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Recommended Citation

Mehmood KT, Rentea RM. Ambiguous Genitalia And Disorders of Sexual Differentiation. In: StatPearls. Treasure Island (FL): StatPearls Publishing; 2021.

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StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2020 Jan-.

Ambiguous Genitalia And Disorders of Sexual Differentiation

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Last Update: April 18, 2020.

Introduction

The birth of an infant with ambiguous genitalia generates difficult multiple medical, surgical, ethical, psychosocial, and physical issues for patients and their parents. Phenotypic sex results from the differentiation of internal ducts and external genitalia under the influence of hormones and other additional factors. When discordance occurs among three processes (chromosomal, gonadal, phenotypic sex determination), a DSD is the result.

Terminology such as hermaphrodite, pseudo-hermaphrodite, and intersex, are considered to be pejorative and dated. These terms have been replaced by the term disorders of sexual development (DSD) by the consensus statement on management of intersex disorders.[1][2] Disorders of sexual development are defined as congenital conditions characterized by atypical development of chromosomal, gonadal, or anatomic sex.[3]

Normal sexual development in utero is dependent upon a precise and coordinated spatiotemporal sequence of various activating and repressing factors.[4] Any deviations from the usual pattern of differentiation can present as DSDs. Two distinct processes occur in normal sexual development. The first of which is sex determination in which the bipotential gonads are induced to form either the male testes or the female ovaries. Secondly, the newly formed gonads secrete hormones to modulate the formation of internal and external genitalia.[5]

The phenotypic manifestation of DSDs are diverse and can include; bilateral undescended testes, severe hypospadias (scrotal or perineal), clitoromegaly, a fusion of posterior labial folds, female external genitalia with palpable gonad, discordant genitalia and sex chromosomes. The inclusion of disorders in which there is no genital/gonadal discordance like Turner syndrome, Klinefelter syndrome, simple hypospadias remains controversial.

Regardless of presentation or severity, individuals require a multidisciplinary approach that is warranted to improve the quality of life and achieve the best possible outcomes.

Etiology

Sexual development in mammals occurs in two sequential stages: the initial phase of sex determination followed by sex differentiation.[5] Sex determination is guided by the complement of sex chromosomes inherited at conception. [6]The inheritance of the Y chromosome and the subsequent expression of the SRY gene drives the bipotential gonad toward differentiation into male-specific testes.[6] In contrast, the absence of the Y chromosome results in the development of the female-specific ovary. The second stage of sex differentiation is characterized by the secretion of certain hormones and other factors by the differentiated gonad, which guides the internal and external genital development and maturation.[7] The secretion of testosterone and anti-mullerian factor by the Leydig and Sertoli cells respectively cause the development of male internal organs and reciprocal regression of female sex organs. The absence of these hormones leads to the formation of the female sexual organs.

A multitude of genes plays an important role in orchestrating this complex sequence of events. A detailed review of these genes is beyond the scope of this article. However, an overview of the most important genetic factors is

provided below.

1. SRY gene: the sex-determining region of the Y chromosome is the chief regulator of male sex differentiation; expression causes translation of SRY protein, which mediated testicular development.[8]
2. SOX9 gene: expression of this gene follows the SRY gene and is responsible for the differentiation of Sertoli cells.
3. NR5A1/SF-1: The steroidogenic factor gene codes an important transcription factor involved in male development and steroid biosynthesis.[9][10]
4. DHH gene: The desert hedgehog gene plays a role in testicular differentiation.[11]
5. DAX/NROB1: Considered as an anti testis factor up-regulated in the ovary.
6. WT1: Codes a transcription factor involved in renal and gonadal development, mutation results in various congenital syndromes of abnormal genitourinary development.
7. Wnt4 and Wnt 7a: Wnt 4 suppresses male sexual differentiation and ovarian androgen production.[12]

A mutation in any of these above genes may lead to the development of DSD. A loss of genes involved in male sexual development can lead to an undervirilized male or 46 XY with a female phenotype.

A finely balanced hormonal milieu is required for normal sexual development; testosterone is necessary to stabilize the Wolffian ducts while secretion of antimüllerian factors is essential for the regression of Müllerian ducts.

