little or no change is often rendered in the protein.
  (a) A frameshift mutation: is a mutation caused by the insertion or deletion of a number of nucleotides in a DNA sequence that is not evenly divisible by three. It can disrupt the reading frame, resulting in a completely different translation from the original [3].
    (i) Insertions add one or more extra nucleotides into the DNA. They are usually caused by transposable elements or errors during replication of repeating elements.
    (ii) Deletions remove one or more nucleotides from the DNA. Similar to insertions, these mutations can alter the reading frame of the gene. They are generally irreversible.
(2) Large-scale mutations in chromosomal structure, including:
  (a) Amplification leading to multiple copies of all chromosomal regions, increasing the dosage of the genes located within them.
  (b) Deletions of large chromosomal regions, leading to loss of the genes within those regions.
  (c) Chromosomal translocations: interchange of genetic parts from nonhomologous chromosomes.
  (d) Chromosomal inversions: reversing the orientation of a chromosomal segment.
  (e) Loss of heterozygosity: loss of one allele, either by a deletion or recombination event, in an organism that previously had two different alleles.

By effect on function

(1) Loss-of-function mutations are the result of a gene product having less or no function: amorphic mutation.
(2) Gain-of-function mutations change the gene product such that it gains a new and abnormal function: neomorphic mutation.
(3) Lethal mutations are mutations that lead to the death of the organisms that carry the mutations.
(4) A back mutation or reversion is a point mutation that restores the original sequence and hence the original phenotype [4].

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Q: Discuss diastolic dysfunction and diastolic heart failure

A: Diastolic dysfunction and diastolic heart failure [1]

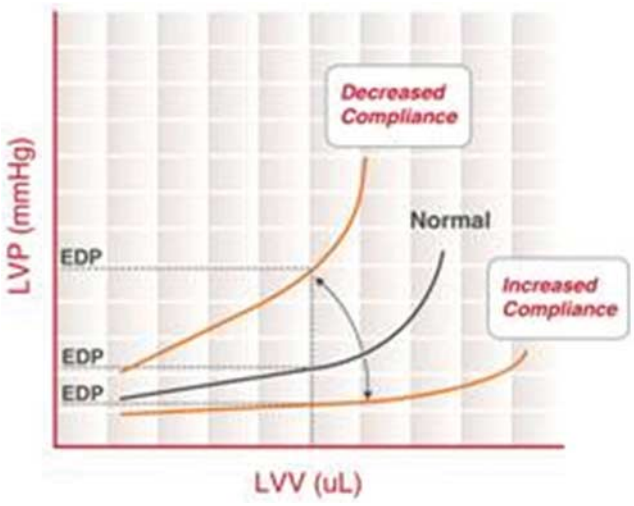
Diastolic heart failure and diastolic dysfunction refer to the decline in performance of one (usually the left) or both (left and right) ventricles during diastole. Diastole is the cardiac cycle phase during which the heart is relaxing and gets filled with incoming blood that is being returned from the body through the inferior and superior vena cava

to the right atrium and from the lungs through the pulmonary veins to the left atrium. In diastolic failure, if the patient has symptoms, there is a pathological cause inducing them. Diastolic dysfunction can be diagnosed when performing Doppler echocardiography in an apparently healthy patient, mainly in an elderly person.

Physiology of diastole

During diastole, the ventricular pressure falls. When this pressure falls below the atrial pressure, the atrioventricular valves open (the mitral valve at the left side and the tricuspid valve at the right side) and the blood passes from the atria into the ventricles. First, the ventricles are filled by a pressure gradient, but near the end, the atria contract (atrial kick) and force more blood to pass into the ventricles. A correct left ventricular filling is essential to maintain a proper cardiac output. Left ventricular filling is dependent upon ventricular relaxation and compliance, the mitral valve area, the atrioventricular gradient, atrial contraction, and the end-systolic volume. The diastole has four phases: isovolumetric relaxation, rapid filling, diastasis, and atrial contraction. All of these phases can be evaluated by Doppler echocardiography.

Pathophysiology



End-diastolic pressure–volume relationship

Diastolic failure appears when the ventricle cannot be filled properly because it cannot relax or because its wall is thick or rigid. This situation usually presents in concentric hypertrophy. In contrast, systolic heart failure is usually represented by eccentric hypertrophy.

