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Celiac Disease: The Past, the Present, the Future

Alessio Fasano

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COMMENTARIES

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Celiac Disease: The Past, the Present, the Future

ABBREVIATIONS. CD, celiac disease; HLA, human leukocyte antigen; EmA, antiendomysium antibodies; TJ, tight junction; TTG, tissue transglutaminase.

Celiac disease (CD) is an autoimmune enteropathy triggered by the ingestion of gluten-containing grains (ie, wheat, barley, and rye) in susceptible individuals. Both *in vivo* challenges and *in vitro* immunologic studies support the possibility that oat (once considered toxic for CD patients) can be safely ingested.¹ However, because of uncontrolled harvesting and milling procedures, a cross-contamination of oat with gluten is a concern. It is the gliadin fraction of wheat gluten, and similar alcohol-soluble proteins in other grains, that are the environmental factors responsible for the development of the intestinal damage. The disease is associated with human leukocyte antigen (HLA) alleles DQA1*0501/DQB1*0201, and in the continued presence of gluten the disease is self-perpetuating.² The typical intestinal damage characterized by loss of absorptive villi and hyperplasia of the crypts completely resolves on elimination of gluten-containing grains from the patients' diet. CD represents a common cause of malabsorption in western countries with apparent geographic variation in incidence.

THE PAST

In the second century AD, Aretaeus from Capadocia described what is believed to be the first report of a gastrointestinal condition resembling CD.³ Approximately 1700 years later, the connection between the ingestion of certain cereals and the onset of gastrointestinal symptoms typical of CD was established.⁴ For the past 18 centuries, CD has been perceived as a disease whose clinical presentation was quite uniform. The case identification was entirely based on the search for symptoms such as chronic diarrhea, abdominal distension, and weight loss (or poor weight gain) occurring in young children a few weeks/months after the introduction of solid food to their diet. Therefore, early epidemiologic studies targeted the pediatric population experiencing this typical clinical presentation of the dis-

ease. In the past 5 decades, a substantial number of epidemiologic studies have been conducted in Europe to establish the frequency of CD, and interesting controversies have arisen. One of the oldest epidemiologic studies on CD conducted in 1950 established that the cumulative incidence of the disease in England and Wales was 1/8000, while an incidence of 1/4000 was detected in Scotland.⁵ The diagnosis at that time was entirely based on the detection of typical symptoms and confirmed by complicated and sometimes nonspecific tests. The awareness of the disease greatly increased in the 1960s when more specific tests for malabsorption and the pediatric peroral biopsy technique became available.⁶ Consequently, an elevated incidence of the disease (that in the middle 1970s reached peaks of 1/450–500) was reported in studies from Ireland,⁷ Scotland,⁸ and Switzerland.⁹ This increased incidence of CD urged changes in the dietary habit, based on the hypothesis that delayed exposure to gluten could prevent the onset of the disease. For the first time in 25 years a decrease in the incidence of CD was reported in the United Kingdom and Ireland^{10,11} after a late introduction of gluten in the infants' diet. Unfortunately, this decrease was deceptive, because subsequent screening studies demonstrated that the reduction of typical cases in infants was counterbalanced by the increase of atypical forms of CD with the onset of the symptoms occurring in older children or in adults.¹²

THE PRESENT

In the past 10 to 15 years, we learned that the clinical expression of CD is more heterogeneous than previously thought.¹³ Besides the classical gastrointestinal form, a series of other clinical manifestations of the disease have been described, thanks to the advent of innovative serologic screening tests such as antigliadin and antiendomysium (EmA) antibodies assays. The combined use of serum antigliadin immunoglobulin G (highly sensitive) and immunoglobulin A (highly specific) and the confirmation with the EmA test resulted in a reliable screening algorithm to study the epidemiology of CD.¹⁴ Based on the use of these new tools, we have learned that the clinical presentation of CD is more protean than previously thought, including previously unrecognized atypical and asymptomatic forms. Moreover, these studies demonstrated that CD is not limited to the pediatric population, but the disease may become clinically apparent during adulthood after years of silent disease. The European experience taught that, despite common genetic and environmental factors, the clinical presentation of CD in neighboring countries may greatly diverge and could justify the dif-

