Risk Factors in Preventable Adverse Drug Events in Pediatric Outpatients

STEPHANIE O. ZANDIEH, MD, MS, DONALD A. GOLDMANN, MD, CAROL A. KEOHANE, RN, BSN, CATHERINE YOON, MS,
DAVID W. BATES, MD, MSC, AND RAINU KAUSHAL, MD, MPH

Objective To determine whether there are racial/ethnic, socioeconomic, parental linguistic, or parental educational disparities in children who experienced an adverse drug event (ADE) in the ambulatory setting.

Study design We conducted a prospective cohort study of pediatric patients <21 years seen during 2-month study periods from July 2002 to April 2003 at 6 office practices in Boston. The primary outcome measure was ADEs. Descriptive analysis of patient characteristics and types of ADEs experienced was followed by multivariate analysis to determine risk factors associated with presence of a preventable ADE.

Results A total of 1689 patients receiving 2155 prescriptions were analyzed via a survey and chart review. Overall, 242 children (14%) experienced an ADE, of which 55 (23%) had a preventable ADE and 186 (77%) had a non-preventable ADE. In multivariate analysis, children with multiple prescriptions (odds ratio, 1.46; 95% CI, 1.01-2.11) were at increased risk of having a preventable ADE, controlling for parental education, racial/ethnic, English proficiency, practice type, and duration of care.

Conclusions Children with multiple prescriptions are at increased risk of having a preventable ADE. Further attention should be directed toward improved communication among healthcare providers and patients. *(J Pediatr 2008;152:225-31)*

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Two reports from the Institute of Medicine have called attention to the need to improve patient safety and the substantial racial and ethnic disparities in healthcare.[1,2] Medications are the most common medical therapy and the most frequent cause of adverse events.[3] Adverse events caused by medication errors occur in about 1% of pediatric hospitalizations[4]; less is known about the ambulatory care setting.

Medication errors are defined as errors in any step of the medication process, and each step is particularly complex and error-prone for children. For example, adult medications typically have 1 standard dose with 1 type of preparation (ie, tablet or capsule). In contrast, pediatric medications involve weight-based dosing requiring calculations and often multiple preparations (ie, infant drops, elixir, chewable tablets, and capsules). At the administration and monitoring stages, young children cannot reliably self-administer or monitor medication use. Moreover, younger children lack the communication skills to tell parents about adverse effects, and an extra step is involved even for older children. The pivotal role of parents as intermediaries between the prescribing physician may be affected by parental linguistic, socioeconomic, or educational challenges and cultural attitudes and belief.[5] A crucial step toward prevention of medication errors is identifying risk factors.

Health care disparities represent a pervasive national problem, affecting health care access, use, and clinical outcomes. Race and ethnicity have been shown to be intimately tied to characteristics such as socioeconomic status (SES), cultural factors such as limited English proficiency (LEP),[5,6] and the child's health needs such as perceived health status and chronic illnesses.[7] Black and Hispanic children are less likely than white children to have a regular source of medical care. Furthermore, non-English speaking families are less likely than English-speaking families to report a regular source of medical care for their children.[8-10] Among hospitalized pediatric patients, those whose parents had LEP had a

ADE	Adverse drug events	OR	Odds ratio
LEP	Limited-English proficiency	SES	Socioeconomic status

From the Department of Pediatrics, Weill Cornell Medical College and Komansky Center for Children's Health at New York Presbyterian Hospital, New York, New York (S.Z., R.K.); Department of Medicine, Children's Hospital Boston, Boston, Massachusetts (D.G.); Institute for Healthcare Improvement, Cambridge, Massachusetts (D.G.); Harvard Medical School, Boston, Massachusetts (D.G., D.B., R.K.); Division of General Internal Medicine, Brigham and Women's Hospital, Boston, Massachusetts (C.K., C.Y., D.B., R.K.); Information Systems, Partners Healthcare System, Boston, Massachusetts (D.B.); and Department of Public Health, Weill Cornell Medical College, New York, New York (R.K.).

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Reprint requests: Dr Stephanie Zandieh, Division of Pediatrics, Weill Cornell Medical College, 525 E 68th St, Box 139, New York, NY 10021. E-mail: stz2001@med.cornell.edu.

