REVIEW ARTICLE

Autism

A Review of the State of the Science for Pediatric Primary Health Care Clinicians

William J. Barbaresi, MD; Slavica K. Katusic, MD; Robert G. Voigt, MD

Autism is a complex neurodevelopmental disorder characterized by impaired reciprocal social interaction, impaired communication, and restricted, repetitive, or stereotyped behaviors. Autism seems to affect more children than was previously believed, although this phenomenon may be due to broadening of the diagnostic criteria and increased awareness of the condition. Recent research has clearly indicated the importance of early identification, since early intensive treatment is associated with better long-term outcome. There are many controversies and competing theories about the etiology and treatment of autism, often leaving families confused about the best course of treatment and intervention. Pediatric primary health care clinicians have an important role in both the early identification and ongoing management of children with autism. It is, therefore, essential that primary care clinicians have up-to-date information about the science of autism. *Arch Pediatr Adolesc Med. 2006;160:1167-1175*

WHY A REVIEW ON AUTISM?

Autism and related conditions in the autism spectrum have become the focus of intense interest fueled by concerns about the apparent increase in the number of children with these developmental disorders.[1,2] Pediatricians have an important role in the identification and ongoing management of children with autism. This article provides pediatric clinicians with a contemporary understanding of autism, including definitions, epidemiology, initial identification, formal diagnostic approaches, medical evaluation, treatment, controversies, and caregiver support.

WHAT IS AUTISM?

Autism, first described in 1943, is a complex developmental disorder characterized by severe impairment in reciprocal social interaction and communication and by a pattern of repetitive or stereotyped behavior.[3,4] The *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision* (*DSM-IV, TR*) includes autistic disorder in the broader category of pervasive developmental disorders, along with pervasive developmental disorder, not otherwise specified (PDD-NOS), Asperger's disorder, Rett's disorder, and childhood disintegrative disorder.[3] Autistic disorder, PDD-NOS, and Asperger's disorder are often collectively referred to as the autism spectrum disorders (ASDs), while the term autism is used interchangeably with the *DSM-IV, TR* term autistic disorder. The term ASDs reflects the notion that these conditions are related and may be difficult to differentiate with current diagnostic tools.[5-8] Pervasive developmental disorder, not otherwise specified is a somewhat ill-defined diagnosis of exclusion reserved for children with problems similar to those seen in autistic disorder but insufficient to meet the criteria for autistic disorder in number, severity, or age at onset.[3,6,7]

The diagnostic criteria for autism require the presence of 6 symptoms from 3 categories: impaired reciprocal social in-

Author Affiliations: Departments of Pediatric and Adolescent Medicine, Division of Developmental and Behavioral Pediatrics (Drs Barbaresi and Voigt), and Health Sciences Research, Division of Epidemiology (Dr Katusic), and Mayo Clinic–Dana Child Development and Learning Disorders Program (Drs Barbaresi, Katusic, and Voigt), Mayo Clinic College of Medicine, Rochester, Minn.

Table 1. Diagnostic Criteria for Autistic Disorder*

A. A total of ≥6 items from the following criteria 1, 2, and 3, with at least 2 from criterion 1 and 1 each from criteria 2 and 3
  1. Qualitative impairment in social interaction as manifested by at least 2 of the following:
    a. Marked impairment in the use of multiple nonverbal behaviors such as eye-to-eye gaze, facial expression, body posture, and gestures to regulate social interaction
    b. Failure to develop peer relationships appropriate to developmental level
    c. Lack of spontaneous seeking to share enjoyment, interests, or achievements with other people (eg, lack of showing, bringing, or pointing out objects of interest)
    d. Lack of social or emotional reciprocity
  2. Qualitative impairments in communication as manifested by at least 1 of the following:
    a. Delay in or total lack of development of spoken language (not accompanied by an attempt to compensate through alternative modes of communication such as gesture or mime)
    b. In individuals with adequate speech, marked impairment in the ability to initiate or sustain a conversation
    c. Stereotyped and repetitive use of language or idiosyncratic language
    d. Lack of varied, spontaneous make-believe play or social imitative play appropriate to developmental level
  3. Restricted, repetitive, and stereotyped patterns of behavior, interests, and activities as manifested by at least 1 of the following:
    a. Encompassing preoccupation with 1 or more stereotyped and restricted patterns of interest that is abnormal either in intensity or focus
    b. Apparently inflexible adherence to specific, nonfunctional routines or rituals
    c. Stereotyped and repetitive motor mannerisms (eg, hand or finger flapping or twisting, or complex whole-body movements
    d. Persistent preoccupation with parts of objects
B. Delay or abnormal functioning in at least 1 of the following areas, with onset before age 3 years:
  1. Social interaction
  2. Language as used in social communication
  3. Symbolic or imaginative play
C. Disturbance not better accounted for by Rett's disorder or childhood disintegrative disorder