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Reprint requests to (A.F.) Center for Celiac Research, University of Maryland School of Medicine, 685 W Baltimore St HSF Bldg, Rm 465, Baltimore, MD 21201. E-mail: afasano@umaryland.edu
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ferent prevalence of the disease previously reported.¹⁵⁻¹⁹ A similar explanation seems to account for the rare prevalence of CD previously reported in the United States.^{20,21} Recent studies conducted by using more appropriate experimental designs and powerful screening tools demonstrated that CD in the United States is as frequent as in Europe in both risks groups²²⁻²⁶ and the general population.^{26,27} Similar results were obtained in Africa,²⁸ South America,²⁹ and Asia,^{30,31} continents where CD was considered a rare disorder. Combined together, these studies revealed that CD is one of the most frequent genetically-based diseases of humankind^{32,33} occurring in 1 out of every 100 to 300 individuals in the general population worldwide.^{26,27,34}

Major progress has also been achieved on the pathogenesis of the disease. It is now evident that CD is the result of an inappropriate T-cell mediated immune response against ingested gluten. Under physiologic circumstances, the intestinal epithelium with its intact intercellular tight junctions (TJs) serves as the main barrier to the passage of macromolecules such as gluten. During this healthy state, quantitatively small but immunologically significant fractions of antigens cross the defense barrier. These antigens are absorbed across the mucosa along 2 functional pathways. The vast majority of absorbed proteins (up to 90%) crosses the intestinal barrier through the transcellular pathway, followed by lysosomal degradation that converts proteins into smaller, nonimmunogenic peptides. The remaining portion of peptides is transported as intact proteins, resulting in antigen-specific immune responses. This latter phenomenon uses the paracellular pathway that involves a subtle but sophisticated regulation of intercellular TJ that leads to antigen tolerance. When the integrity of the TJ system is compromised, such as in CD,^{35,36} an immune response to environmental antigens (ie, gluten) may develop. The upregulation of zonulin, a recently described intestinal peptide involved in TJ regulation,³⁷ seems to be responsible, at least in part, for the increased gut permeability characteristic of the early phase of CD.³⁸ This zonulin-dependent increased permeability may also be responsible for the increased incidence of autoimmune disorders reported in untreated CD patients³⁹

Another important factor for the intestinal immunologic responsiveness is the major histocompatibility complex. HLA class I and class II genes are located in the major histocompatibility complex on chromosome 6. These genes code for glycoproteins, which bind peptides, and this HLA-peptide complex is recognized by certain T-cell receptors in the intestinal mucosa.^{40,41} Susceptibility to at least 50 diseases, including CD, has been associated with specific HLA class I or class II alleles. The primary HLA association in CD is to the HLA-DQA1*0501, DQB1*0201 genes encoding DQ2 molecules.² Interestingly, it seems that non-HLA genes together contribute more to genetic susceptibility than do the HLA genes, but the contribution from each single, predisposing non-HLA gene appears to be modest.⁴²

Dieterich et al⁴³ have recently demonstrated that the target of the EmA is the tissue transglutaminase (TTG). The deamidating activity of this enzyme seems to generate gliadin peptides that bind to DQ2 to be recognized by disease-specific intestinal T cells.⁴²

Because TTG is the target of a specific autoimmune response,⁴² this enzyme has also been used to develop innovative diagnostic tools. The routine use of the EmA assay is limited by elevated costs, the time-consuming protocols unsuitable for testing large numbers of samples, and the use of the esophagus of an endangered species (such as the monkey) as the substrate for the immunofluorescent analysis. Even if this last issue has been resolved by using the human umbilical cord as a valid alternative to the monkey esophagus,²⁷ it has been reported that the subjective interpretation of the EmA assay may lead to unacceptable variability among laboratories that perform this test.⁴⁴ Therefore, major effort has been placed on the development of a TTG-based enzyme-linked immunosorbent assay, using either the commercially-available guinea pig TTG^{45,46} or human recombinant TTG.^{47,48}

THE FUTURE

A multidisciplinary research effort to understand the pathogenesis of CD is currently taking place worldwide. This effort is fueled by the appreciation that CD represents a unique example of an autoimmune disease in which the environmental factor(s) that induces the immune response has been identified. Therefore, scientists view CD as a model to tackle key questions on the pathogenic mechanisms involved in other autoimmune diseases (ie, multiple sclerosis, diabetes mellitus, rheumatoid arthritis, etc) whose environmental triggers are still unknown. Future directions in CD research have been clearly identified and recently discussed at the Ninth International Symposium on Celiac Disease that was held August 10-13 in Baltimore, Maryland⁴⁹ (Table 1). Although some of these goals are in an advanced state of development (ie, engineering gluten-free grains), others (ie, the search for the CD genes) are extremely challenging and will require an international task force to generate meaningful data. Nevertheless, the appreciation that CD is a global problem affecting not only Europe, but also continents, such as North and South America, Africa, and Asia, where it was historically considered an extremely rare condition, is catalyzing the scientific attention of