The male external genitalia requires the presence of dihydrotestosterone for normal phenotypic development. The deficiency of this hormone or resistance may lead to undervirilized genitalia. Exposure of female genitalia to excess androgens leads to virilization, which may be due to excess production or exogenous exposure.

Epidemiology

The incidence of a child with a disorder of sexual development (DSD) is approximately 1 in 1000 to 4500 live births. [13][1] The most frequently occurring etiology was congenital adrenal hyperplasia (CAH) followed by androgen insensitivity and mixed gonadal dysgenesis.

Pathophysiology

To fully appreciate the diversity and complexity of disorders with sexual development, the complex embryological process requires review. The following paragraphs will outline the basics of sexual development and hopefully tie in the important etiologies.

During early fetal development, males and females share a common anlage. This phase lasts for up to 7 weeks, after which development proceeds down two distinct genetic pathways.

Inheritance of 46 XY chromosome leads to the expression of the SRY gene located on the Y chromosome.[14] The SRY can be considered as the control switch for male sex development; its appearance triggering significant downstream effects that eventually result in the formation of male-specific gonads.[15] Definitive missense mutations provide evidence of this fact in this gene leading to 46, XY gonadal dysgenesis.[16] Whereas its translocation and expression in individuals with 46 XX, result in male or ambiguous genitalia.

The second most crucial gene in male sexual determination encodes the transcription factor SOX9. Mutation in this all-important gene is responsible for the autosomal dominant campomelic dysplasia characterized by 46XY genotype and ambiguous or female external genitalia.[17] Furthermore, duplication of this gene results in male or ambiguous genitalia in a 46 XX infant.

Mutations in various other transcription factor encoding genes that promote testicular differentiation have also been implicated in aberrant sexual development. The NR5A1 (also known as steroidogenic factor 1 SF-1 gene) is a key

regulator of testicular development along with the formation of the hypothalamic-pituitary-adrenal axis.[18] Mutation results in gonadal and adrenal dysgenesis in individuals with 46 XY genotype and female external genitalia.[19]

Similarly, mutations in other essential genes involved in male development such as DHH, NROB1, GATA4, ZFMP2 all lead to 46XY individuals having female or ambiguous genitalia.

Once the testes have developed, the Sertoli cells secrete the anti-Mullerian factor, which causes involution of paramesonephric duct (Mullerian), and Leydig cells produce testosterone, which stabilized mesonephric (Wolffian) ducts. Deficiency of testosterone due to a biosynthetic defect such as enzyme deficiencies like cholesterol desmolase (CYP11A1), 3 beta-hydroxysteroid dehydrogenase(HSD3B2), 17 alpha-hydroxylase (CYP17), P450 Oxidoreductase (POR) among others can present with ambiguous genitalia or micropenis along with symptoms of adrenal insufficiency. Similar female phenotypes can be seen in the absence of adrenal receptor deficiency, which is characteristic of androgen insensitivity syndromes. Deficiency of anti-Mullerian hormone or its receptor presents as male external genitalia with cryptorchidism and persistent Mullerian ducts.[20]

Dihydrotestosterone controls the external genital development, characterized by phallic enlargement and fusion of urogenital folds to form the penile urethra. The labio-scrotal fold fusion to form scrotum is governed by the enzyme 5 alpha-reductase type 2. The deficiency of these enzymes leads to undervirilized males with micropenis or males with ambiguous genitalia with normally functioning testes.[21]

In contrast, individuals with 46 XX genotype lack the SRY gene, leading to the progression of bipotential gonad towards ovarian development. However, contrary to previous belief, ovarian development is not merely a passive default pathway.[22] Initially, there is increased expression of WNT4 and RSPO1, which upregulate and stabilize the beta-catenin transcription factor, which suppresses the male-specific SOX gene. Maintenance of the ovarian phenotype is promoted by the expression of FoxL2 gene and the estrogen receptors. Mutation in this gene results in 46, XX gonadal dysgenesis with BPES (blepharophimosis, ptosis, and epicanthus inversus syndrome).[23]

The absence of testosterone leads to involution of Wolffian ducts and Mullerian duct differentiate into fallopian tubes and uterus due to the absence of anti-mullerian factors.