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2-fold increase in risk for an unintended or potentially adverse outcome.[11] Earlier literature has also found that individuals who have LEP also face significant health literacy challenges.[12] Individuals with low functional health literacy often are unable to read and correctly interpret instructions on medication bottles.[13-15]

To date, relatively little research has examined whether there are increased risks of adverse drug events for vulnerable children in the ambulatory setting, where children receive most medical care.[16] Therefore, we undertook this study to examine the rates and types of preventable ADEs and determine whether there are racial/ethnic, socioeconomic, linguistic, or educational disparities for children who experience an ADE in the pediatric ambulatory care setting.

METHODS

Definitions

Medication errors can be categorized as errors with little potential for harm (medication errors), errors with significant potential for harm (near misses), and errors with actual harm (preventable ADE).[4,17] One example of a preventable ADE would be delay in giving a child a necessary antibiotic for a serious infection, resulting in worsening symptoms requiring a visit to the emergency department for intravenous antibiotics. This complication could have been prevented had the parents given the antibiotic appropriately. ADEs not associated with errors are considered non-preventable ADEs. An example of a non-preventable ADE occurs when parents give the appropriate doses of antibiotics for a bacterial infection and their child develops diarrhea, which represents a well-known adverse effect of antibiotics.

Population and Setting

The study population was a prospective cohort of patients <21 years old who were seen from July 2002 to April 2003, in Boston, as previously described.[18] Six diverse practice sites were sampled: 2 associated with a teaching hospital, 2 urban health clinics, and 2 suburban practices. Children <21 years old who had an office visit during the study period, received at least 1 prescription, and spoke English, Spanish, or Cambodian were eligible. Patients seen multiple times during the study period were included only once. All prescriptions for oral contraceptives and possible treatment for sexually transmitted diseases were excluded because of concerns about patient privacy. Prescriptions for equipment and formula were also excluded. Furthermore, we excluded patients when they opted out of the study, did not meet study criteria, were lost to follow-up, or had incomplete data. This study received human subjects' approval by Weill Cornell Medical College of Cornell University and Brigham and Women's Hospital.

Data Collection

We collected data from practice data sources (review of duplicate prescriptions, chart review, and administrative data) and telephone surveys. At the time of the patient's clinic visit, families were asked to participate in the study. Ten to 14 days after that visit, the patient's parents (or main caregivers for the child) were telephoned and asked to read the labels of all prescription bottles and report about any new symptoms that might be related to a drug. When any symptoms were reported, further structured questions were asked about timing and any actions the parent took (eg, stopping the medication, telling their child's pediatrician). Then, approximately 3 months after the index visit, a research nurse examined the child's medical chart to confirm ADEs or medication errors detected on telephone interview, discover previously undetected ADEs, and collect additional patient data regarding comorbidities, disease severity, medication regimens, and preexisting conditions.

Outcome Measures

The primary outcome measure was the presence of a preventable ADE, defined as actual harm from medication use. All ADEs identified by a trained research nurse were presented to a pair of physician reviewers who independently categorized these events into medication errors, near misses, and ADEs. ADEs were identified and classified by using an established and validated protocol used in several earlier studies.[4,17,19,20] Physician reviewers reconciled discordance through discussion and consensus. Each ADE was further defined as either preventable (associated with a medication error) or non-preventable (not associated with a medication error), and given a severity rating. The kappa statistics for inter-rater reliability were 0.89 for classification of event, 0.75 for severity of event, and 0.95 for preventability of event.

Predictors

Our primary predictor variables were gathered from telephone surveys. These included: race/ethnicity, reported annual family income, parental educational attainment, and parental self-reported English proficiency. Race/ethnicity was obtained with the question, "Which of the following describes your child's race?" (white, black, Hispanic, or other).[21] Annual reported family income was obtained with the question, "What is your average yearly income?" (≤$30,000, $30,000-49,999, $50,000-79,999, and >$80,000). Parental educational attainment was obtained with the question, "What is the highest level of education you have completed?" (less than high school, high school graduate, some college, and college graduate/post-graduate). Self-reported English proficiency was determined with the question, "How well do you think you speak English?" (very well, well, poorly, and not at all).[5,22] English proficiency was defined as "proficient" when the response was very well, and "LEP" combined responses well, poorly, and not at all.