TABLE 1. Research Priorities Identified at the Ninth International Symposium on Celiac Disease

Area of Research
1. Hunting for the CD genes
2. Developing a vaccine against CD
3. Who, when, and how to screen for CD
4. Engineering gluten-free grains
5. Preventing zonulin-dependent increased intestinal permeability
6. Developing noninvasive, fast, and reliable tests for the diagnosis and follow-up of CD

new generations of investigators that will surely contribute to achieve these challenging targets.

ALESSIO FASANO, MD
Center for Celiac Research and Division of Pediatric
Gastroenterology and Nutrition
University of Maryland Hospital for Children
Baltimore, MD 21201

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Adolescent Hepatitis B Immunization: Making It Simpler

ABBREVIATIONS. ACIP, Advisory Committee on Immunization Practices; HBs, hepatitis B surface; HBV, hepatitis B vaccine.

In October 1999 the Advisory Committee on Immunization Practices (ACIP) recommended a new regimen for hepatitis B immunization of individuals 11 to 15 years old, using two (2) 1.0-mL 10- μ g doses of Recombivax (Merck Research Laboratories, Blue Bell, PA) on a 0 and 4- to 6-month schedule.¹ The Canadian National Advisory Committee on Immunization made similar recommendations in 2000.² These recommendations were made after the results of studies showing that 2 doses of vaccine were similar in terms of antibody concentrations, seroprotection rates, and rates of adverse events to 3 doses of vaccine. One limitation, however, was that no data were available on the issues of long-term protection or immune memory equivalence of the 2 schedules. The article by Cassidy et al³ in this issue of *Pediatrics* adds meaningful and practical data to the ACIP recommendation for a 2-dose adolescent hepatitis B immunization strategy, and provides an answer to the question of immune memory induction by the 2-dose schedule.

In the study by Cassidy et al, 1026 adolescents 11 to 19 years old were enrolled and randomized to 1 of 5 Recombivax active immunization groups (10 μ g at 0 and 4 months or 0 and 6 months, or 5 μ g at 0 and 6 months or 0, 2, and 4 months or 0, 1, and 6 months).³ A subset of study participants who had received 5- μ g doses at 0 and 6 months or 0, 1, and 6 months had blood samples drawn 2 years after the last dose to determine antibody persistence, and received a 5 μ g "booster" dose of vaccine to assess immune memory. The results generally followed the large body of literature already known on the major issues; namely that higher doses, 3 versus 2 doses, and longer intervals between doses lead to higher antibody levels. However, the results demonstrated no difference in the percent seroprotected (defined as developing ≥ 10 mIU/mL of anti-hepatitis B surface [anti-HBs]), after any of the regimens. Many practitioners may not be aware that the absolute height of the antibody level may be clinically less meaningful, compared with the percent who reach an anti-HBs antibody level ≥ 10 mIU/mL.^{4,5} These data provide additional confidence that higher antibody levels per se may be of less importance compared with the rate of seroprotection induced by the vaccine while allowing for fewer doses to be administered. Similarly, no significant differences between regimens for any adverse experience was found, with the exception of

a posthoc comparison that found a higher rate of transient injection site reactions after the first 10- μ g dose, compared with the 5- μ g dose (30% vs 19.9%; $P < .001$).

An important issue addressed in this study is that of induction of immune memory. Anamnestic antibody responses were found in 92% of the 0- and 6-month schedule study participants, and 95% of the 0-, 1-, and 6-month study participants. The data of Cassidy et al provide reassurance that immunologic memory, at least 2 years later, is present and results in an anamnestic antibody response. In turn, this allows confidence that a 2-dose immunization schedule is likely to be equally effective in providing long-term protection against symptomatic hepatitis B infection and chronic carriage of the virus.

