ARTICLE

Ethanol-Lock Technique for Persistent Bacteremia of Long-term Intravascular Devices in Pediatric Patients

Wes Onland, MD; Cathy E. Shin, MD; Stana Fustar, RN, CRNI; Teresa Rushing, PharmD, BCPS; Wing-Yen Wong, MD

Objectives: To use the ethanol-lock technique (in conjunction with systemic antibiotics) to salvage central lines from removal and to prevent persistence of catheter-related infections among pediatric patients with long-term intravascular devices.

Design: Medical records of patients treated with ethanol locks were retrospectively reviewed from June 1, 2004, through June 22, 2005.

Setting: Childrens Hospital Los Angeles, Los Angeles, Calif, a tertiary care pediatric hospital.

Patients: Forty children with diverse underlying disorders were treated for 51 catheter-related infections using the Childrens Hospital Los Angeles ethanol-lock technique.

Interventions: Eligible infected central lines were instilled with a dose volume of 0.8 to 1.4 mL of 70% ethanol into the catheter lumen during 12 to 24 hours and then withdrawn. The volume of ethanol used was based on the type of intravascular device.

Main Outcome Measures: Clearance of infection and incidence of recurrence.

Results: Of the 51 ethanol-lock treatments in 40 children, no catheters were removed because of persistent infection. Eighty-eight percent (45/51) of the treated episodes cleared without recurrence (defined as a relapse within 30 days with the same pathogen). Twelve (75%) of 16 polymicrobial isolates and 33 (94%) of 35 monomicrobial isolates were successfully treated. There were no adverse reactions or adverse effects reported.

Conclusion: This retrospective study supports the use of the ethanol-lock technique in conjunction with systemic antibiotics as an effective and safe method to retain the use of a previously infected central venous catheter, decrease the need for line removal, and eradicate persistent pathogens in catheter-related infections.

Arch Pediatr Adolesc Med. 2006;160:1049-1053

LONG-TERM INTRAVASCULAR devices (IVDs) are crucial for the care of children requiring chemotherapy, apheresis, parenteral nutrition, frequent transfusion of blood products, or prolonged intravenous medications. However, catheter-related infections (CRIs) are a major complication of IVDs, necessitating removal and replacement when venous access sites are severely limited. Most nosocomial bloodstream infections in pediatric patients are related to the use of an IVD.[1] Bacterial colonization of the catheter hub and lumen is a significant problem in patients with long-term IVDs,[2,3] leading to increased patient morbidity, costs and length of hospitalization,[4-6] and mortality in critically ill patients.[7] The incidence of IVD-related infection ranges from 3% to 60%, with a rate of 0.2 to 2.4 infections per 1000 catheter-days.[8-12]

Repeated replacement of IVDs should be prevented because of the added cost of care, the delay in therapy, and (most important) the problem of limited access sites, especially in young children. To salvage infected IVDs, several methods of prophylaxis or treatment have been developed, such as antibiotic locks with or without anticoagulation agents or antiseptic chamber–containing hubs, with variable success.[13-15] Dannenberg et al[16] used ethanol locks in oncology patients with CRIs, in conjunction with systemic antibiotics. To our knowledge, there have been no other reports on the use of ethanol-lock techniques for the treatment of CRIs. The ethanol-lock technique was introduced at Childrens Hospital Los Angeles, Los Angeles, Calif, in early 2004. In this study, we report our experience with the ethanol-lock technique, as an adjunctive therapy to systemic antibiotics, to intraluminally

Author Affiliations: Department of Pediatrics, Emma Children's Hospital, Academic Medical Center, Amsterdam, the Netherlands (Dr Onland); and Divisions of Pediatric Surgery (Dr Shin), Hematology-Oncology (Ms Fustar and Drs Rushing and Wong), and Pharmacy (Dr Rushing), Childrens Hospital Los Angeles, Los Angeles, Calif.

