(7/22/11) Important recommendation changes for the Evaluation of the Azoospermic Male Best Practice Statement.

Please see page 11 for revisions to Recommendation 7 and page 15 for revisions to Recommendation 9.

The Evaluation of the Azoospermic Male: AUA Best Practice Statement

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Abbreviations and Acronyms

AUA	American Urological Association
BOD	Board of Directors
CBAVD	congenital bilateral absence of the vasa deferentia
CFTR	cystic fibrosis transmembrane conductance regulator
EDO	ejaculatory duct obstruction
FSH	follicle-stimulating hormone
ICSI	intracytoplasmic sperm injection
LH	luteinizing hormone
PGC	Practice Guidelines Committee
STS	sequence tagged sites
TRUS	transrectal ultrasonography
WHO	World Health Organization

Introduction

Approximately 15% of couples are unable to conceive after one year of unprotected intercourse. A male factor is solely responsible in about 20% of infertile couples and contributory in another 30-40%.[1] Azoospermia, defined as complete absence of sperm from the ejaculate, is present in about 1% of all men[2] and in approximately 15% of infertile men[3]. Azoospermia is different from aspermia, in that aspermia is the complete absence of seminal fluid emission upon ejaculation. Differentiation of azoospermia from severe oligospermia is accomplished by examination of the pellet of a centrifuged semen sample on at least two occasions. This review offers recommendations for diagnosing and defining the etiology of azoospermia. Patients with severe oligospermia may be evaluated in a similar manner.

Methodology

This best practice statement, *Evaluation of the Azoospermic Male,* is part of an updated series on male infertility prepared by the Male Infertility Best Practice Statement Panel (Appendix 1). Other titles include: *Best Practice Statement on Optimal Evaluation of the Infertile Male*, *Best Practice Statement on Management of Obstructive Azoospermia* and *Best Practice Statement on Varicocele and Infertility*. The first editions (2001) of these 4 reports were prepared by the Male Infertility Best Practice Policy Committee of the American Urological Association, Inc.® (AUA; Appendix 1) and the Practice Committee of the American Society for Reproductive Medicine. The two organizations agreed to collaborate to prepare documents of importance in the field of male infertility.

In October 2007, an updated assessment of the literature on male infertility by the AUA Practice Guidelines Committee (PGC) found insufficient outcomes data to support a formal meta-analysis

and an evidence-based guideline. The evidence was generally of a low level, being derived overwhelmingly from nonrandomized studies. Thus, the Male Infertility Best Practice Statement Panel, which included many of the members of the 2001 Committee, was created by the Board of Directors (BOD) of the AUA. The Panel was charged with developing a best practice statement, based on the previous report, by employing published data in concert with expert opinion. The Panel co-chairmen and members were selected by the PGC. The mission of the Panel was to develop recommendations, based on expert opinion, for optimal clinical practices in the diagnosis and treatment of male infertility. It was not the intention of the Panel to produce a comprehensive treatise on male infertility.

The Medline search spanning 1999 through October 2007 was supplemented by review of bibliographies and additional focused searches. In all, 341 articles were deemed by the Panel members to be suitable for scrutiny. Three of the four original 2001 reports were updated with new findings and are presented in the documents in colored font. The updated document was submitted for peer review, and comments from 21 physicians and researchers were considered by the Panel in making revisions. The final document has been approved by the AUA PGC and the BOD. Funding of the Panel was provided by the AUA; members received no remuneration for their work. Each Panel member provided a conflict of interest disclosure to the AUA.

Initial diagnosis of azoospermia

The initial diagnosis of azoospermia is made when no spermatozoa can be detected on high-powered microscopic examination of centrifuged seminal fluid on at least two occasions. *The World Health Organization (WHO) Laboratory Manual for the Examination of Human Semen and Semen-Cervical Mucus Interactions* recommends that the seminal fluid be centrifuged for 15

minutes at a centrifugation speed of, preferably, 3000 x g or greater.[4]

Recommendation 1: The diagnosis of azoospermia requires the absence of sperm from at least two separate centrifuged semen samples.