Diastolic failure is characterized by an elevated diastolic pressure in the left ventricle, despite an essentially normal/physiological end-diastolic volume. Histological evidence shows interstitial collagen deposition and infiltration of the myocardium, leading to a downhill in distensibility and elasticity (ability to stretch) of the myocardium. As a consequence, the cardiac output becomes diminished. When the left ventricular diastolic pressure is elevated, the venous pressure in the lungs must also become elevated: left ventricular stiffness makes it more difficult for blood to enter the lung from the left atrium. As a result, pressure rises in the atrium and is transmitted back to the pulmonary venous system, thereby increasing its hydrostatic pressure and promoting pulmonary edema.

The diastolic function is determined by the relative end-diastolic volume in relation to the end-diastolic pressure and is therefore independent of the left ventricular systolic function.

Risk factors and causes

Any condition or process that leads to stiffening of the left ventricle can lead to diastolic dysfunction. The causes of left ventricular stiffening include:

(1) Long-standing hypertension as a result of left ventricular muscle hypertrophy.
(2) Aortic stenosis of any cause: the ventricular muscle becomes hypertrophied and hence stiff.
(3) Diabetes.
(4) Old age, especially if hypertension is present.

The causes of isolated right ventricular diastolic failure are uncommon and include:

(1) Constrictive pericarditis.
(2) Restrictive cardiomyopathy, which includes amyloidosis (most common), sarcoidosis, and fibrosis.

Diagnosis

Diastolic dysfunction must be differentiated from diastolic heart failure.

If diastolic dysfunction describes an abnormal mechanical property, diastolic heart failure describes a clinical syndrome.

The criteria for diagnosis of diastolic dysfunction or diastolic heart failure remain imprecise. The problem is compounded by the fact that systolic and diastolic heart failure commonly coexist. Diastolic failure has often been defined as 'heart failure with a normal systolic function' (i.e. left ventricular ejection fraction of $\geq 60\%$). Chagasic heart disease may represent an optimal academic model of diastolic heart failure that spares systolic function.

A patient is said to have diastolic dysfunction if he has signs and symptoms of heart failure but the left ventricular ejection fraction is normal.

A second approach is to use an elevated BNP level in the presence of a normal ejection fraction to diagnose diastolic heart failure.

Concordance of both volumetric and biochemical measurements and markers lends to an even stronger terminology for scientific/mathematical expression of diastolic heart failure.

Echocardiography can be used to diagnose diastolic dysfunction but is a limited modality unless it is supplemented by stress imaging.

No one single echocardiographic parameter can confirm the diagnosis of diastolic heart failure. Multiple echocardiographic parameters have been proposed as being sufficiently sensitive and specific, including mitral inflow velocity patterns, pulmonary vein flow patterns, E/A reversal, tissue Doppler measurements, and M-mode echocardiographic measurements (i.e. of the left atrial size). Algorithms that combine multiple echocardiographic parameters to diagnose diastolic heart failure have also been developed.

There are four basic echocardiographic patterns of diastolic heart failure, which are graded I–IV.

(1) The mildest form is called an 'abnormal relaxation pattern' or grade I diastolic dysfunction. On the mitral inflow Doppler echocardiogram, a reversal of the normal E/A ratio is observed. This pattern may develop normally with age in some patients and many grade I patients will not develop any clinical signs or symptoms of heart failure.
(2) Grade II diastolic dysfunction is called 'pseudonormal filling dynamics'. This is considered as a moderate diastolic dysfunction and is associated with elevated left atrial filling pressures. These patients more commonly have symptoms of heart failure and many patients have left atrial enlargement due to the elevated pressures in the left heart.

Grades III and IV diastolic dysfunctions are called 'restrictive filling dynamics'. Both of these dysfunctions comprise severe forms of diastolic dysfunction and the patients tend to have advanced heart failure symptoms:

(1) Class III diastolic dysfunction patients will demonstrate reversal of their diastolic abnormalities on an echocardiogram when they perform the Valsalva maneuver. This is referred to as 'reversible restrictive diastolic dysfunction'.
(2) Class IV diastolic dysfunction patients will not demonstrate reversibility of their echocardiogram abnormalities and are therefore said to suffer from 'fixed restrictive diastolic dysfunction'.