©2006 American Medical Association. All rights reserved.
Downloaded From: http://archpedi.jamanetwork.com/ on 07/24/2017

Table 1. Protocol of the Childrens Hospital Los Angeles Ethanol-Lock Technique

Withdraw 1 mL of 98% dehydrated ethanol with filter needle into a 10-mL syringe
Add 0.4 mL of sterile saline (0.9% sodium chloride) to withdrawn syringe containing 98% ethanol (final concentration, 1.4 mL of 70% ethanol)
Assemble 3-way stopcock
Administration of ethanol lock
1. Attach a 3-way stopcock to injection cap
2. Unclamp the catheter and gently flush with isotonic sodium chloride solution to ensure patency of the catheter
3. Instill ethanol into the catheter to fill volume
4. Remove 3-way stopcock and clamp the catheter; ethanol should remain within the lumen a minimum of 12 h (24 h for best results)

Doses are based on the intravascular device intraluminal volume
- Type of catheter
  1. Single-lumen tunneled
     - Broviac
       - 4.2F (ID, 0.7 mm) (dose volume, 0.8 mL)
       - 6.6F (ID, 1 mm) (dose volume, 0.8 mL)
     - Medcomp (dose volume, 1.2 mL)
  2. Double-lumen tunneled
     - Hickman
       - 7F distal (red) (ID, 1 mm) (dose volume, 1.2 mL)
       - 9F proximal (white) (ID, 0.7 mm) (dose volume, 1.2 mL)
     - Medcomp 8F or 10F (dose volume, 1.2 mL)
  3. Port-A-Cath
     - Any port (dose volume, 1.4 mL)

Repeat procedure for 5 d

Abbreviation: ID, inner diameter.

disinfect and salvage long-term IVDs among children with CRIs.

METHODS

A retrospective review of patients' medical records and pharmacy dispensing records of ethanol locks from June 1, 2004, through June 22, 2005, was undertaken after appropriate approval from the Childrens Hospital Los Angeles Institutional Review Board. Catheter-related infections were as defined by the Centers for Disease Control and Prevention.[12] No concomitant peripheral blood cultures were obtained.

Eligibility criteria for ethanol-lock treatment included age older than 6 months, a patent lumen before initiation of ethanol locks, a negative history of allergy to ethanol, and persistence of positive blood cultures (persistent positive blood cultures after 48 hours' administration of appropriate intravenous antimicrobial therapy) or incidence of multiple CRIs. Only silicone catheters qualified for ethanol-lock procedures.

The instilled ethanol lock had to dwell for 12 to 24 hours in a single-lumen IVD. After this period, the ethanol lock was withdrawn and discarded, followed by an isotonic sodium chloride solution flush. This procedure was repeated for 5 consecutive days. A separate peripheral line was placed for intravenous antibiotics. With double-lumen IVDs, ethanol was instilled in one lumen for 24 hours, while the other lumen was used for infusion. During the next 24 hours, the other lumen was locked with ethanol, while the first lumen was used for infusions. Both lumens were alternately treated for 10 days. Any adverse effects of the treatment were documented. Details of the ethanol-lock procedure are summarized in **Table 1**.

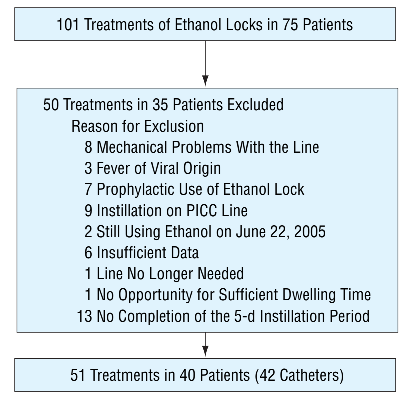

Figure. Study sample inclusions and exclusions. PICC indicates peripherally inserted central catheter.

Data of CRIs treated with ethanol locks were reviewed from the first day of insertion (or the beginning of the study period) until the end of the study period. When the subsequent CRI in the same catheter was not treated with ethanol locks, the consecutive data were excluded.

A total of 101 ethanol-lock treatments were dispensed to 75 patients. Fifty treatments in 35 patients were excluded (**Figure**). Eleven treatments had no documented CRI but were associated with mechanical problems with the line (n=8) or with fever of viral origin (n=3). Nine treatments were carried out on peripherally inserted central catheters, 6 had inadequate data documentation, and 7 had prophylactic ethanol locks instilled before any proven infection. In 2 treatments, the patients were still receiving ethanol locks on the last day of the study period. In 1 treatment, the line was deemed clinically expendable after ethanol had been instilled, and it was removed halfway through the treatment protocol. One treatment was excluded because the patient's medical management required the use of both lumens for continuous infusion of parenteral nutrition and systemic antibiotics, leaving no opportunity for the minimum dwelling period of 12 to 24 hours. Of the 50 excluded ethanol-lock treatments, 13 were judged to be unevaluable because the patients' medical records showed that the IVDs were ordered to be removed before completion of the 5-day instillation period.