*Reprinted with permission from the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision*.[3]

Table 2. Autism-Specific Screening Tools

Screening Tool	Characteristics
Checklist for Autism in Toddlers (CHAT)	For use in children aged 18 mo; 14 items, 9 derived from parent history and 5 from direct observation; specificity 98%, sensitivity 38%; does not discriminate well between children with autism and children with mental retardation
Social Communication Questionnaire (formerly called Autism Screening Questionnaire)	For use in children aged ≥4 y
Modified Checklist for Autism in Toddlers (M-CHAT)	For use in children aged 24 mo; 23 items, all based on parental report; specificity 87%, sensitivity 99%; efficient for use in a primary care setting

teraction (at least 2 symptoms), impaired communication, and restricted, repetitive, or stereotyped behaviors (**Table 1**). These criteria reflect the central role of deficits in social behavior in children with ASDs.[3,9,10] One of the earliest and most important indicators of autism is the failure to develop joint attention,[7,11,12] which refers to the child's ability to share interests, pleasurable experiences, or requests by using gestures or verbal communication in combination with eye contact with another person.

EPIDEMIOLOGY

There is widespread public concern about the apparent increase in autism, based on prevalence studies during the last 20 years.[1,13-17] Studies from the 1980s and early 1990s reported a prevalence of 4 to 10 per 10 000 children, whereas recent studies have reported prevalences of 30 to 50 per 10 000 children.[1,13-18] Studies that rely on administrative data for children who receive special education services have reported significant increases in prevalence from 1992 to 2001.[19] A recent study in a single US county demonstrated an apparent increase in the incidence of research-identified autism among individuals 21 years of age or younger, from 5.5 per 100 000 in the 1980-1983 period to 44.9 per 100 000 in the 1995-1997 period.[1] The advantage this incidence study had over previous prevalence studies was in its reporting rates of newly identified cases in the same community over many years with the use of consistent *DSM-IV, TR*–based research criteria for case identification. The timing of this apparent increase coincided with the introduction of broader diagnostic criteria, increased availability of educational services, and increased awareness of autism. These findings were not consistent with the hypotheses that immunization policy or the vaccine preservative thimerosal have contributed to this epidemiologic phenomenon.[1,20] A recent review also noted the absence of published literature that demonstrates increased rates of autism in children who have been immunized with vaccines containing thimerosal.[20] A study from the United Kingdom also concluded that the observed increase in the rate of diagnosis of pervasive developmental disorder is likely the result of better case ascertainment rather than a true increase in autism.[21]

IDENTIFICATION OF AUTISM BY PEDIATRIC PRIMARY HEALTH CARE CLINICIANS

Early identification of autism is important because early intervention services may be more effective in children with autism than in children with other developmental disabilities.[22] Pediatric clinicians are ideally positioned to assume this role, aided by practice guidelines for the diagnosis and management of ASDs in children.[7,23,24] A 2-level approach to autism screening and diagnosis is recommended.[7] In children who fail routine developmental screening, specific screening for autism should be performed[25-28] (**Table 2**). In children who fail specific autism screening, referral for a formal evaluation by an experienced clinician is recommended. Referral is also recommended for any child who does not babble or point or use other gestures by the age

of 12 months, who uses no single words by 16 months or no spontaneous (nonecholalic) 2-word phrases by 24 months, or who experiences any loss of any language or social skills at any age.[7]

Deficits in joint attention differentiate infants with autism from those with mental retardation or typical development.[29-32] These behaviors include deficits in the following areas: eye contact, orientation to name being called, pointing, and showing. In the toddler age group, a lack of pretend play and imitation, deficits in nonverbal communication, and disproportionate language delays differentiate autism from other developmental disorders.[7] Although repetitive behaviors, stereotypic motor mannerisms, atypical sensory responses, and behavioral outbursts are generally observed in children with autism, these behaviors do not consistently differentiate autism from other developmental disorders at early ages.[7]