Differential diagnosis of the azoospermic patient

The evaluation of a patient with azoospermia is performed to determine the etiology of the patient's condition. This allows the physician to: 1) establish whether the cause of azoospermia is amenable to therapy; 2) identify appropriate treatment options; and 3) determine whether a significant medical disorder is the underlying cause of the azoospermia. The numerous etiologies for azoospermia fall into three categories: pre-testicular, testicular and post-testicular. Pre-testicular causes of azoospermia are endocrine abnormalities that adversely affect spermatogenesis (secondary testicular failure) and are relatively rare. Testicular etiologies (primary testicular failure) involve disorders of spermatogenesis intrinsic to the testes. Post-testicular etiologies of azoospermia are due to either ejaculatory dysfunction or obstruction of sperm delivery to the urethral meatus, and are found in approximately 40% of patients.[3] The pre-testicular and post-testicular abnormalities that cause azoospermia are frequently correctable. Testicular disorders are generally irreversible, with the possible exception of impaired spermatogenesis associated with varicoceles.

Initial evaluation of the azoospermic patient

To help differentiate between reversible and irreversible causes of azoospermia, the minimum initial evaluation of an azoospermic patient should include a complete medical history, physical examination and hormone level measurements. Relevant history includes: 1) prior fertility; 2) childhood illnesses such as viral orchitis or cryptorchidism; 3) genital trauma or prior pelvic or inguinal surgery; 4) infections such as epididymitis or urethritis; 5) gonadotoxin exposures such

as prior radiation therapy/chemotherapy, recent fever or heat exposure and current medications; and 6) family history of birth defects, mental retardation, reproductive failure or cystic fibrosis. Physical examination should note: 1) testis size (normal testis volume greater than 19 ml) and consistency; 2) secondary sex characteristics including body habitus, hair distribution and gynecomastia; 3) presence of and consistency of the vasa deferentia; 4) consistency of the epididymides; 5) presence of a varicocele; and 6) masses upon digital rectal examination. The initial hormonal evaluation should include measurement of serum testosterone and follicle-stimulating hormone (FSH) levels.

Recommendation 2: The minimum initial evaluation of an azoospermic patient should include a full medical history, physical examination, and measurement of serum testosterone and follicle-stimulating hormone levels.

Evaluation of specific conditions associated with azoospermia

The results of the initial evaluation will direct the strategy that must be used in order to determine the cause of the azoospermia. The following sections discuss the evaluation of several specific conditions associated with azoospermia.

Absence of the vasa deferentia (vasal agenesis)

The most common cause of congenital bilateral absence of the vas deferens (CBAVD) is a mutation of the cystic fibrosis transmembrane conductance regulator (CFTR) gene. Almost all males with clinical cystic fibrosis have CBAVD, and approximately 70% of men with CBAVD and no clinical evidence of a cystic fibrosis have an identifiable abnormality of CFTR gene.[5-6] Since normal vasa are easily palpable within the scrotum, the diagnosis of vasal agenesis, either bilateral or unilateral, is made by physical examination. Imaging studies and surgical exploration are not necessary to confirm the diagnosis, but may be useful for diagnosing abnormalities

associated with vasal agenesis. Due to the embryological association between the vasa and seminal vesicles, most patients with vasal agenesis also have seminal vesicle hypoplasia or agenesis. Since the majority of semen is derived from the seminal vesicles, almost all patients with CBAVD have low semen volume. In the azoospermic patient who has unilateral vasal agenesis, radiologic imaging with transrectal ultrasonography (TRUS) may be useful to evaluate the ampullary portion of the contralateral vas deferens and the seminal vesicles, because unilateral vasal agenesis can be associated with contralateral segmental atresia of the vas deferens or seminal vesicle, resulting in obstructive azoospermia.[7]

Both partners should undergo genetic counseling and testing of the CFTR gene to rule out abnormalities. Failure to identify a CFTR abnormality in a man with congenital bilateral absence of the vasa deferentia (CBAVD) however, does not absolutely rule out the presence of a mutation, since many mutations may not be detected by routine testing methods. Since it is assumed that most men with CBAVD harbor a genetic abnormality in the CFTR gene, whether or not their testing is positive, it is important to test the spouse for CFTR gene abnormalities prior to performing a treatment that utilizes his sperm because of the (approximately 4% in North American Caucasian) risk that she may be a carrier. Ideally, genetic counseling should be offered both before and after genetic testing of both partners. The main arguments for genetic testing of patients with CBAVD, regardless of whether or not they will be using their sperm for IVF is that this information is important for counseling the patient regarding future health effects of CFTR mutations[8-9] as well as counseling siblings about their risk of being carriers of CFTR mutations. There is a strong association between unilateral vasal agenesis and ipsilateral renal anomalies due to their common embryological origin. In contrast, the association of renal anomalies and congenital bilateral absence of the vasa deferentia (CBAVD) is much weaker with a prevalence