External genitalia develops into the female phenotype due to the absence of androgens. Disorders of enzyme biosynthesis, which shunt steroid precursor towards formation androgens lead to virilization of female external genitalia. The most frequent of these disorders are due to a deficiency of 21 alpha-hydroxylase, causing the classical variant of congenital adrenal hyperplasia characterized by female virilization and potential salt-wasting crises in neonates. Other less severe forms of CAH arises due to deficiencies in hydroxysteroid dehydrogenase, 11 beta-hydroxylase, and p450 oxidoreductase. Exogenous androgen exposure or maternal aromatase deficiency also gives rise to a fetus with virilized genitalia.

In summary, any deviation from the intricate sequence of sexual development may give rise to disorders of sexual development.

History and Physical

As with most diseases, a careful history and thorough examination are crucial for making an early diagnosis. A newborn with bilateral non-palpable testes or a unilateral impalpable testis and severe hypospadias should be regarded as having a DSD until proven otherwise, whether or not the genitalia grossly appears ambiguous. The incidence of DSD in individuals born with hypospadias and cryptorchidism ranges between 17% and 50%.

History should include any maternal exposure to androgens (e.g., Danazol) during the current pregnancy and any history of maternal virilization during pregnancy.[24][25] Maternal virilization can be caused by a deficiency of placental aromatase as well as by luteomas of pregnancy. A report of maternal ingestion of exogenous maternal hormones (such as those used in assisted reproductive techniques), and maternal use of oral contraceptives or soy products during pregnancy. Family history is essential, including those with urologic abnormalities, precocious puberty, amenorrhea, infertility, or neonatal deaths. History or family history of consanguinity among partners

increases the likelihood of various autosomal recessive causes of ambiguous genitalia (e.g., congenital adrenal hyperplasia). History of previous neonatal deaths may also provide a clue towards CAH. Siblings with primary amenorrhea and XY karyotype are seen in patients with the X linked androgen insensitivity syndrome.[26]

A careful and detailed physical evaluation is paramount for an accurate diagnosis. An examination should be focused on inspection and palpation of genitalia. The child should be examined in a warm room, supine and in the frog-leg position, completely freely moving legs. This allows for the testicle (s) that may not have descended to be palpated along their course: the inguinal canal, the superficial inguinal pouch, the upper scrotum, or rarely the perineal, femoral or contralateral scrotal regions.

Documentation of the size of the penis or clitoris, number on perineal openings, presence of testes in labial, or inguinal regions should be considered.

The average stretched penile length in a term male infant is between 2.8 to 4.2 cm.[9] Though the penile length is dependent upon fetal gestational age as well as race. Microphallus itself is not a marker of Disorder of sexual development. Typical findings include bilateral non-palpable testes, scrotal or perineal hypospadias, and hypospadias with unpalpable gonad.

The normal clitoral length in full-term female infants is 3.3 -6.5 mm, with clitoromegaly defined as length greater than 9 mm. Other findings include fused labial folds, inguinal masses, and urogenital sinus formation.

A uterus can be palpated on a digital rectal examination as an anterior midline cord-like structure.

Other non-genital abnormalities and dysmorphic features should be documented. For example, patients with Smith-Lemli-Opitz syndrome have ambiguous genitalia and microcephaly, posteriorly rotated low set ears, and fusion of second and third toes.[27] Additional findings include a short, broad neck, widely spaced nipples, and aniridia.

Evaluation

The initial evaluation should include karyotyping, which is usually performed of peripheral leukocytes. Depending on the result of karyotype, individuals are categorized into three main types 46XX DSD, 46 XY DSD, and mixed chromosome DSD.[2]

Another critical test is the fluorescent in situ hybridization (FISH) for the SRY gene. This gene is the master regulator of male sex development. The absence of the SRY gene in a 46XY karyotype indicates deletion and can result in DSD ranging from ambiguous genitalia to sex reversal.[15][8]

Investigations for congenital adrenal hyperplasia (CAH) should be prioritized as a delayed diagnosis can lead to salt-wasting and high morbidity and mortality. Measuring of 17 hydroxyprogesterone should be performed in all neonates with atypical genitalia and absent inguinal swellings to exclude classical CAH. Measurement of dehydroepiandrosterone (DHEA), 17-hydroxypregnenolone, and 11-deoxycortisol will help in diagnosis other causes of CAH.[28]

Other tests include the analysis of testosterone after stimulation and measuring gonadotrophins.