The Modified Checklist for Autism in Toddlers (M-CHAT) has been developed as an autism-specific screening tool for use in 24-month-old children (Table 2).[33-36] It consists of 23 items based on parental report, which makes this checklist efficient for use in primary care settings. Other promising screening instruments include the Pervasive Developmental Disorders Screening Test–II[37] and the Screening Tool for Autism in Two-Year Olds.[38] For children who are 4 years or older, the Social Communication Questionnaire may be used as an autism screening instrument.[7,27,28]

Children with autism can also be identified by a characteristic early developmental profile, with relative strengths in visuomotor problem solving and discrepant and disproportionate weaknesses in language.[39-50] The Cognitive Adaptive Test/Clinical Linguistic and Auditory Milestone Scale (Capute Scales) provides quantitative information about a child's development in the domains of language and visuomotor problem solving and can be used efficiently for this purpose in primary care settings.[51]

DIAGNOSING AUTISM

A comprehensive, multidisciplinary assessment is required to evaluate a child for an ASD and to differentiate ASDs from other developmental disorders.[5-7,12,52] Since there are no definitive diagnostic tests, a clinical diagnosis by an expert, based on *DSM-IV, TR* criteria, remains the gold standard of ASD diagnosis.[6,7,12,52] The *DSM-IV, TR* criteria consist of a list of behaviors that are not described in detail, leaving considerable latitude for clinical judgment.[3,7,12] Children who have been evaluated exclusively by school or early intervention staff should not be considered to have undergone a thorough diagnostic assessment. This can be confusing to both parents and pediatricians, given the existence of the explicit special education category "Autism Spectrum Disorders" (Individuals with Disabilities Education Act [IDEA] 97, Pub L No. 105-17).[53] An ASD designation for special education purposes may be obtained without a clinical diagnosis of an ASD. Furthermore, children with autism or PDD-NOS often have severe cognitive, communicative, and behavioral problems that can only be assessed by a team of professionals (**Table 3**). The clinical diagnosis of an ASD is facilitated by the use of rating scales and direct assessment tools specifically developed for this purpose (**Table 4**).[54-59]

Approximately 60% to 75% of children with autistic disorder or PDD-NOS have cognitive skills in the mentally retarded range (standard scores <70 on formal cognitive tests).[1,3] Fewer children with PDD-NOS are likely to function in the mentally retarded range.[52] Children with autism or PDD-NOS often demonstrate relative strength in visual problem-solving skills and relative weakness in language-based cognitive skills; this discrepant cogni-

Table 3. Professionals Who May Be Included in Multidisciplinary Assessment for Autism

Discipline	Role
Developmental and behavioral pediatrician, child psychiatrist, child neurologist or neurodevelopmental disabilities pediatrician	Clinical diagnostic assessment based on *DSM-IV, TR* criteria, case coordination for medical workup and treatment
Child psychologist	Psychometric testing, administration of Autism Diagnostic Observation Schedule if indicated
Speech pathologist	Formal speech, language, and communication assessment
Medical geneticist	Clinical dysmorphology examination, coordination of genetic and metabolic testing
Physiatrist, occupational therapist, physical therapist	Assessment of fine and gross motor disorders and development of treatment recommendations
Medical social worker	Assessment of family resources, coordination of services, family support

Abbreviation: *DSM-IV, TR, Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision.*

Table 4. Autism-Specific Diagnostic Tools

Instrument	Characteristics
Autism Diagnostic Interview-Revised (ADI-R)*	Semistructured interview that is reliable, valid, and differentiates autism from other developmental disorders; takes 1½ h to administer, limiting clinical use
Autism Diagnostic Observation Schedule-Generic (ADOS-G)*	Reliable, valid, direct assessment that helps to differentiate ASDs from other developmental disorders; requires specific training; takes 30 min to administer, making it practical for clinical use
Gilliam Autism Rating Scale	Checklist that may be used by parents and teachers and other professionals to quantify autism symptoms
Childhood Autism Rating Scale	Structured interview and observational tool designed to be used by experienced clinicians or other professionals to identify symptoms consistent with ASDs

Abbreviation: ASDs, autistic spectrum disorders.
*Neither the ADI-R nor the ADOS-G is sufficient to enable a diagnosis of autism. The diagnosis depends on assessment by an experienced clinician.