of only 11%. However, for those patients who have CBAVD and CFTR mutations the prevalence of renal anomalies is extremely rare.[10] Therefore, imaging of the kidneys with ultrasound or CT scan is most useful in men with unilateral vasal agenesis or men with CBAVD who do not have mutations in CFTR.

Recommendation 3: Men with congenital bilateral absence of the vasa deferentia should be offered genetic counseling and testing for cystic fibrosis transmembrane conductance regulator mutations. The female partner should also be offered cystic fibrosis transmembrane conductance regulator mutations testing before proceeding with treatments that utilize the sperm of a man with congenital bilateral absence of the vasa deferentia.

Recommendation 4: Imaging for renal abnormalities should be offered to men with unilateral vasal agenesis or congenital bilateral absence of the vasa deferentia and no evidence of cystic fibrosis transmembrane conductance regulator abnormalities.

Cystic fibrosis transmembrane conductance regulator testing

Cystic fibrosis transmembrane conductance regulator mutations are currently identified by searching for specific mutations. The CFTR gene (introns and exons) is extremely large and the number of mutations extremely numerous. Clinical laboratories typically test for the 30–50 most common mutations found in patients with clinical cystic fibrosis.[11] However, the mutations associated with CBAVD may be different. There are more extended panels that test up to 100 mutations available. Because over 1,300 different mutations have been identified in this gene, this type of limited analysis is only informative if a mutation is found. A negative test result only indicates that the CBAVD patient does not have the most common mutations causing cystic fibrosis. Direct sequence analysis of the entire gene is commercially available but very costly. In

addition to point mutations, variations of intron 8 of the CFTR gene where repeat sequences act as a rheostat controlling the expression of the CFTR protein can result in an abnormal phenotype. For instance, a polythymidine sequence located at the end of intron 8 that is only 5 bases long (5T allele), rather than 7 or 9, exacerbates skipping of exon 9, thereby reducing the production of functional protein.[12-13] In addition, there is an inverse relationship between the lengths of an adjacent thymidine-guanine (TG) repeat sequence that affects expression of CFTR when the 5T variant is present. Those individuals with the 5T variant adjacent to either 12 or 13 TG repeats are significantly more likely to exhibit CBAVD than individuals with only 11 TG repeats. Variants in the number of TG repeats only decreases CFTR production when the 5T allele is present. Therefore, testing for the TG repeat in a patient without the 5T variant has no clinical implication.

Recommendation 5: Testing for cystic fibrosis transmembrane conductance regulator abnormalities should include at minimum a panel of common point mutations and the 5T allele. There currently is no consensus on the minimum number of mutations that should be tested.

Recommendation 6: Gene sequencing may be considered in couples where the wife is a carrier and the husband with congenital bilateral absence of the vasa deferentia tests negative on a routine panel of cystic fibrosis transmembrane conductance regulator mutations.

Bilateral testicular atrophy

When accompanied by low serum testosterone levels, bilateral testicular atrophy is often associated with low semen volume. Bilateral testicular atrophy may be caused by either primary or secondary testicular failure. The results of the initial endocrine tests are used to distinguish

between these two possibilities. An elevated serum follicle stimulating hormone (FSH) level associated with either a normal or low serum testosterone level is consistent with primary testicular failure. All patients with these findings should be offered genetic testing for chromosomal abnormalities and Y-chromosome microdeletions. A separate, detailed discussion of genetic testing for men with non-obstructive azoospermia appears later in this document. A low serum FSH level associated with bilaterally small testes and a low serum testosterone level is consistent with hypogonadotropic hypogonadism (secondary testicular failure). These patients usually have low serum luteinizing hormone (LH) levels as well. Hypogonadotropic hypogonadism can be caused by hypothalamic disorders, e.g., congenital abnormalities such as Kallmann syndrome or acquired pituitary disorders, e.g., functioning and non-functioning pituitary tumors. Therefore, these patients should undergo further evaluation, including serum prolactin level measurement and imaging of the pituitary, with either CT or MRI.