Independent variables of interest were gathered from telephone survey and chart review. These included the child's sociodemographic characteristics (age, sex, health status, presence of a chronic disease, and Medicaid status), the family's

Table I. Demographics of patients eligible for initial survey

	Non-respondents of initial survey (n = 1801)	Respondents of initial survey, 10 day follow-up, and chart review (n = 1689)	
	n (%)	n (%)	*P* value
Female sex	912 (51%)	835 (50%)	.53
Age			
Neonates	38 (2%)	41 (2%)	.0004
Infants	442 (25%)	455 (27%)	
Toddlers	580 (32%)	511 (30%)	
School age	547 (30%)	565 (33%)	
Adolescents	194 (11%)	117 (7%)	
Race/Ethnicity			
White	910 (50%)	815 (49%)	.0001
Black	328 (18%)	256 (15%)	
Hispanic	445 (25%)	343 (21%)	
Other	115 (6%)	239 (5%)	
Missing	3 (<1%)		
Insurance			
Medicaid	271 (15%)	213 (13%)	.04
Non-Medicaid	1530 (85%)	1476 (87%)	

Because of rounding, some categories may not total 100%.
There were 92 participants who had a 10-day follow-up, but not a chart review, and therefore were not included in this analysis.

poverty status (above or below the 2003 Department of Health and Human Services poverty guidelines), health care access (practice site and continuity of care), and medication regimen complexity (number of prescriptions at index visit). Health status was obtained with the question, "In general how would you rate your child's health at the present time?" (excellent, very good, good, poor, and fair).[23] Presence of a chronic disease was determined with the question, "Does your child have a chronic or long-term health condition (a condition lasting longer than 3 months)?" (yes/no). Continuity of care was determined through chart review, in which the duration of continuous care at the office practice was recorded. Poverty status was calculated by taking a family's annual income and number of family members, comparing them with the 2003 poverty guidelines issued by the Department of Health and Human Services,[24] and then classifying families in 2 groups, either less than the Federal Poverty Level or higher than the Federal Poverty Level.

Statistical Analysis

We analyzed all patients who participated in the 10-day survey and had a chart review, particularly because parental report is a critical method for detection of preventable ADEs. Five percent of patients who had the initial survey did not have a chart review because of the lack of the medical chart. We report rates of ADEs and preventable ADEs per 100 patients. Descriptive statistics were used to examine child and parental characteristics associated with the occurrence of ADEs and preventable ADEs. The associations of independent variables with each outcome variable were assessed with univariate analysis with the χ^2 or Fisher exact (categorical data) or Student t (continuous data) tests ($P < .05$ was considered significant). SAS software (SAS Institute, Cary, NC) was used for statistical analysis.

Next, we assessed for correlation between our predictor variables and found all to be statistically correlated. However, the highest correlation was found between annual income and parental education ($r = .67$, $P \leq .001$).To reduce collinearity, in multivariate analysis, we included only parental education and not annual income in our final model.

Our multivariate analyses compared children who experienced a preventable ADE with children without any ADE. Through this analysis, we identified among all children receiving a medication prescription risk factors (patient/family, medication, healthcare system) associated with a preventable ADE. Logistic regression with a forward stepwise approach was performed; variables with a P value $<.05$ and variables that were part of our *a priori* hypothesis were retained. The final model included these independent variables: race/ethnicity, parental educational attainment, parental English proficiency, continuity of care, practice type, and number of prescriptions. We also performed a similar analysis that assumed an over-dispersion of preventable ADEs per person relative to a Poisson distribution and found no significant difference in results, thus we report only our logistic analyses.

RESULTS

Population Characteristics

During the study period, 21,209 visits were made by 13,919 patients, 3838 of whom received a prescription. Of these, we studied 1689 patients who had both completed the 10-day survey and had a chart review (Table I).

Characteristics of the study group are marked in Table II. These 1689 patients were given 2155 prescriptions, for an average of 1.3 prescriptions per patient. The number of prescriptions at the index visit ranged from 1 to 7. Children who had a chronic illness were more likely to have >3 medications prescribed at their visit than children without a chronic illness (7% in children with a chronic illness and 3% in children without, $P \leq .05$).

Our study population was 49% white, 15% black, 21% Hispanic, and 14% other ethnic groups (eg, Native Americans, Asians, and Native Pacific Islanders; Table III). Comparing the racial/ethnic mixture of our study population for SES measures we found that Hispanic parents were more likely to have lower educational attainment, lower annual income, and 2-times as likely to have LEP.