Table 5. Cognitive Assessment Tools

Bayley Scales of Infant Development
Mullen Scales of Early Learning
Differential Abilities Scales
Stanford-Binet IV
Wechsler Scales of Intelligence for Children, Fourth Edition
Leiter International Performance Scale–Revised*
Merrill-Palmer Scale*

*May be more appropriate for use in nonverbal children.

Table 6. Medical and Genetic Evaluation of Children With Autism

Required evaluations
Careful examination to identify dysmorphic physical features
Wood's lamp examination for tuberous sclerosis
Formal audiologic evaluation
Lead test; repeat periodically in children with pica
High-resolution karyotype
Molecular DNA testing for fragile X syndrome
Consider if results of above evaluations are normal, and in children with comorbid mental retardation
FISH test for region 15q11q13 to rule out duplications in Prader-Willi/Angelman syndrome region
FISH test for telomeric abnormalities
Test for mutations in *MECP2* gene (Rett syndrome)
Metabolic testing to consider based on other clinical features
Fasting blood glucose
Plasma amino acids
Ammonia and lactate
Fatty acid profile, paroxysmal
Carnitine
Acylcarnitine, quantitative
Homocysteine
Plasma 7-dehydrocholesterol (Smith-Lemli-Opitz disease screening)
Urine amino acids
Urine organic acids
Urine testing for purines and pyrimidines
Urine acylglycine, random
Other testing to consider based on clinical features
Liver enzymes
Thyroxine, thyroid-stimulating hormone
Biotinidase
Complete blood cell count
Ceruloplasmin and serum copper
Electroencephalography if the following clinical features are noted
Clinically observable seizures
History of significant regression in social or communication functioning

Abbreviation: FISH, fluorescent in situ hybridization.

tive profile may be reflected in a significant discrepancy between verbal and performance IQ scores.[3,7,39-50,52] Formal cognitive assessment should be completed using instruments that have been demonstrated to be appropriate[60-67] (**Table 5**).

Similarly, formal speech and language assessment is essential because communication deficits of varying severity are always present in children with ASD.[3,7,12] Children with ASD may have specific deficits in the social use of language, often referred to as pragmatic language.[3,7,12] For example, a child may be able to recite long segments of dialogue from a favorite video yet not be able to use a 3-word sentence to ask for something to eat. Problems with pragmatic language are often identified only by a careful history or direct observation of the child in his or her natural environment.[3,7,12]

Social-adaptive behavioral assessments should include assessment of functional skills such as sleeping, eating, and toileting and problem behaviors such as aggression, oppositionality, and self-injury. This assessment is facilitated by the use of formal questionnaires and rating scales including, among others, the Vineland Adaptive Behavior Scales and the Scales of Independent Behavior.[68,69] Formal assessments of fine and gross motor skills may be incorporated into the evaluation as indicated. Parent resources should be carefully assessed to enable the team to understand the context of the child's developmental problems and to ensure that plans are made to provide appropriate support to the family.

MEDICAL EVALUATION OF CHILDREN WITH AUTISM

Every child with autism should undergo a formal audiologic evaluation, whether or not the child passed a newborn hearing screening test. In addition, children with autism are at risk of lead toxicity, given their high prevalence of putting objects in their mouths.[70] Thus, periodic lead screening should be performed until pica resolves.[7]

Although a recognizable etiologic disorder is found in fewer than 25% of individuals with autism, attempts to establish an etiologic diagnosis to account for this clinical syndrome are important to identify diagnoses that may affect prognosis, risk of recurrence, and associated medical morbidity. A thorough history and physical examination should guide the medical diagnostic workup[71-77] (**Table 6**). Since tuberous sclerosis accounts for up to 3% to 4% of autism cases, Wood's lamp examinations should be performed in every child with autism to detect the hypopigmented macules associated with this syndrome, especially if the child has an intercurrent seizure disorder.[78] While routine head imaging (computed tomography or magnetic resonance imaging) is not recommended, recent studies have reported abnormal patterns of brain growth in individuals with autism.[79] Functional imaging techniques are currently used as research tools but are not indicated in routine clinical practice.[7,80,81]