Recommendation 7 (revised 7/22/11): All patients with non-obstructive azoospermia due to primary testicular failure should be offered genetic testing. Patients with acquired hypogonadotropic hypogonadism should be evaluated for functioning and non-functioning pituitary tumors by measurement of serum prolactin and imaging of the pituitary gland.

~~**Recommendation Deleted (7/22/11): All patients with azoospermia due to primary hypogonadism should be offered genetic testing. Patients with acquired hypogonadotropic hypogonadism should be evaluated for functioning and non-functioning pituitary tumors by measurement of serum prolactin and imaging of the pituitary gland.**~~

Ductal obstruction

When the vasa and testes are palpably normal, semen volume and serum FSH are key factors in determining the etiology of the azoospermia. Azoospermic patients with normal ejaculate volume may have either obstruction of the reproductive system or abnormalities of spermatogenesis. Azoospermic patients with low semen volume and normal sized testes may have ejaculatory dysfunction or ejaculatory duct obstruction.

Patients with normal ejaculate volume

The serum FSH of a patient with normal semen volume is a critical factor in determining whether a diagnostic testicular biopsy is needed to establish the presence or absence of normal spermatogenesis[14]. It is important to understand that the typical "normal" ranges listed on clinical laboratory reports were not necessarily determined from fertile men with normal semen parameters. In fact, FSH values in the upper normal range usually indicate impaired spermatogenesis while marked elevation of serum FSH is diagnostic of abnormal spermatogenesis – usually nonobstructive azoospermia. Although a diagnostic testicular biopsy will determine if spermatogenesis is impaired, it does not provide accurate prognostic information as to whether or not sperm will be found on future sperm retrieval attempts for patients with nonobstructive azoospermia. In addition, in cases of nonobstructive azoospermia, the presence or absence of sperm in a diagnostic testicular biopsy specimen does not absolutely predict whether sperm are present elsewhere in that or the opposite testis. Therefore, a testicular biopsy is not necessary to either establish the diagnosis or to gain clinically useful prognostic information for patients with clinical findings consistent with the diagnosis of nonobstructive azoospermia (i.e. testicular atrophy or markedly elevated FSH). Conversely, patients who have a normal serum FSH should undergo a diagnostic testicular biopsy, as a normal serum FSH level does not assure the presence of normal spermatogenesis.[14] This may be done at the time of an

attempt at reconstruction or separately. Although there is a well established inverse relationship between serum FSH levels and the probability of obstruction being the cause of azoospermia,[15] patients with normal or borderline elevated serum FSH levels may have either obstruction or abnormal spermatogenesis and should therefore, undergo a diagnostic testicular biopsy. It is acceptable to perform either a unilateral or bilateral testicular biopsy in these patients, as there is currently no clear consensus on this issue. If a unilateral biopsy is undertaken, it should be performed on the larger of the two testes.

Testicular biopsy can be performed by a standard open incision technique or by percutaneous methods. A routine open testicular biopsy, performed under local anesthesia, is the most common method. This should be performed through a small scrotal incision without delivering the testis outside the skin or tunica vaginalis. This minimizes postoperative scarring and therefore facilitates subsequent scrotal reconstructive surgery. The testicular biopsy specimen should be placed in an appropriate fixative such as Bouin's, Zenker's or glutaraldehyde. Formalin should not be used. At the time of a diagnostic or prognostic biopsy, it is possible to obtain a portion of testicular tissue for cryopreservation and use in a future in vitro fertilization /ICSI cycle, thus obviating the need for a second surgery.

If the testicular biopsy is normal, obstruction at some level in the reproductive system must be present and the location of the obstruction may then be determined. Most men with obstructive azoospermia, palpable vasa and no history suggesting iatrogenic vasal injury have bilateral epididymal obstruction. Epididymal obstruction can be identified only by surgical exploration. Vasography may be utilized to determine whether there is an obstruction in the vas deferens or

ejaculatory ducts. Because of the risk of vasal scarring and obstruction, vasography should not be performed at the time of diagnostic testicular biopsy, unless reconstructive surgery is undertaken at the same time.