Treatment success was defined as resolution of fever within 24 hours, no recurrence of positive blood cultures with the same organism, and retention of the IVD. *Treatment failure* was defined as recurrence within 30 days with the same pathogen or removal of the IVD because of a persistent infection. When the catheter was removed because of a mechanical event or completion of therapy, it was not classified as a treatment failure. Data were analyzed using Intercooled STATA version 8.0 (StataCorp LP, College Station, Tex).

RESULTS

Data from 51 ethanol-lock treatments on 40 patients and 42 catheters were analyzed. Two patients received a second IVD of the same type that they previously had, and in both cases the catheter was removed after a CRI that was not treated with ethanol locks. The patients' characteristics are summarized in **Table 2**. There were more boys than girls. The median age was 3.9 years (age range, 1.9-13.5 years). Solid tumors accounted for 38% (15/40) of the underlying diagnoses. Other diagnoses included severe immunocompromise after bone marrow or

©2006 American Medical Association. All rights reserved.
Downloaded From: http://archpedi.jamanetwork.com/ on 07/24/2017

Table 2. Characteristics Among 40 Patients

Characteristic	Total No.
Male/female ratio	24:16
Age, median (interquartile range), y	3.9 (1.9-13.5)
Diagnosis (n = 40)	
Oncology, solid tumors	15
Oncology, malignant hematology	3
Hematology, benign	3
Bone marrow or small-bowel transplantation	9
Metabolic disorder	1
Gastroenterological disorder	9
Type of catheter (n = 42)	
Broviac single lumen	11
Hickman double lumen	17
Port-A-Cath	9
Medcomp double lumen	5
Catheter-days	
Mean ± SD	201.4 ± 201.5
Total	8045
Infection rate per 1000 catheter-days	6.3
Median (25%-75% interquartile range)	126.5 (70-258)
No. of treatments (n = 51)	
1	34
2	5
7	1

Table 3. Monomicrobial or Polymicrobial Pathogens Isolated in 51 Catheter-Related Infections

Pathogen	No. of Cases
Monomicrobial cultures	
Gram-positive isolates (n = 29)	
Coagulase-negative staphylococci	18
Enterococcus faecalis (group D)	4
Enterococcus faecium	1
Methicillin-resistant *Staphylococcus aureus*	2
S aureus	3
Bacillus species (not *Bacillus anthracis*)	1
Gram-negative isolates (n = 5)	
Enterobacter cloacae	1
Klebsiella oxytoca	1
Klebsiella pneumoniae	1
Serratia marcescens	1
Actinobacter species	1
Yeast (n = 1)	
Candida glabrata	1
Polymicrobial cultures (n = 16)	
Gram-positive isolates	19
Gram-negative isolates	19
Yeast	1

small-bowel transplantation (23% [9/40]) and gastroenterological disorders requiring long-term dependence on parenteral nutrition associated with short-bowel syndrome, pseudo-obstruction syndrome, or microvillous inclusion syndrome (23% [9/40]). Most of the 42 catheters were Hickman catheters (40% [17/42]), followed by Broviac catheters (26% [11/42]) and Port-A-Cath catheters (21% [9/42]).

Among the 40 patients, 34 were treated once with ethanol locks, 5 were treated twice, and 1 received the therapy 7 times during the study period. We registered 3863 catheter-days in 40 patients from the day of insertion (or the previous CRI not treated with ethanol locks) until the date of the first positive CRI, an infection rate of 10 per 1000 catheter-days. The total number of catheter-days among 42 catheters was 8054 days, with an infection rate of 6.3 per 1000 catheter-days (Table 2). The distribution of catheter-days from insertion to the first CRI (median, 34.5 catheter-days [interquartile range, 16-85 catheter-days] and the total catheter-days (median, 126.5 catheter-days [interquartile range, 70-258 catheter-days]) were not normally divided.

Table 3 lists the organisms isolated. Monomicrobial culture was isolated in 69% of the CRIs. Gram-positive organisms accounted for 57% of 51 infections; 35% of them were coagulase-negative staphylococci. Polymicrobial isolates grew in 16 CRIs (31%); 1 CRI (2%) was a mixed culture of yeast and bacteria. In 38% of the polymicrobial isolates, there were more than 2 different bacteria. More gram-negative isolates grew out of the polymicrobial cultures (49%) than out of the monomicrobial cultures.