Autism has been associated with many genetic syndromes, including Down syndrome, Angelman syndrome, de Lange syndrome, Smith-Magenis syndrome, and Smith-Lemli-Opitz syndrome.[82,83] Seven percent to 8% of individuals with autism have fragile X syndrome.[84] In addition, anomalies in almost every chromosome have been reported in individuals with autism, although more consistent linkage findings have been associated with chromosomes 2q, 7q, and 15q.[85] Thus, DNA testing for fragile X syndrome and high-resolution chromosome analyses are recommended in the laboratory workup in children with autism, especially those with mental retardation, dysmorphic features, congenital anomalies, or a family history of autism or mental retardation.[7,84] Fluorescent in situ hybridization testing for specific chromosome deletions, duplications, or inversions

should be considered if initial investigations produce negative results[84-87] (Table 6). Even in the absence of a specific genetic diagnosis, the recurrence rate in siblings of children with autism is between 2% and 8%, increasing the risk of having a second child with autism nearly 50-fold over that in the general population.[84]

Although a wide range of inborn errors of metabolism have been associated with autistic behavior, less than 5% of children with autism have identifiable metabolic disorders.[88-93] Thus, metabolic testing is particularly indicated when the autistic behaviors are accompanied by a history of developmental plateauing or regression; decompensation with mild illness, unusual odors, or food intolerance; failure to thrive; episodic lethargy; cyclic vomiting; seizures; coarse features; mental retardation; questionable newborn screening results; or birth outside the United States[7] (Table 6).

By adulthood, about one third of individuals with autism will have at least 2 unprovoked epileptic seizures.[82] Onset of seizures in individuals with autism follows a bimodal age distribution, with peaks in early childhood and adolescence.[7,94] All seizure types, including infantile spasms, can be associated with autism, but partial complex seizures, with electroencephalographic abnormalities occurring most often over the temporal lobes, appear to be most prevalent.[95] About one third of parents of children with autism report regression of language in their children, most commonly the loss of their toddler's first few words, between age 18 and 24 months.[94,96] Approximately 10% of children with autism also have a paroxysmal electroencephalographic pattern similar to that seen in Landau-Kleffner syndrome (acquired epileptic aphasia) or electrical status epilepticus during slow-wave sleep.[94] While there have been reports of the use of anticonvulsant therapy and even epilepsy surgery, there is insufficient evidence to recommend routine electroencephalography in all children with autism.[97-99] Indications for prolonged sleep-deprived electroencephalography with adequate sampling of slow-wave sleep are listed in Table 6.[7]

EDUCATIONAL AND BEHAVIORAL INTERVENTIONS

Pediatricians have an important role in helping to guide families toward intervention approaches that have been empirically demonstrated as effective.[5,52,100] In the Internet era, families have access to virtually limitless information about treatments and interventions for autism. Since family resources of time, energy, and finances are limited, it is essential to ensure that these resources are directed toward interventions that offer the best hope for improved outcome.

The Individuals with Disabilities Education Act mandates educational services for children in the special education category of Autism Spectrum Disorders.[52] The provisions of the Individuals with Disabilities Education Act do not, however, ensure that children will receive empirically validated interventions of appropriate intensity. There is, therefore, considerable variability in the quality of educational interventions for children with ASD. This is an additional important reason for pediatricians to understand and advocate for optimal services.

Decades-worth of scientific research provide clear and convincing support for the technique referred to as Applied Behavior Analysis (ABA).[5,100] This technique uses the principles of operant conditioning to teach specific social, communicative, and behavioral skills to children with ASD.[5,100] It involves teaching new behaviors by explicit reinforcement of these behaviors; problem behaviors are often addressed by carefully analyzing triggers or antecedents of the problem behavior in order to change the factors in the environment that are contributing to the problem behavior. Applied Behavior Analysis also uses careful collection of data to demonstrate the efficacy of treatment in the individual child; the data are used to assess progress and to continually modify the intervention as the child progresses toward specific learning objectives.[101]

Interest in ABA as a primary, comprehensive treatment approach in children with ASD was sparked by the research of Lovaas,[102,103] who reported that 9 (47%) of 19 young children with autism who received intensive, early ABA (40 hours per week for ≥2 years) had outcomes that were indistinguishable from their normally developing peers.[103] Subsequent studies have led many experts in the field to conclude that intensive ABA is an effective intervention but that it is unlikely that 50% of children who receive early, intensive ABA will achieve completely normal developmental outcomes.[100,104-107] Practice guidelines have used these and other research findings to formulate recommendations on the key features of appropriate intervention for children with autism.[5,52,100] Characteristics of effective intervention are believed to include a minimum of 20 hours per week of carefully organized services initiated at an early age (preferably younger than 4 years) and involving direct adult attention in individual or very small group instruction.[5,7,52,100] Recent studies have concluded that intensity of intervention is important (ie, a minimum of 20 hours per week) and that ABA is superior to other intervention strategies.[100,108]