Imaging modalities such as ultrasound and MRI help delineate the anatomy and to visualize gonads, uterus, and vagina. Vaginoscopy is also an essential modality for accurate visualization of vaginal anatomy.

The results of the karyotype and SRY gene further guide the management.

Individuals with 46 XX Disorders of Sexual Development

In individuals with ambiguous genitalia and 46 XX, FISH for SRY determines further investigations. Individuals with SRY positivity have SRY gene translocation causing ambiguous genitals.

Those with SRY negativity can be evaluated by measuring the concentration of 17 hydroxyprogesterone. Elevated levels point towards congenital adrenal hyperplasia as a cause for virilization of the female fetus. Though the most

common deficiency for CAH is of 21 alpha-hydroxylase, other enzyme deficiencies such as 11 beta-hydroxylase, 3 beta dehydrogenase, and P450 oxidoreductase should be considered. These less common causes for CAH can be distinguished based on the measurement of 17-hydroxypregnenolone, cortisol, dehydroepiandrosterone, and 11 deoxycortisol.

Individuals with normal levels of 17 hydroxy progesterone should then undergo a pelvic ultrasound to ascertain the internal anatomy. Those with normal internal female anatomy are likely exposed to androgens during gestation. The androgens can be exogenous, e.g., danazol, synthetic progestins, etc. or can be endogenous, e.g., luteomas of pregnancy, Placental aromatase deficiency.

Patients in whom ultrasound reveals abnormal female internal organs are then tested for anti-Mullerian hormone levels and testosterone levels and human chorionic gonadotrophin. Elevated levels are suggestive of ovotesticular DSD.

Individuals with 46 XY and Disorders of Sexual Development

In individuals with 46 XY karyotype and ambiguous genitalia, FISH for the SRY gene guides further investigations. Individuals with the absence of the SRY gene are due to deletion.

Those with SRY positivity are more difficult to evaluate due to a plethora of diverse etiologies. Congenital adrenal hyperplasia can also lead to an undervirilized 46XY fetus. The etiologies include deficiency of 17 alpha-hydroxylase, 3 beta-hydroxysteroid dehydrogenase, steroid acute regulatory protein, P450 oxidoreductase, P450 side-chain cleaving enzyme. Measurement of 17-hydroxypregnenolone, deoxycorticosterone, and DHEA serve to differentiate among these conditions. To confirm a deficiency of 17 alpha-hydroxylase or 3 beta-hydroxysteroid dehydrogenase, an ACTH stimulation test to measure the steroid precursors are required.

In other individuals, the presence of testicular tissue can be ascertained by either performing ultrasound or measuring the concentration of anti-Mullerian hormone (AMH), which serves as a marker of testicular tissue. In patients with low AMH, gonadal dysgenesis, testicular regression syndrome, vanishing testicular syndrome, or persistent Mullerian duct syndrome are likely causes.

Patients have a normal testicular reserve as evidenced by normal levels of anti-Mullerian hormone and the subjected to beta chorionic gonadotrophin stimulation to differentiate between abnormal androgen synthesis versus abnormal androgen response. Beta HCG is administered, followed by measurement of testosterone, dihydrotestosterone (DHT), and androstenedione.

Patients who have normal responses to beta HCG stimulation as evidenced by 4 fold increase in testosterone by day 6, testosterone to DHT ratio of less than 10 to 1 and testosterone to androstenedione greater than 0.8, may have LH receptor defects, 5 alpha-reductase deficiency or 17 hydroxysteroid dehydrogenase deficiency.

Individuals with normal response to beta HCG likely have androgen insensitivity syndrome, AMH receptor defect, or exposure to endocrine disruptors such as phenytoin.

Individuals with Sex Chromosome DSD

These are individuals who on karyotyping are found to have 45x/46xy mosaicism or 46XX/46XY mosaic. Individuals without atypical genitalia such as Turner syndrome or Klinefelter syndrome are also included in this subgroup.