All of the IVDs treated with ethanol locks were successfully retained and used. Five of the catheters were later removed when patients ended their chemotherapy or before allogenic bone marrow transplantation, as standard practice. All of these removals occurred after 30 days (**Table 4**). One of the patients died of disease progression unrelated to a CRI.

Table 4. Removal of Intravascular Device for Reason Other Than Catheter-Related Infection (CRI) in 5 Patients

Patient No.	No. of CRIs	Reason for Removal	Interval Between Last CRI and Removal, d
1	1	No longer in use	136
2	1	No longer in use	74
3	1	No longer in use	65
4	2	Upcoming ABMT	53
5	1	Died of disease progression	85

Abbreviation: ABMT, allogenic bone marrow transplantation.

In 6 cases, bacteremia recurred within 30 days with the same pathogen (**Table 5**). These recurrences occurred in 3 patients and comprised 4 different polymicrobial isolates in the first CRIs that recurred in the subsequent CRIs. In patient 8 in Table 5, the pathogen (*Klebsiella pneumoniae*) recurred twice with different pathogens in a polymicrobial isolate.

Ethanol-lock treatments were well tolerated in all children. No adverse effects were reported.

COMMENT

Infection of long-term IVDs results from invasion of organisms present at insertion sites, contaminated infusates, hematogenous seeding of the catheter tips, and contamination of the hubs, the hubs being the most common site of CRIs. Microorganisms causing CRIs are en-

©2006 American Medical Association. All rights reserved.
Downloaded From: http://archpedi.jamanetwork.com/ on 07/24/2017

Table 5. Recurrence Within 30 Days With the Same Pathogen in 3 Patients

Patient No.	Interval Between CRIs, d	Pathogen of First CRI	Pathogen of Subsequent CRI
6	19	MRSA	MRSA*
7	27	CNS	CNS
	29	CNS†	CNS
8	30	*Serratia marcescens*†	*S marcescens*
	17	*Klebsiella pneumoniae*†	*K pneumoniae*†
	28	*K pneumoniae*†	*K pneumoniae*†

Abbreviations: CNS, coagulase-negative staphylococci; CRI, catheter-related infection; MRSA, methicillin-resistant *Staphylococcus aureus*.

*At the subsequent CRI, no ethanol locks were used, and the intravascular device was removed.

†In polymicrobial isolate.

countered in 2 forms, the planktonic free-floating form and the sessile form, with bacteria embedded in a biofilm.[17] In most cases, the planktonic free-floating form can effectively be eradicated by appropriate systemic antibiotics. The sessile form poses a significant and often persistent problem. Bacteria adherent to implanted medical devices or damaged tissue can cause persistent infections by forming a biofilm. These bacteria encase themselves in a hydrated matrix of polysaccharide and protein, causing their inherent resistance to antibiotic therapy, neutrophil function, phagocytes, and antibodies.[18,19] Another part of this biofilm that is composed of host-derived glycoproteins, such as fibrinogen, fibronectin, collagen, and laminin, enhances bacterial adherence to foreign material.[6,17] Susceptibility tests using in vitro biofilm models have shown survival of bacterial biofilms after treatment with antibiotics at concentrations hundreds of times (or even 1000 times) the minimum inhibitory concentration of the bacteria measured in a suspension culture.[20,21]

We performed a retrospective review of the efficacy and safety of ethanol locks as an adjunctive therapy to systemic antibiotics in persistent CRIs among children with long-term IVDs. Ethanol is an effective disinfectant against a broad range of microorganisms, including bacteria and fungi. Two hours of exposure to 70% ethanol is required to kill established biofilms of gram-positive bacteria, gram-negative bacteria, and *Candida* species in vitro.[22]

The number of infections in our study period per 1000 catheter-days (6.3 infections) is higher than that reported in the study by Dannenberg et al.[16] This is probably because 5 of the 42 catheters were inserted before the beginning of the study period, and these catheter-days without CRIs were excluded in the analyses. Other reasons may include our inclusion of younger and sicker children, different groups of underlying illnesses, and various types of catheters at high risk for CRIs. To minimize venipunctures in these children with significant venous access difficulties, no peripheral blood cultures were obtained. Cultures of blood samples, drawn from an indwelling IVD, were assessed in a study by Martinez et al.[23] The positive predictive value of IVD and peripheral blood cultures was low (63% and 73%, respectively) and required clinical interpretation and conformation; however, the negative predictive values were 99% and 98%, respectively, obviating the need for a concomitant separate peripheral blood culture.