We found 283 ADEs occurred in 242 children (14%), of which 57 were preventable ADEs (rate, 3%; 95% CI, 35-4%) in 55 children and 226 were non-preventable ADEs (rate, 14%; 95% CI, 11%-15%) in 186 children. Forty-nine children experienced only a preventable ADE, and 6 children had both a preventable ADE and a non-preventable ADE. None of the preventable ADEs was life threatening or fatal, 14% were serious, and 86% were significant. An example of a serious preventable ADE was a 9-year-old child with streptococcal pharyngitis for whom amoxicillin was prescribed whose parent did not complete the course of medicine, which resulted in a return visit for persistent symptoms. Forty preventable ADEs (70%) occurred during parental administration of medication to their child, and 15 preventable ADEs (26%) occurred at ordering. The most common drugs involved in preventable ADEs were amoxicillin or amoxicillin-clavulanate (26%), inhaled steroids (11%), topical anti-fungal (7%), antihistamines (7%), and inhaled bronchodilators (5%).

Detection Method of ADEs

Of the 283 ADEs discovered, 218 were identified by surveying patients and 51 ADEs were discovered by reviewing charts, and 14 ADEs were identified by both means. The distinction in the identifying source of the ADE has important implications for the results. For example, we found that black children, when compared with white children, had a 1.8-fold (95% CI, 0.74-3) higher odds of an ADE through chart review, but a 0.58-fold lower (95% CI, 0.36-0.94) odds of having an ADE reported by parental survey. Many other vulnerable subgroups of children showed the same phenomena. Objective chart review found higher rates of ADEs for Hispanic children (odds ratio [OR], 1.4; 95% CI, 0.73-2.7; compared with white children) and for children of parents with LEP (OR, 1.5; 95% CI, 0.7-2.2; compared with parents who were English proficient); parents in these subgroups may have been reticent to report ADEs on the telephone survey (Hispanic versus white children: OR, 0.64; 95% CI, 0.42-0.97; LEP versus English proficient: OR, 0.54; 95% CI, 0.35-0.84).

Table II. Characteristics of study sample

Characteristics	Total (n = 1689)
Child	n (%)
Race	
White	815 (49)
Black	256 (15)
Hispanic	343 (21)
Other	239 (14)
Age (years)*	5.6 (4.5)
Female sex	835 (50)
Health status good/fair/poor	412 (25)
Chronic Condition	499 (30)
Insurance type	
Medicaid	727 (43)
Non-Medicaid	962 (57)
Caregiver	
Educational attainment >12 years	1153 (70)
Annual income	
≥80,000	465 (36)
50,000 < 80,000	200 (16)
30,000 < 50,000	158 (12)
≤30,000	63 (34)
Above Federal Poverty Level†	1073 (86)
English proficiency	
Very well	1315 (79)
Well	160 (10)
Poorly	121 (7)
Not at all	74 (4)
Use	
Practice Site	
Teaching hospital	463 (27)
Urban health center	409 (24)
Suburban practices	814 (48)
Continuity of care ≤1 year	385 (23)
Number of prescriptions	
1	316 (78)
2	304 (18)
3	51 (3)
>4	18 (1)

*Mean (SD).

†Poverty status was calculated by taking the family's annual income and number of family members, comparing them with the 2003 poverty guidelines issued by the Department of Health and Human Services, and then classifying families in 2 groups, either at the Federal Poverty Level or above the Federal Poverty Level.

Children with Preventable ADEs Compared with Children without ADEs

In the univariate analysis, we found that children of parents who reported they spoke English poorly were twice as likely to have a preventable ADE (OR, 2.3; 95% CI, 1.01-5.34) than children of parents who spoke English very well (Table IV). Similarly, children with less continuity of care (<1 year) were more likely to have a preventable ADE than children with more continuity of care (OR, 1.83; 95% CI, 1.01-3.34). In multivariate analysis, only children with multiple prescriptions were at increased risk of having a preventable ADE (OR, 1.46; 95% CI, 1.01-2.11).