Treatment / Management

The management of individuals with disorders of sexual development can be complex. This is because psychosexual development is dependant on various factors such as societal and cultural norms, in utero exposure to androgen, genetic differences, and familial dynamics. The previous management guidelines of early genital surgery based on expected fertility outcomes and phallic functionality are being challenged due to evolving evidence. A need to move away from the physician-directed early gender assignment surgeries is warranted, because of poor long term outcomes.[29][30][31]

The management should be focused on three main domains; initial stabilization, accurate diagnosis, and decisions on the gender of rearing and planning of surgical intervention and hormonal treatment.

Congenital adrenal hyperplasia, which is the most common cause of ambiguous genitalia, can present as life-threatening salt-wasting crises. Prompt diagnosis and treatment with glucocorticoids should be instituted.

Accurate diagnosis is essential; in some cases, diagnosis may be obvious; however, it is prudent to transfer cases to a center experienced in the management of DSDs. A frank and honest discussion with the parents regarding the delay of gender assignment until the diagnosis is clear is warranted.

The decision for gender assignment should be made upon the best available evidence and considerations of such as type of DSD, prenatal androgen exposure, the possibility of fertility and sexual functionality, and psychosocial factors.[32][33][34]. There are strongly differing viewpoints regarding the timing of gender assignment. The first is to assign complete genital reconstruction after birth to avoid internal conflicts with the patient or external societal conflicts as the child develops. The opposing viewpoint is that gender assignment is a shared decision that the affected individual participates in during puberty- essentially, physicians and family cannot predict future gender identity or sexual orientation. Three considerations in the discussion of gender assignment include the functional and anatomic ability of the genitalia (size of the phallus or vagina, fertility potential), the cause of the DSD, and the values and desires of the family.

The basic principles of surgery are to ensure the best cosmetic results, preserve sexual functioning, preserve fertility if possible, and decrease the risk of malignancy in the dysgenetic gonad. Deferring surgery is often advocated until the child is old enough to confirm his/her gender identity.

Surgical management of certain common DSDs is listed below.

Congenital adrenal hyperplasia 46XX: The management of individuals is straightforward. Those up to Prader stage 1 to 4 virilizations are recommended for a female gender of rearing. However, individuals with severe virilization and those in whom the diagnosis is delayed, male rearing should be considered. Surgery is aimed to restore the vaginal and urethral position and to correct the fistula between the vagina and urogenital sinus. Preservation of clitoral function is another important consideration.[35][36]

Gonadal dysgenesis 45X/46XY mosaic: These individuals have virilization, a Y chromosome, and exposure to androgens in utero. Therefore, the male gender of rearing is recommended. A hypospadias correction and removal of streak gonad is recommended. These individuals are at increased risk of malignancy. Therefore post-puberty biopsy and gonadectomy are recommended if the biopsy is positive.[37]

46 XY DSD: For individuals with a deficiency of 17 beta-hydroxy dehydrogenase or deficiency of 5 alpha-reductase, a male gender of rearing is recommended. Hormonal stimulation for phallic growth followed by hypospadias correction and orchidopexy is advocated.

Certain DSDs predispose to an increased risk of gonadal cancer. Mixed gonadal dysgenesis and partial androgen insensitivity are associated with higher oncologic risk. The timing of gonadectomy depends on the risk, gender of rearing, and functionality of gonad. Individuals to be raised as females removal is advocated at the time of genitoplasty. For males, orchidopexy and biopsy after puberty are recommended. Streak gonads are preferably removed as early as possible.

In addition, psychosocial support and education should be provided to both parents as well as children with DSD.

Differential Diagnosis

The diagnosis of DSD is often suspected following external evaluation of the genital area. Additional diagnoses encountered in the differential diagnosis include cloaca, urogenital sinus, rectovaginal fistula, various congenital duplications such as caudal duplication.[38] Certain conditions such as cryptorchid testes, penile hypospadias,

micropenis, etc. mimic DSD; however, unlike true DSD, there are no inconsistencies between karyotype and genitalia.

Prognosis

Though the prognosis is good, the disease is associated with considerable psychosocial morbidity. Additionally, associated medical and surgical conditions contribute to the overall prognosis.

Complications

The most severe complication can arise due to neonatal salt wasting in congenital adrenal hyperplasia (CAH). Early diagnosis is crucial to prevent neonatal morbidity and mortality. Individuals with dysgenetic gonads are at risk of developing gonadal tumors, especially those with a Y chromosome in their karyotype. Surgery and treatment may not be able to achieve satisfactory sexual functionality, and fertility remains suboptimal.