Another intervention model with a long history and well-defined instructional methods is TEACCH (Treatment and Education of Autistic and Related Communication Handicapped Children).[109] The TEACCH approach takes advantage of relative strengths in visual information processing, characteristic of many children with ASD, using strategies such as visual schedules, clearly structured and organized classrooms, and highly structured learning activities that are broken down into manageable, visually organized steps. Published reports demonstrate improvement in behaviors and functional skills and parent satisfaction with the TEACCH approach.[52,109,110] However, there appear to be no direct studies of treatment outcomes attributable to TEACCH interventions.

While other intervention strategies are often recommended, there do not appear to be approaches that have the empirical support of ABA or the long history and well-developed curricula of TEACCH. The weight of currently available scientific evidence, however, indicates that ABA should be viewed as the optimal, comprehensive treatment approach in young children with ASD.

Pediatricians should also be aware of sensory integration therapy because this approach is often used in spe-

cial education programs. Interest in sensory integration is related to the observation that children with ASD often exhibit unusual sensory responses, such as hypersensitivity to certain noises. Techniques used in this therapy include "brushing" of the skin, "swinging" to stimulate vestibular responses, and deep-pressure massage applied in an effort to calm the child.[52] There is no available empirical support for sensory integration therapy, and it should, therefore, neither be routinely recommended nor viewed as a primary intervention strategy in children with ASD.[5,52]

Many other unproved nonmedical therapies have been recommended for use in children with autism. There is no evidence to support the use of facilitated communication, auditory integration training, or music therapy.[5,111-115]

MEDICAL INTERVENTIONS FOR CHILDREN WITH AUTISM

Although psychopharmacologic therapies have been studied for more than 50 years, there are no Food and Drug Administration–approved indications for the treatment of autism with any agent and there is no medication available for treatment of the core deficits in communication and social interaction.[116] In addition, when used to treat similar target behaviors, psychotropic medications tend to be less effective and result in more adverse effects when used in children with autism compared with children without autism because of similar target behavioral symptoms. However, there is an evidence base for prescribing risperidone to assist in managing tantrums, aggression, and self-injurious and stereotypic behaviors and for prescribing methylphenidate to manage inattentive, impulsive, and hyperactive behaviors in children with autism.[117,118] To date, there is insufficient evidence to support the use of selective serotonin reuptake inhibitors, α_2-adrenergic agonists, or mood stabilizers, despite reports of their effectiveness in managing target behavioral symptoms in some children with autism in short-term open-label trials with small sample sizes.[119-121] Psychotropic medications should never be used in isolation but used only in conjunction with behavioral, educational, and habilitative therapies.[122] If psychotropic medications are used, initial dosage should be low, with gradual increases in dosage until optimal positive effects, without significant adverse effects, are achieved.

UNPROVED THEORIES OF CAUSATION AND UNPROVED OR INEFFECTIVE TREATMENTS IN CHILDREN WITH AUTISM

Traditional medicine does not offer a cure for autism. As a result, unproved complementary and alternative treatments are often provided to children with autism by parents who are seeking effective biomedical interventions.[123] Patients with chronic conditions with unclear pathophysiologic features, fluctuating courses, highly subjective symptoms, and few effective evidence-based treatments are most vulnerable to the placebo effect.[124] Such is clearly the case in autism, and unproved explanations of causation and unproved therapies abound.

One example is the controversy about whether the mercury-containing compound thimerosal, which has been included in certain vaccines to protect multiple-dose vials from bacterial and fungal contamination, is related to the increased prevalence of autism.[125] However, no children with autism have been reported to have an abnormal body burden of mercury or an excess of mercury in hair, urine, or blood.[126] Neither the clinical signs and symptoms of mercury-induced neurologic damage nor the neuropathologic changes associated with mercury exposure parallel the clinical signs and symptoms of autism.[20] Population-based studies have also shown that the risk of autism in children given thimerosal-containing vaccines is no different from that in children given thimerosal-free vaccines.[20,127] Further, since thimerosal was removed from childhood vaccines in Denmark in 1992, the incidence of autism in that country has continued to rise.[128] Despite this overwhelming scientific evidence, some children with autism are receiving treatment with chelating agents.[129] However, even if exposure to mercury or other heavy metals was causative of autism, chelation therapy has not been found to improve the neurodevelopmental sequelae of heavy metal toxicity.[130] Also, children being treated with chelating agents are at risk of renal and hepatic toxic adverse effects.[129]