Table III. Characteristics of sample by race/ethnicity

Characteristics	White n = 815 n/total n (%)	Black n = 256 n/total n (%)	Hispanic n = 343 n/total n (%)	Other n = 239 n/total n (%)	*P* value
Educational attainment					.0001
≤12 years	120/811 (15)	82/254 (32)	224/338 (66)	70/236 (30)	
>12 years	691/811 (85)	172/254 (68)	114/338 (34)	166/236 (70)	
Annual income					.0001
≥80,000	388/638 (61)	22/179 (12)	9/291 (3)	45/162 (28)	
50,000 to <80,000	128/638 (20)	31/179 (17)	5/291 (3)	35/162 (22)	
30,000 to ≤50,000	70/638 (11)	35/179 (20)	34/291 (12)	18/162 (11)	
≤30,000	52/638 (8)	91/179 (51)	243/291 (84)	64/162 (40)	
English*					.0001
Proficient	793/814 (97)	215/256 (84)	111/343 (32)	184/239 (77)	
LEP	21/814 (3)	41/256 (16)	232/343 (68)	55/239 (23)	

Percentages may not add to 100 because of rounding.
*English proficient: parent report of speaking English very well.

DISCUSSION

Relatively little research has described the risk factors for ADEs in the pediatric outpatient setting. In this study of 6 primary care practices, we found that 14% of patients experienced an ADE, of which approximately a quarter were preventable. Children with complex medication regimens were at increased risk of having a preventable ADE. We did not find any disparities in preventable ADEs in pediatric outpatients.

As expected, children with chronic illnesses had more medications prescribed, which in turn increased their risk of experiencing a preventable ADE. We do not believe that these findings are caused by prescribing of less familiar medications, because most drugs resulting in preventable ADEs were associated with common medications, such as antibiotics. Perhaps more likely is that providers did not sufficiently or accurately communicate medication administration information to parents, because most preventable ADEs occurred during home administration. Improved communication among healthcare providers and patients potentially could prevent ADEs in the outpatient setting, as in the inpatient setting.[19]

We used a well-known and effective method for detection of ADEs.[20,25-28] Detection of voluntarily reported ADEs depends on who is responsible for reporting the data. In the outpatient setting, patients tend to be better reporters than health professionals.[17,29] Gandhi et al showed in the adult ambulatory care setting that patient surveys identified most ADEs.[20] These results are comparable with ours in that we identified 81% of ADEs through survey and 19% by chart review. The differences between patients and health professionals reporting ADEs may be caused by patients being more prone to report symptoms in hopes of feeling better, whereas health professionals may be afraid of the potential ramifications (eg, fear of malpractice risk or damage to their reputation).[30] In an outpatient setting, interviewing patients directly is an important source of information about medication incidents.[31]

An apparent ascertainment bias was found in our response rates: more ADEs were identified through chart review than parental report in black and Hispanic parents. This is a surprising result because, as just stated, overall more ADEs tend to be found through parental report. We suspect that the low odds of reported ADEs by survey reflect the conservative reporting style of black and Hispanic parents rather than an actual reduction in the occurrence of ADEs. Thus, the overall odds for ADEs that we reported may underestimate the true difference between black and Hispanic children compared with white children. Furthermore, these differences may reflect that black and Hispanic parents are not recognizing that new symptoms in their children may be caused by a medication or perhaps because they worry about the consequences of reporting their own errors (eg, not completing a 10-day course of antibiotics).[32] Conversely, these findings may suggest that more educated white parents over-report medical symptoms.

We also found that children of parents with LEP were significantly less likely to report that their child had an ADE, which may also make it more difficult for these parents to communicate about ADEs with health care providers. Parents with LEP may not be able to communicate adequately the possible medication incidents in a telephone interview. Although LEP does not represent the same thing as limited health literacy, both may lead to harm. Patients with limited health literacy not only struggle with written communication, but also with oral communication.[33]

Our study had several limitations. First, although we included 6 diverse pediatric practices that were hospital- and community-based, the results may not be generalizable to other settings. Second, we found an ascertainment bias because black and Hispanic parents were relatively less likely to report an ADE. This may have affected the number of

Table IV. Unadjusted and adjusted odds ratio of patients with preventable adverse drug events