Until recently, official recommendations were for 3 doses of vaccine on a 0-, 1-, and 6-month schedule, regardless of age.⁶ Although this regimen is safe, immunogenic, and efficacious, it is nonetheless both burdensome and expensive. The increasing number of vaccines listed on the vaccine schedule, the increasing role of cost issues, and the difficulty of delivering 3 doses over a 6-month time period have all conspired to hamper efforts at fully protecting this population against this vaccine-preventable disease. Difficulties in delivering a full 3 doses are evidenced by a chart review performed at the Kaiser Permanente adolescent clinic, which documented that only 11% of the adolescents counseled about the need for hepatitis B vaccine (HBV) actually received 3 doses of the vaccine.⁷ Clinical and public health experience suggests that the number of persons completing a vaccine series decreases as more doses are included. The first large-scale school-based HBV program that attempted to offer vaccine to over 43 000 students, while successful, nonetheless had over 5% (almost 2000 students) who did not complete the series, although this was a closely managed prospective study.⁸ A statewide hepatitis B immunization program in Oregon, targeting all adolescents 11 to 18 years old reported that almost 92% of students completed 2 doses of vaccine, while only 84% completed 3 doses.⁹ A recent report of students attending either a clinic-based or school-based adolescent clinic in Boston demonstrated that <50% of the study participants completed the 3-dose series within 12 months of the first dose.¹⁰ In fact, by 26 months after the first dose, only 72% had received 3 doses of vaccine while almost 88% had managed to receive 2 doses. Additionally, study participants receiving Medicaid and study participants who were not white had increased time to completion of the series, suggesting that increased numbers of poor and minority participants at high risk for infection, might be better protected with a 2-dose regimen.

As Cassidy et al point out, additional advantages of a 2-dose regimen include reduced cost both of vaccine purchase, and the resources necessary to deliver vaccine. Additionally, a regimen involving only 2 doses over a 4-month time period is likely to be better received psychologically, and result in higher rates of compliance, than a 3-dose, 6-month regimen. As universal immunization is likely to occur in

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Reprint requests to (G.A.P.) Department of Medicine, Clinical Pharmacology and Infectious Diseases, Mayo Vaccine Research Group, 611C Guggenheim Bldg, 200 First St SW, Rochester, MN 55905. E-mail: poland.gregory@mayo.edu

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school-based settings,¹¹ a 2-dose, 4- to 6-month schedule also allows for more realistic completion within a school year, whereas a 3-dose schedule imposes constraints on timing of doses within a given school year. In fact, the benefits of a 2-dose strategy are congruent with the recommendations from a recent independent nonfederal Task Force on Community Preventive Services designed to improve vaccination coverage among children, adolescents, and adults.¹²

Numerous studies have documented the relationship between diminished antibody response to the vaccine and increasing age at the time of receipt.^{13,14} Thus, an advantage to immunizing adolescents that is not well-appreciated at the clinical or public health population level are data demonstrating that increasing age has an adverse effect on the rate of seroprotection as was also shown in this current study.³ In this study, the authors demonstrate that age was the single factor found in logistic regression analysis to be associated with a lower proportion of participants achieving antibody levels of ≥ 10 mIU/mL of anti-HBs ($P = .03$) and a lower geometric mean (antibody) titer ($P < .001$). Younger (age: 11–15 years) children demonstrated higher rates of seroprotection and higher geometric mean (antibody) titers (two-fold higher) than children 16 to 19 years old. Thus, starting the series before the age of 15 years, with the convenience of a 2-dose regimen, offers enhanced and early seroprotection. By “getting 2 doses rather than 3 doses later,” the effect may be to decrease the age at which the vaccine is sought by parents and encouraged by health care providers, thereby improving rates of protection.

A summary of the advantages that a 2-dose regimen offers includes: 1) lower cost compared with 3 doses, 2) better compliance leading to higher rates of immunity among the adolescent population—particularly hard to reach sub-populations,¹⁵ 3) equal immunogenicity in terms of seroprotection, compared with a 3-dose regimen 4) higher rates of seroprotection after one (1) 10- μ g dose compared with the 5- μ g 3-dose regimen, 5) equal evidence of induction of immunologic memory compared with the standard regimen, and 6) a potential safety factor with less doses and less chance for an allergic or adverse reaction. In addition, a 2-dose regimen allows for further efficiency by making it possible to combine the hepatitis A and B vaccines into 1 formulation for adolescents, just as in infants.¹⁶