None of the catheters treated with ethanol were removed, and 45 (88%) of the 51 CRIs showed no recurrence within 30 days with the same pathogen. Of the recurrences in 3 patients (Table 5), patient 6 had methicillin-resistant *Staphylococcus aureus* at the time of the catheter insertion. After the recurrence of methicillin-resistant *S aureus* in patient 6, ethanol locks were not instilled and the IVD was removed. Patient 7, with stage IV neuroblastoma requiring intensive chemotherapy, had a recurrence of coagulase-negative staphylococci 27 days after the first CRI, which was treated with ethanol locks, and a second recurrence 29 days after the first recurrence. Patient 8, with 3 recurrences in 7 CRIs, had short-bowel syndrome and was dependent on parenteral nutrition. Five of the 7 CRIs were treated with ethanol locks for a second or third time, with good effect. The IVDs in patients 2 and 3 were not removed. Because this was a retrospective review, we could not evaluate the DNA type of each pathogen and whether the CRI was localized intraluminally.

Coagulase-negative staphylococci, *S aureus*, aerobic gram-negative bacilli, and *Candida albicans* are most commonly associated with CRIs.[24,25] We found equal numbers of the different bacteria but also found a considerable amount of polymicrobial isolates, constituting 49% of the gram-negative bacteria grown, and a mixed bacterial and fungal isolate. Of the polymicrobial isolates, 75% (12/16) did not show a recurrence, and of the 35 monomicrobial isolates, 94% (33/35) were successfully treated. The treatments of 2 yeast isolates were also successful.

CONCLUSIONS

Despite the limitations of this retrospective study, our results suggest that using the ethanol-lock technique for persistent CRIs in children with long-term IVDs is effective in salvaging the line, with a low rate of recurrences. It is a safe, well-tolerated, and low-cost method, without risks of inducing multiresistant bacteria. A prospective, randomized, double-blind trial comparing the ethanol-lock technique with placebo and the alternatives would be needed to determine the best method to treat persistent CRIs.

Accepted for Publication: June 13, 2006.
Correspondence: Wing-Yen Wong, MD, Division of Hematology-Oncology, Childrens Hospital Los Angeles, 4650 Sunset Blvd, Mail Stop 54, Los Angeles, CA 90027 (wwong@chla.usc.edu).
Author Contributions: *Study concept and design:* Onland, Shin, Rushing, and Wong. *Acquisition of data:* Onland, Shin, Rushing, and Wong. *Analysis and interpretation of data:* Onland, Fustar, and Wong. *Drafting of the manuscript:* Onland, Fustar, and Wong. *Critical revision of the manuscript for important intellectual content*: Onland,

©2006 American Medical Association. All rights reserved.
Downloaded From: http://archpedi.jamanetwork.com/ on 07/24/2017

Shin, Rushing, and Wong. *Administrative, technical, and material support:* Onland and Rushing. *Study supervision:* Shin and Wong.