There have been concerns about the potential role of the measles-mumps-rubella (MMR) vaccine in the causation of autism, based on findings that have been partially retracted.[131] This theory hypothesizes that the MMR vaccine produces enterocolitis, causing "leaky gut," which then leads to increased absorption of peptides with bioactive properties of endogenous opioids that produce the symptoms of autism.[123] However, large-scale epidemiologic studies have failed to show an association between the MMR vaccine and autism.[1,132-135] Furthermore, a dramatically increased incidence of autism has been associated with the withdrawal of the MMR vaccine in Japan.[135] Despite strong evidence against an association between either thimerosal or MMR vaccines and autism, fear generated by these scientifically disproved theories may be leading more parents to decline to have their children immunized.[136]

The leaky gut hypothesis has also led to unproved claims that variants of celiac disease, yeast overgrowth, and immunologic abnormalities can cause autism.[123,129] Many children with autism have been given very restrictive gluten- and casein-free diets because of unfounded fears that opioidlike peptides derived from gluten and casein are absorbed through their leaky guts and can be detected in their urine. However, children with autism have not been found to have an increased rate of celiac disease and do not have excessive amounts of opioidlike compounds in their urine.[137-142]

Although hypothesized as another cause of leaky gut, fungal overgrowth in the intestines has not been documented at endoscopy in children with autism.[143] While there is no evidence that systemic antifungal medications improve autistic behavior, these medications are associated with liver toxicity, anemia, diarrhea, and exfoliative dermatitis.[123,129]

It has been hypothesized that autism is an autoimmune disorder; however, treatment with intravenous immunoglobulin has not proved effective.[144] The pancreatic hormone secretin has also been proposed as a

treatment of autism. However, more than a dozen published, peer-reviewed, randomized, double-blind, placebo-controlled trials have failed to show secretin to be effective in treating the symptoms of autism.[129] Other medical therapies that have been recommended but that do not have sufficient evidence to support their effectiveness or safety include vitamin and mineral supplements (vitamin B_6 and magnesium, vitamin C, vitamin B_{12}, and folic acid), amino acid and peptide supplements (dimethyl glycine and carnosine), and ω-3 long-chain polyunsaturated fatty acids.[129]

Clinicians should counsel parents of children with autism to be sure that any treatment they may consider is supported by evidence from randomized, double-blind, placebo-controlled clinical trials published in the peer-reviewed medical literature. Families should be informed about potential health risks associated with unproved therapies. Finally, parents should be reminded that such treatments may take time, effort, and financial resources away from effective, evidence-based interventions.

FAMILY AND CAREGIVER SUPPORT

Families that include a child with one of the ASDs experience considerable stress as they are confronted with extraordinary demands on their time, energy, and financial resources. It is essential to offer clear explanations of diagnostic findings and treatment recommendations and to guide families toward effective treatment approaches. This requires the combined effort of experts in the ASD field working collaboratively with primary care clinicians.

Parents need reliable sources of information about ASDs. This is particularly important in an era when the Internet makes misinformation as easily available as accurate information. The Web sites sponsored by the Autism Society of America (www.autism-society.org/site/PageServer), TEACCH (www.teacch.com), and the National Institute of Child Health and Human Development (www.nichd.nih.gov/publications/pubs/autismfacts.pdf) are particularly useful sources of reliable information. However, even accurate information about ASDs is subject to misinterpretation because of the inherent complexity of the topic and the many unanswered questions in the field. There is no substitute for knowledgeable professionals who provide ongoing advice in the context of regular primary care management of children with ASDs.

Accepted for Publication: May 5, 2006.
Correspondence: William J. Barbaresi, MD, Departments of Pediatric and Adolescent Medicine, Division of Developmental and Behavioral Pediatrics, Mayo Clinic College of Medicine, 200 First St SW, Rochester, MN 55905 (barbaresi.william@mayo.edu).
Author Contributions: *Study concept and design:* Barbaresi, Katusic, and Voigt. *Drafting of the manuscript:* Barbaresi, Katusic, and Voigt. *Critical revision of the manuscript for important intellectual content:* Barbaresi, Katusic, and Voigt. *Administrative, technical, and material support:* Barbaresi, Katusic, and Voigt. *Study supervision:* Barbaresi.
Financial Disclosure: None reported.

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