The presence of either class III or IV diastolic dysfunction is associated with a significantly worse prognosis. These patients will have left atrial enlargement and many will have a reduced left ventricular ejection fraction that indicates a combination of systolic and diastolic dysfunction.

Treatment

Generally, diastolic dysfunction is a chronic process.

The role of specific treatments for diastolic dysfunction *per se* is as yet unclear. Diuretics are useful, as these patients develop significant congestion. However, these patients must be monitored because they frequently develop hypotension.

β-Blockers are the first-line therapy as they induce bradycardia and allow time for the ventricles to fill.

There is some evidence that calcium channel blocker drugs may be of benefit in reducing ventricular stiffness in some cases (verapamil has the benefit of lowering the heart rate). Likewise, treatment with angiotensin-converting-enzyme inhibitors, such as enalapril, ramipril, and many others, may be of benefit owing to their effect on preventing ventricular remodeling but in a controlled manner so as to avoid hypotension.

References: 1 Topol EJ; Califf RM. *Textbook of cardiovascular medicine. ISBN 978-0-7817-7012-5.* Philadelphia: Lippincott Williams & Wilkins; 2007. pp. 420.

Q: Discuss brittle diabetes

A: Almost all diabetic patients experience swings in blood glucose levels, which are larger and less predictable than those in nondiabetics. When these swings become intolerable and cause disruption to the person's daily life and/or prolonged hospitalization, the person is labeled as having 'labile' or 'brittle' diabetes.

Although brittle diabetes is uncommon (<1% of insulin-taking diabetic patients) [1], it can cause a considerable burden on the hospital and the social and family resources because of multiple hospital admissions.

Clinical manifestations

The manifestations include unpredictable episodes of hypoglycemia and/or ketoacidosis that disrupt quality of life because of an absolute insulin dependency (undetectable C-peptide levels).

Brittle diabetic patients virtually always have type 1 diabetes.

With the availability of basal and bolus insulin regimens, using long and rapid-acting insulin analogs or insulin pump therapy, there has been substantial improvement in the ability to treat most patients with type 1 diabetes effectively [2].

Three clinical presentations of brittle diabetes have been described: (a) predominant hyperglycemia with recurrent ketoacidosis, (b) predominant hypoglycemia, and (c) mixed hyperglycemia and hypoglycemia [3]. Frequent hypoglycemia, even if asymptomatic, causes both defective glucose counterregulation and hypoglycemia unawareness and thus a vicious cycle of recurrent hypoglycemia.

Recommendations

The approach to management will obviously vary depending on the specific etiology in each case. It is important to take a detailed history to include several specific points, including the duration of diabetes and descriptions of all episodes of ketoacidosis and severe hypoglycemia. It should also be determined whether there was a period of 'stable' diabetes preceding the brittleness and what happened in the patient's life circumstances coincident with the onset of brittleness.

Psychotherapy has been shown to be effective in selected patients [4].

For patients with recurrent episodes of ketoacidosis, a possible chronic cryptic infection (such as sinusitis, osteomyelitis, renal or perinephric abscess, and lung abscess) should be excluded.

These problems are more likely in a patient using intravenous drugs. Thus, a urinary drug screen for opiates and amphetamines may be helpful if drug use is suspected.

For patients with recurrent episodes of severe hypoglycemia, a number of conditions should be considered:

Gastroparesis can lead to a severe mismatch between food absorption and insulin absorption, causing unexplained hypoglycemia [4]. Gastric emptying studies and/or a trial of medical therapy may be helpful in this setting.

Hypothyroidism and adrenal insufficiency are also causes of recurrent severe hypoglycemia; they can be treated easily once the condition is recognized [5].

A diabetic educational assessment is useful to evaluate whether the patient knows how to manage diabetes. As many as one-third of patients with brittle diabetes have a 'communication disorder' (which can be diagnosed by speech language pathologists) as the major cause of their brittleness; specific treatment is beneficial in 75% of cases [4].

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Conflicts of interest

There are no conflicts of interest.