The work by Cassidy et al is an important observation and has meaningful and practical clinical utility for health care providers who care for adolescent patients. This data confirms previous data that led to the ACIP recommendation for adolescents. All providers should adopt the 2-dose regimen for adolescents 11 to 15 years old as it is safe, effective, requires fewer visits and numbers of injections, and therefore decreases health care costs. Nonetheless, caution dictates that we should recognize the lack of data supporting this recommendation for adolescents in specific groups, particularly those with preexisting risk factors for vaccine failure.^{5,17} Whether such persons should have 2 or 3 doses is unclear. Prudence would

suggest that if only 2 doses are administered to individuals at high risk of vaccine failure, anti-HBs testing should be performed 1 to 3 months after the last dose to determine vaccine success or failure. Having now achieved success with a 2-dose regimen, what the world really needs is a 1-dose HBV.

GREGORY A. POLAND, MD
Mayo Vaccine Research Group
Mayo Clinic and Foundation
Rochester, MN 55905

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Guidelines for Preparedness of Emergency Departments That Care for Children: A Call to Action*

ABBREVIATIONS. ACEP, American College of Emergency Physicians; AAP, American Academy of Pediatrics; ED, emergency department; EMS, emergency medical services; EMSC, Emergency Medical Services for Children.

In this month's issues of *Pediatrics* and *Annals of Emergency Medicine*, there is a policy statement from the American College of Emergency Physicians (ACEP) and the American Academy of Pediatrics (AAP) on guidelines for preparedness of emergency departments (EDs) that care for children.¹ This joint effort by 2 large professional organizations to tackle the issue of preparedness for children seeking emergency care should be applauded. The ACEP, in its review of policies related to emergency care for children, recognized the need to unify these policies in a single document. The AAP also recognized that a policy addressing emergency care for children nationally was an important concept. Both the ACEP and the AAP are committed to quality care for the patients served by its members and this policy statement reflects that commitment.

Now that the policy statement is in print, one might ask several questions:

Why is there a need for this policy statement?

Who should implement this policy statement?

Let's direct our attention to the first question: *Why is there a need for this policy statement?* In 1984 Seidel and colleagues² noted that pediatric patient "needs" were not being met by emergency medical services (EMS) systems that included prehospital and ED care. Their study showed that death rates from trauma were higher for children (12%) compared with adults (7%). They also showed that 22% of all pediatric patients seen in EDs were transported to a second facility, indicating a possible lack of necessary services at the first hospital.² These data, as well as subsequent studies comparing frequency of advanced life support treatment use by prehospital providers for adult and children, highlight differences in care received by pediatric patients.³⁻⁶ It is not clear from these data whether the differences in care rendered for children have a true effect on patient outcomes or whether differences in outcomes are attributable to underlying differences in the cause and severity of illness and injury in adults and children.⁷ Although use of advanced skills in this setting may seem appropriate, a recent prospective study of advanced airway management in children showed a detriment in patient outcome for children in selected subgroups receiving endotracheal intuba-

tion versus the basic skill of bag-mask ventilation.^{8,9} Finally, it is neither practical nor financially feasible for all hospitals to have pediatric subspecialty and intensive care capability.

Other data addressing emergency preparedness have been obtained from surveys.^{10,11} The federal Emergency Medical Services for Children (EMSC) Program worked with the Consumer Product Safety Commission to survey hospitals through the Consumer Product Safety Commission National Electronic Injury Surveillance System to study distribution of pediatric services, the location of emergency care for children, availability of pediatric specialists, and availability of appropriately sized equipment.¹⁰ The sample of 101 hospitals surveyed was designed to represent the approximately 5300 hospitals in the United States with 24-hour emergency services. Athey and colleagues¹⁰ showed that 7% of hospitals routinely admitted critically injured children requiring intensive care to adult intensive care units, rather than transferring them to a facility with a pediatric intensive care unit. In addition, appropriately sized equipment for care of pediatric patients was more likely to be missing than comparable equipment for adult patients.