> **Recommendation 8: In order to distinguish between obstructive and nonobstructive causes of azoospermia, diagnostic testicular biopsy is indicated for patients with normal testicular size, at least one palpable vas deferens and a normal serum follicle-stimulating hormone level. Vasography should not be performed at the time of diagnostic testicular biopsy unless reconstructive surgery is undertaken at the same time.**

Patients with low ejaculate volume

Low ejaculate volume (< 1.0 ml) that is not caused by hypogonadism or CBAVD (see previous sections) can be caused by ejaculatory dysfunction, but is most likely caused by ejaculatory duct obstruction (EDO). Ejaculatory dysfunction rarely, if ever, causes low ejaculate volume with azoospermia, although it is a well-known cause of aspermia or low ejaculate volume with oligospermia. Additional seminal parameters that can be helpful in determining the presence of EDO are seminal pH and fructose, since the seminal vesicle secretions are alkaline and contain fructose. However, the results of semen pH and fructose testing may be misleading when these tests are not properly performed and, therefore, many experts tend to give less weight to these parameters over other clinical findings.

Transrectal ultrasonography (TRUS) is indicated for the diagnosis of EDO in men with low ejaculate volume and palpable vasa. While vasography is an alternative diagnostic test for EDO, TRUS is minimally invasive and avoids the risk of vasal injury associated with vasography.[16]

The finding of midline cysts, dilated ejaculatory ducts and/or dilated seminal vesicles (greater than 1.5 cm in anteroposterior diameter) on TRUS is suggestive, but not diagnostic, of ejaculatory duct obstruction.[17-18] Conversely, normal seminal vesicle size does not completely rule out the possibility of obstruction. Therefore, seminal vesicle aspiration (SVA) and seminal vesiculography may be performed under TRUS guidance to make a more definitive diagnosis of EDO.[19] The presence of large numbers of sperm in the seminal vesicle of an azoospermic patient is highly suggestive of EDO. Seminal vesiculography performed concurrently with SVA can determine the anatomic site of the obstruction. Vasography with simultaneous examination of intravasal fluid for sperm, and simultaneous testicular biopsy constitute the alternative approach for diagnosing ejaculatory duct obstruction in the patient with low-ejaculate-volume azoospermia.

Recommendation 9 (Revised 7/22/11): Transrectal ultrasonography, with or without seminal vesicle aspiration and seminal vesiculography, should be considered as an initial minimally invasive diagnostic choice to identify ejaculatory duct obstruction in azoospermic men with low ejaculate volume and bilateral palpable vasa. In patients with ejaculatory duct obstruction demonstrated by TRUS, testis biopsy may be considered if needed to confirm normal spermatogenesis. Vasography with or without testicular biopsy should be considered a second line choice to identify the site of reproductive tract obstruction in these patients, and should not be done unless reconstructive surgery is undertaken at the same surgical procedure. Patients with unilateral absence of the vas and low volume azoospermia, may have a varient of CBAVD and should have CFTR and 5T testing and if positive do not need TRUS.

~~**Recommendation Deleted (7/22/11): Testicular biopsy may be performed to confirm the presence of reproductive tract obstruction in patients with low ejaculate volume azoospermia and palpable vasa. Transrectal ultrasonography, with or without seminal vesicle aspiration and seminal vesiculography, may be used to identify obstruction in the distal male reproductive tract. Alternatively, vasography may be used to identify the site of reproductive tract obstruction in patients with low ejaculate volume azoospermia and palpable vasa but should not be done unless reconstructive surgery is undertaken at the same surgical procedure.**~~

Genetic testing in patients with azoospermia

In addition to mutations in the CFTR gene that give rise to CBAVD, genetic factors may play a role in nonobstructive forms of azoospermia. The two most common categories of genetic factors associated with nonobstructive azoospermia are: 1) chromosomal abnormalities resulting in impaired testicular function; and 2) Y-chromosome microdeletions leading to isolated spermatogenic impairment.

Karyotype

A karyotype analyzes all chromosomes for the gain or loss of entire chromosomes as well as structural defects, including chromosome rearrangements (translocations), duplications, deletions, and inversions. Chromosomal abnormalities account for about 6% of all male infertility, and the prevalence increases with increased spermatogenic impairment (severe oligospermia and nonobstructive azoospermia). Paternal transmission of chromosome defects can result in pregnancy loss, birth defects, infertility in male offspring, and other genomic syndromes.