Consultations

An interprofessional dedicated clinical practice is often required for optimal management. The group of providers present in the multidisciplinary care of children with DSD includes a pediatric surgeon with expertise in DSD, pediatric urology, pediatric gynecologist, endocrinologist, and psychologist.

Deterrence and Patient Education

A holistic and interprofessional approach is required when dealing with a patient of disorder of sex development (DSD). A comprehensive discussion regarding specific outcomes and delaying gender assignment until the diagnosis is confirmed is advocated. Delayed surgery is now recommended to decrease the incidence of gender dysphoria and improve functional outcomes.

Pearls and Other Issues

The term disorder of sex development or disorder of sexual development (DSD) has replaced outdated terms such as 'intersex' or 'ambiguous genitalia.'

The differential diagnosis can be overwhelming, so a systematic multidisciplinary approach is paramount.

A disorder of sex development (DSD) is suspected in any infant who has the physical examination findings of bilateral nonpalpable undescended testes or hypospadias with unilateral undescended testis.

Three essential details on the evaluation of a newborn with suspected DSD are ascertaining if there is a patent anus on assessment, are the genitalia symmetric or asymmetric and does the infant have a XX or XY karyotype?

Up to one-half of males with hypospadias and cryptorchidism will have a DSD.

The most important initial finding on physical examination is the presence and number of gonads.

A uterus may be palpable on digital rectal examination.

The newborn period requires a karyotype and laboratory evaluation.

To summarize DSD evaluation:

Evaluation Begins with Palpation of the Gonads

0 gonads palpated (46XX DSD, GD, 46 XY, ovotesticular DSD)

1 gonad palpated (partial GD ovotesticular DSD, 46 XYDSD)

2 gonads palpated (46 XY DSD Ovotesticular DSD (rare))

The most important aspects of diagnosis and treatment include:

1. Karyotype evaluation
2. Laboratory evaluation: serum electrolytes, 17-hydroxyprogesterone (17 OH-P), testosterone (T), dihydrotestosterone (DHT), luteinizing hormone (LH) and follicle-stimulating hormone (FSH) levels
3. Pelvic ultrasound
4. Possible laparoscopy with gonadal biopsy

Based on Laboratory Values

1. If 17 OH-P (>2000 ng/dl) and high testosterone with uterus present, then the diagnosis is 46 XX DSD (CAH). There is further differentiation based on 11 deoxycortisol level and deoxycortisone (DOC)- (if low 11 deoxycortisol and low DOC, then 46XX DSD or 21 alpha-hydroxylase deficiency) (if high 11 deoxycortisol and high DOC, then 11 beta-hydroxylase deficiency)
2. If normal 17 OH-P (testosterone increased and uterus seen, and on laparoscopy, with gonadal biopsy, and there are ovaries 46 XX DSD (maternal virilizing syndrome)
3. If normal 17 OH-P (possible uterus and normal testosterone, perform laparoscopy with gonadal biopsy). If testis, ovary, ovotestis- diagnosis is ovotesticular DSD: 46XX, 46 XX/XY, 45X/46XY. If streak, this is gonadal dysgenesis, either pure 45X, 45X/46XX, 46XX, 45X/46/XY, or partial 45X/46XY, 46XY.
4. If normal 17 OH-P (possible uterus and normal testosterone, perform laparoscopy with gonadal biopsy). Two testes, HCG stimulation pre/post, are performed, testosterone/DHT, and DHEA/androstenedione obtained. The diagnosis is 46XY DSD: 46XY, 46XX, 45X/46XY. Consider one of the following diagnoses: 5 alpha-reductase deficiency, androgen insensitivity syndrome (AIS), steroid deficiency- male CAH, dysgenetic testes, persistent Mullerian duct syndrome (PMDS), and primary testicular failure.

Enhancing Healthcare Team Outcomes

An interprofessional approach is required in a tertiary center for dealing with individuals with DSDs. A working liaison with a pediatrician, pediatric surgeon, pediatric endocrinologist, and child psychologist is required. The patient and their family should be involved in the discussion. As the understanding of this disease and its psychosocial aspects become clear, a more patient-centric approach is advocated.

Questions

To access free multiple choice questions on this topic, [click here](#).

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