McGillivray and colleagues¹¹ performed a survey of more than 700 EDs in Canada and found that pediatric resuscitation equipment was often unavailable. Specifically, intraosseous needles were unavailable in 16% of the EDs, pediatric drug dose guidelines in 7%, infant blood pressure cuffs in 15%, pediatric defibrillator paddles in 10%, infant warming devices in 59%, infant bag-valve masks in 4%, infant laryngoscope blades in 4%, 3-mm endotracheal tubes in 2%, and pediatric pulse oximeters in 18%.¹¹ They also conducted onsite surveys of equipment at 38 hospitals and found that equipment was generally even less available than the written survey indicated. Smaller, low pediatric volume EDs were 3 to 5 times more likely to be missing equipment compared with higher pediatric volume EDs. The cost of pediatric equipment, being less than \$1000 (Canadian), was not felt to be a barrier to availability at these hospitals.¹¹

The Institute of Medicine Report on EMSC also concluded that agencies with jurisdiction over hospitals should "require that hospital EDs . . . have available and maintain equipment and supplies appropriate for the emergency care of children."¹²

Both the ACEP and the AAP have addressed issues of facility preparedness for care of children and, in the case of the ACEP, for patients of all ages seeking emergency care.¹³⁻¹⁶ The ACEP's policy statement on emergency care guidelines states that "hospital EDs must possess the staff and resources necessary to evaluate all persons presenting to the ED."¹⁴ In addition, a number of guidelines for preparedness have been promulgated by the federal EMSC Program and states seeking to regionalize pediatric care.¹⁷⁻²⁰ In 1995, the AAP published guidelines that categorized facilities into different levels in their policy statement entitled "Guidelines for Pediatric Emergency Care Facilities."¹⁵ This categorization defines 4 different levels of services for emergency care facilities, including Standby, Basic, General, and Comprehensive Regional Pediatric

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Address correspondence to Marianne Gausche-Hill, MD, Harbor-UCLA Medical Center, 1000 W Carson St, Box 21, Torrance, CA 90509. E-mail: mgausche@emedharbor.edu

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Center.¹⁵ Each of these policies has addressed the issue of preparedness of the ED to care for children in different ways. Despite these efforts, the need for universally accepted guidelines to achieve pediatric emergency readiness remains.

Some EMS systems have opted for regionalization of pediatric care in an attempt to bring children to the “right place at the right time”; however, these plans do not necessarily affect triage practices of parents for their children. Parents often bring their children to the closest emergency facility, regardless of that facility’s preordained category of emergency capability. It is also true that most children are brought to EDs not affiliated with a children’s hospital or other tertiary care facility, because there are almost 90 times the number of EDs as children’s hospitals.¹⁰ An appreciation of these statistics is important if one wants to develop an effective strategy for improving the availability of pediatric resources. One would not want parents with a critically ill child to bypass capable EDs to bring them to the tertiary care facility when a delay in seeking care could result in added morbidity or mortality. Nor should a parent bypass hospital EDs on the basis of insurance issues for similar reasons. Finally, EMS administrators must balance the risk of additional minutes in transport of a critically ill or injured child to a pediatric tertiary care facility and the benefit of additional pediatric resources available at that facility. Thus, it may be prudent to adopt a strategy that ensures that all hospitals that serve as pediatric receiving facilities for emergency care, no matter their size, pediatric volume, or inpatient services, be prepared to handle the pediatric patient who may enter their doors and that protocols and transfer agreements are in place to ensure timely transfer of critically ill or injured children to the facility with subspecialists available to meet the complex needs of certain pediatric patients. The promotion of this strategy is the goal the “Care of Children in the Emergency Department: Guidelines for Preparedness” policy statement that is published in this month’s issues of *Pediatrics* and *Annals of Emergency Medicine*.

Now to address the second question: *Who should implement this policy statement?* The simple answer to this question is all emergency physicians, pediatricians, administrators, hospital accrediting organizations, and health care organizations that are vested in quality care for children. This policy statement empowers emergency physicians and pediatricians to address the preparedness of their facility for the care of children with their hospital and health maintenance organization administrators. It is hoped that a statement by these 2 major professional organizations, whose members care for many of the nation’s children, will be implemented widely by hospitals and hospital accrediting organizations. Some EMS systems may opt to further expand on these guidelines, as has been done in California; however, this policy statement is intended to serve as the benchmark. As an emergency medicine community, let’s embrace it by implementing them. It is through such joint efforts that we can strive to improve care for children.

MARIANNE GAUSCHE-HILL, MD
UCLA School of Medicine
Harbor-UCLA Medical Center
Department of Emergency Medicine
Torrance, CA 90509

ROBERT A. WIEBE, MD
University of Texas Southwestern Medical Center
Children’s Medical Center at Dallas
Division of Emergency Medicine
Department of Pediatrics
Dallas, TX 75390

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Alessio Fasano

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