Recommendation 10: Karyotyping and genetic counseling should be offered to all patients with nonobstructive azoospermia and severe oligospermia (<5 million sperm/mL).

Y chromosome microdeletion

Approximately 13 % of men with nonobstructive azoospermia or severe oligospermia may have an underlying Y-chromosome microdeletion.[20] Y chromosome microdeletions responsible for infertility — regions AZF a, b, or c — are detected using sequence tagged sites (STS) and polymerase chain reaction analysis. There is no consensus on the number of STS's required for optimal detection of AZF deletions. Y chromosome microdeletions carry both prognostic significance for finding sperm and consequences for offspring if these sperm are utilized. Successful testicular sperm extraction has not been reported in infertile men with large deletions involving AZFa or AZFb regions but the total number of reports is limited.[21] However, up to 80% of men with AZFc deletions may have retrievable sperm for ICSI. Furthermore, the couple must be counseled on the inheritance of this compromised fertility potential in all male offspring.[22-23]

Recommendation 11: There are insufficient data to recommend a minimal number of sequence tagged sites to test for in patients undergoing Y chromosome microdeletion analysis. Although the prognosis for sperm retrieval is poor for patients with large deletions involving AZF region a or b, the results of Y chromosome deletion analysis cannot absolutely predict the absence of sperm.

Conflict of Interest Disclosure

All panel members completed Conflict of Interest disclosure. Those marked with (C) indicate that compensation was received; relationships designated by (U) indicate no compensation was received; (A) indicates affiliation.

Consultant or Advisor: Larry I. Lipshultz, Humagen (C), Pfizer (C), Lilly ICOS (C), Allergan (AU), Auxilium (AC); **Scientific Study or Trial:** Larry I. Lipshultz, Auxilium Prostate/T Study (AU), Auxilium Registry Study (AU); **Meeting Participant or Lecturer:** Larry I. Lipshultz, Solvay (C); Pfizer (C); Auxilium (AC**); Investigator:** Mark Sigman**,** GlaxoSmithKline (AC), **Other:** Peter Niles Schlegel, Theralogix (C), American Board of Urology (AU)

Acknowledgements and Disclaimers

The Evaluation of the Azoospermic Male: Best Practice Statement

The supporting systematic literature review and the drafting of this document were conducted by the Infertility Best Practice Statement Panel (the Panel) created in 2007 by the AUA. The PGC of the AUA selected the Panel chair who in turn appointed the additional Panel members with specific expertise in evaluation of the infertile male. The mission of the Panel was to develop either analysis- or consensus-based recommendations, depending on the type of evidence available and Panel processes, to support optimal clinical practices concerning the infertile male. This document was submitted to 58 urologists and other health care professionals for peer review. After revision of the document based upon the peer review comments, the best practice statement guideline was submitted to and approved by the PGC and the BOD of the AUA. Funding of the Panel and of the PGC was provided by the AUA. Panel members received no remuneration for their work. Each member of the PGC and of the Panel furnished a current conflict of interest disclosure to the AUA. The final report is intended to provide medical practitioners with a current understanding of the principles and strategies for the evaluation of the azoospermic male. The report is based on review of available professional literature as well as clinical experience and expert opinion. This document provides guidance only and does not establish a fixed set of rules or define the legal standard of care. As medical knowledge expands and technology advances, this best practice statement will change. Today they represent not absolute mandates but provisional proposals or recommendations for treatment under the specific conditions described. For all these reasons, this best practice statement does not preempt physician judgment in individual cases. Also, treating physicians must take into account variations in resources, and in patient tolerances, needs and preferences. Conformance with the

best practice statement reflected in this document cannot guarantee a successful outcome.

Appendix 1. Male Infertility Best Practice Statement Panel

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This best practice statement is intended to provide medical practitioners with a consensus of principles and strategies for the care of couples with male infertility problems. The document is based on current professional literature, clinical experience and expert opinion. It does not establish a fixed set of rules or define the legal standard of care and it does not preempt physician judgment in individual cases. Physician judgment must take into account variations in resources and in patient needs and preferences. Conformance with this best practice statement cannot ensure a successful result.

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