REFERENCES

1. Jarvis WR, Edwards JR, Culver DH, et al. Nosocomial infection rates in adult and pediatric intensive care units in the United States: National Nosocomial Infections Surveillance System. *Am J Med*. 1991;91:185S-191S.
2. Maki DG, Mermel LA. Infections due to infusion therapy. In: Bennet JV, Brachman PS, eds. *Hospital Infections.* Philadelphia, Pa: Lippincott-Raven Publishers; 1998:689-724.
3. Mayhall CG. Diagnosis and management of infections of implantable devices used for prolonged venous access. *Curr Clin Top Infect Dis*. 1992;12:83-110.
4. Digiovine B, Chenoweth C, Watts C, Higgins M. The attributable mortality and costs of primary nosocomial bloodstream infections in the intensive care unit. *Am J Respir Crit Care Med*. 1999;160:976-981.
5. Rello J, Ochagavia A, Sabanes E, et al. Evaluation of outcome of intravenous catheter-related infections in critically ill patients. *Am J Respir Crit Care Med*. 2000;162:1027-1030.
6. Eggimann P, Sax H, Pittet D. Catheter-related infections. *Microbes Infect*. 2004;6:1033-1042.
7. Pittet D, Tarara D, Wenzel RP. Nosocomial bloodstream infection in critically ill patients: excess length of stay, extra costs, and attributable mortality. *JAMA*. 1994;271:1598-1601.
8. Develter W, De Cubber A, Van Biesen W, Vanholder R, Lameire N. Survival and complications of indwelling venous catheters for permanent use in hemodialysis patients. *Artif Organs*. 2005;29:399-405.
9. Wiener ES. Catheter sepsis: the central venous line Achilles' heel. *Semin Pediatr Surg*. 1995;4:207-214.
10. Stovroff M, Teague WG. Intravenous access in infants and children. *Pediatr Clin North Am*. 1998;45:1373-1393, viii.
11. Crnich CJ, Maki DG. The promise of novel technology for the prevention of intravascular device–related bloodstream infection, II: long-term devices. *Clin Infect Dis*. 2002;34:1362-1368.
12. de Jonge RC, Polderman KH, Gemke RJ. Central venous catheter use in the pediatric patient: mechanical and infectious complications. *Pediatr Crit Care Med*. 2005;6:329-339.
13. Berrington A, Gould FK. Use of antibiotic locks to treat colonized central venous catheters. *J Antimicrob Chemother*. 2001;48:597-603.
14. Leon C, Alvarez-Lerma F, Ruiz-Santana S, et al. Antiseptic chamber–containing hub reduces central venous catheter-related infection: a prospective, randomized study. *Crit Care Med*. 2003;31:1318-1324.
15. Bestul MB, Vandenbussche HL. Antibiotic lock technique: review of the literature. *Pharmacotherapy*. 2005;25:211-227.
16. Dannenberg C, Bierbach U, Rothe A, Beer J, Korholz D. Ethanol-lock technique in the treatment of bloodstream infections in pediatric oncology patients with Broviac catheter. *J Pediatr Hematol Oncol*. 2003;25:616-621.
17. Raad I. Intravascular-catheter–related infections. *Lancet*. 1998;351:893-898.
18. Stewart PS, Costerton JW. Antibiotic resistance of bacteria in biofilms. *Lancet*. 2001;358:135-138.
19. Donlan RM. Biofilm formation: a clinically relevant microbiological process. *Clin Infect Dis*. 2001;33:1387-1392.
20. Ceri H, Olson ME, Stremick C, Read RR, Morck D, Buret A. The Calgary Biofilm Device: new technology for rapid determination of antibiotic susceptibilities of bacterial biofilms. *J Clin Microbiol*. 1999;37:1771-1776.
21. Williams I, Venables WA, Lloyd D, Paul F, Critchley I. The effects of adherence to silicone surfaces on antibiotic susceptibility in *Staphylococcus aureus*. *Microbiology*. 1997;143:2407-2413.
22. Metcalf SC, Chambers ST, Pithie AD. Use of ethanol locks to prevent recurrent central line sepsis. *J Infect*. 2004;49:20-22.
23. Martinez JA, DesJardin JA, Aronoff M, Supran S, Nasraway SA, Snydman DR. Clinical utility of blood cultures drawn from central venous or arterial catheters in critically ill surgical patients. *Crit Care Med*. 2002;30:7-13.
24. Raad II, Hanna HA. Intravascular catheter–related infections: new horizons and recent advances. *Arch Intern Med*. 2002;162:871-878.
25. Mermel LA, Farr BM, Sherertz RJ, et al. Guidelines for the management of intravascular catheter–related infections. *Clin Infect Dis*. 2001;32:1249-1272.

Announcement

Submissions. The Editors welcome contributions to Picture of the Month. Submissions should describe common problems presenting uncommonly, rather than total zebras. Cases should be of interest to practicing pediatricians, highlighting problems that they are likely to at least occasionally encounter in the office or hospital setting. High-quality clinical images (in either 35-mm slide or electronic format) along with parent or patient permission to use these images must accompany the submission. The entire discussion should comprise no more than 750 words. Articles and photographs accepted for publication will bear the contributor's name. There is no charge for reproduction and printing of color illustrations. For details regarding electronic submission, please see: http://archpedi.ama-assn.org.

©2006 American Medical Association. All rights reserved.
Downloaded From: http://archpedi.jamanetwork.com/ on 07/24/2017