	Preventable ADE	
	Unadjusted OR (95% CI)	**Adjusted* OR (95% CI)**
Practice site		
Hospital clinic	1 (referent)	1 (referent)
Urban health center	1.14 (0.56-2.30)	0.99 (0.41-2.35)
Suburban practice	0.6 (0.30-1.19)	0.7 (0.32-1.51)
Number of prescriptions	1.35 (0.93-1.97)	1.46 (1.01-2.11)†
Race/Ethnicity		
White	1 (referent)	1 (referent)
Black	2.03 (0.91-4.53)	1.33 (0.56-3.20)
Hispanic	1.66 (0.76-3.60)	0.68 (0.21-2.17)
Other	2.18 (0.98-4.87)	1.35 (0.57-3.17)
Parental education		
College, post graduate	1 (referent)	1 (referent)
Some college	1.09 (0.49-2.39)	0.99 (0.45-2.20)
High school	1.11 (0.50-2.46)	0.91 (0.40-2.09)
Less than high school	1.53 (0.64-3.66)	1.35 (0.57-3.17)
English proficiency		
Very well	1 (referent)	1 (referent)
Well	0.48 (0.11-2.00)	0.36 (0.08-1.55)
Poorly	2.31 (1.01-5.34)†	1.62 (0.54-4.89)
Not at all	2.15 (0.74-6.24)	2.36 (0.6-9.35)
Duration of care		
>1 year	1 (referent)	1 (referent)
≤1 year	1.83 (1.01-3.34)†	1.53 (0.83-2.81)
Annual income		
>80,000	1 (referent)	
50,000-80,000	1.89 (0.74-4.88)	
30,000-50,000	1.79 (0.64-5.02)	
≤30,000	1.45 (0.64-3.30)	

Model compared 49 children with the presence of a preventable ADEs to 1640 children without ADEs.

*Adjusted for all variables listed except annual income, which is highly correlated with education.

†$P < .05$.

adverse events identified. Third, the respondent to the survey may not have been the same person who spoke to the physician or was the primary caretaker for the child, therefore the accuracy of parental recall associated to either the recognition or reporting of an adverse drug event is unknown. Lastly, and most important, although this is the largest study to date examining ADEs in the pediatric ambulatory care setting, our small sample size limits our findings.

Our findings have 2 important policy implications. For policymakers and providers who are interested in improving patient safety, better methods are needed to identify preventable ADEs, especially among black and Hispanic parents with LEP. Second, identification of parents' health literacy and appropriate tailoring of medication-related information are required. Improving the effectiveness of physician-patient communication should ultimately lead to a decrease in preventable ADEs.

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50 Years Ago in *The Journal of Pediatrics*

Acne: A new approach to an old problem

Baird JW. J Pediatr 1958;52:152-7

Baird argued that acne is the "scourge of youth" and should not be allowed to run its course but rather should be treated. The mainstay of the new approach recommended was diet, including avoiding an excess of carbohydrates (especially candy and carbonated cola beverages), chocolate, nuts, peanut butter, pork, and fried food. The authors recommended that milk and milk products should not be used in excess but rather the diet should be rich in lean meats, fruits, vegetables, and vitamins. Local treatment with a cream with drying and keratolytic powers was recommended to be accompanied when necessary by the manual expression of comedones by a physician "using one of the mechanical devices available for this purpose." Treatment of severe cases could be supplemented with x-ray, short courses of oral antibiotics, *Staphylococcus* vaccines, and estrogen hormones in girls over 18 years if acne exacerbations were associated with menstruation.

Today, the realization that acne can be emotionally and physically scarring and that treatment is generally effective and indicated is well accepted by the medical community and general population. However, much has changed in what is considered acceptable treatment of acne over the last 50 years and most of what appeared to be promising at the time this article was written is not longer indicated. Current mainstays of acne treatment do not include diet, the manual expression of comedones, irradiation, or short courses of antibiotics. Rather, topical retinoids are now the primary treatment although other topical agents (benzoyl peroxide, topical antibiotics, and azelaic acid) can also be used. Systemic antibiotics (especially tetracycline and its derivatives) for at least 6 to 8 weeks are indicated if response to topicals has been inadequate, if patients have moderate to severe acne, and/or a propensity for scarring. Trials of hormone therapy may be appropriate or, in severe, nonresponsive cases, of isotretinoin. Surgical approaches are largely limited to intralesional injection of low-dose glucocorticoids for persistent, painful lesions. (Dermabrasion and laser peel are used after the active process has quieted.) Trials of phototherapy and vaccines offer some promise.

Bonita Stanton, MD
Professor and Schotanus Family Endowed Chair of Pediatrics
Pediatrician-in-Chief
Carman and Ann Adams Department of Pediatrics
Children's Hospital of Michigan
Wayne State University School of Medicine
Detroit, Michigan
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