Application of the procedural consolidation concept to surgical treatment of children with epidermolysis bullosa: a retrospective analysis

Aim To assess the efficacy of the procedural consolidation concept (PCC) at reducing the number of sessions of general anesthesia necessary for treating children with epidermolysis bullosa (EB).

Methods We examined the records of children treated at Children’s Hospital of Zagreb between April 1999 and December 2007. Children treated before the introduction of PCC in January 2005 (n = 39) and after (n = 48) were analyzed in order to determine the effect of PCC on the occurrence of complications, days of hospitalization, and number of hospitalizations.

Results During the study period, 53 patients underwent 220 sessions of general anesthesia for a total of 743 surgical interventions per session. Before the introduction of PCC (n = 39 patients, 83 sessions), the median number of interventions per session was 2 (range 1-5), and after the introduction of PCC (n = 48 patients, 137 sessions) it was 4 (range 3-7, \( P < 0.001 \)). After the introduction of PCC, the median number of complications per anesthesia session increased from 2 (range 0-10) to 3 (range 0-10) \( (P = 0.027) \), but the median number of complications per surgical procedure decreased from 1 (range 0-10) to 0.6 (range 0-2.5) \( (P < 0.001) \). PCC lengthened each anesthesia session from a median of 65 minutes (range 35-655) to 95 minutes (range 50-405), \( (P < 0.001) \). Total length of hospitalization was similar before (median 1, range 1-4) and after (median 1, range 1-3) introduction of PCC \( (P = 0.169) \). The number of hospitalization days per procedure was 3 times lower after the introduction of PCC (median 0.3, range 0.2-3) than before (median 1, range 0.75-17) \( (P < 0.001) \).

Conclusion PCC should be considered an option in the surgical treatment of children with EB.
Epidermolysis bullosa (EB) refers to a group of rare genetic disorders characterized by cutaneous and extracutaneous fragility, blistering, and subsequent scarring even after a mild mechanical stress (1). The hallmark feature of inherited EB is mechanical fragility (2). The illness is chronic, degenerative, difficult to treat, and lethal. Although the most common symptom of EB is bullae of skin epithelium, blisters may arise on virtually any mucosal surface (3). Bullae usually heal, leaving atrophic scars. Digital fusion following scar formation is common, rendering the hands useless (3).

Traditionally, EB is divided into three major types based on phenotype, mode of inheritance, and genotype (4): EB simplex, junctional EB, and dystrophic EB. More recently, a fourth form, hemidesmosomal EB, was introduced to describe EB in which blisters emerge in the dermal-epidermal circuit. Dystrophic EB is probably the most common form of surgically treated EB (5). Each major EB type has subtypes (4,6,7); two major subtypes of dystrophic EB are dominant dystrophic EB and recessive dystrophic EB. The overall prevalence for inherited EB in the American population is 8.22 per million (8). Prevalence of EB simplex, junctional EB, dominant dystrophic EB, and recessive dystrophic EB in the United States of America (USA) is 10.75, 2.04, 2.86, and 2.04 per million, respectively (8). Determining accurate prevalence and incidence data on inherited EB in the USA became possible only after the national EB registry was established in 1986 (9-11). A Croatian national EB registry does not yet exist. According to a study in 1990 on a limited number of EB patients, the prevalence of the Hallopeau-Siemens subtype of recessive dystrophic EB in Croatia was estimated at 9.6 people per million (12).

EB has become recognized as a multisystem disorder that poses a number of pre-, peri-, and postoperative challenges (13). Scars, strictures, and stenoses are some of the problems that require surgical treatment (14). In addition, EB affects the oral-gastrointestinal system, creating the need for operative treatment and significantly affecting perioperative care (13).

Patients with EB are a high-risk group for anesthesiology because of malnutrition, anemia, hypoproteinemia, dilated cardiomyopathy, and limited mouth opening (15,16).

A multidisciplinary team approach to EB treatment is recommended. Preoperative preparation must be individualized, with special attention given to the potential anesthetic problems. When procedures under anesthesia are planned, it is best to coordinate as many surgical procedures as possible to avoid repeated anesthesia (17).

Surgical care for EB patients at the Children’s Hospital of Zagreb was for many years quite basic and was not codified into a uniform and standard procedure. In January 2005, the hospital adopted a team approach to treating EB, which led to implementation of a procedural consolidation concept (PCC). The standard approach of repeated sessions of anesthesia with no more than two surgical procedures performed each time (18-20) was replaced with PCC, which implied multiple surgical approaches and procedures during the same session of anesthesia. PCC is based on multidisciplinary team-based treatment planning aimed at reducing the number of times that patients with EB are subjected to general anesthesia. In this study, we analyzed whether PCC was successful at reducing the number of anesthesia sessions without increasing complications or length of hospitalization.

METHODS

This is a retrospective study of medical records of all patients with EB who were surgically treated under general anesthesia in Children’s Hospital of Zagreb between April 1999 and December 2007. The study was approved by the Institutional Review Board of Children’s Hospital of Zagreb. Written informed consent was obtained from patients, their parents, or their legal guardians prior to each anesthesia session.

All patients scheduled for surgery were reviewed by an EB team composed of a pediatrician, dermatologist, anesthesiologist, and two surgeons. Based on clinical examination by the multidisciplinary team and laboratory findings, individual plans for surgical treatment were created for patients with EB. Patients were hospitalized on the day of surgery.

A total of 220 anesthesia sessions were divided into two groups, those performed before (n = 83 sessions, 39 patients) and after (n = 137 sessions, 48 patients) the introduction of PCC. The groups of patients treated before and after the introduction of PCC were compared in terms of observed complications per general anesthesia session, per 10 minutes of anesthesia, total length of hospital stay, and number of hospitalizations. All perioperative complications were defined as short-term complications the occurrence of which did not affect duration of hospital stay. Follow-up period was during the hospital stay.
Premedication and anesthesia

Oral premedication was used in 41 (19%) of 220 sessions of general anesthesia. Midasolam was administered in syrup form. Intravenous (IV) access before induction in anesthesia was achieved in only 36 (16%) of 220 sessions, 21 of which were in children who had been premedicated. In all cases, induction in anesthesia was by inhalation. Until 2004, the inhalational anesthetic was Halothane (Halotan); from 2004 onwards, it was Sevofluran (Sevoran). Of the total of 220 sessions of anesthesia, 127 (58%) were carried out entirely with a “face” mask, while in the remaining 93 (42%) there were indications for endotracheal tube insertion. Most intubations (62 of 93, 67%) were performed after introduction of PCC. A fiber-optic bronchoscope (Olympus BF-3C-20; Olympus Europa GmbH, Hamburg, Germany) was used for intubation of infants and small children. For children over 10 years, an Olympus BF-P-20-D was used. The patients did not consent to the use of regional anesthesia.

The neuromuscular relaxant rocuronium and the opioid analgesic fentanyl were used to ensure good intubation and calmness during the surgery. Pulse oximeter oxygen saturation, electrocardiography, non-invasive blood pressure, blood loss, and body temperature were monitored during surgery. The face mask and skin exposed to friction were lubricated with Vaseline. Electrocardiogram electrodes were kept in place with bandages, and Mepitel (Mölnlycke Healthcare AB, Göteborg, Sweden) and soft gauze bandages were used to care for wounds and to secure the IV line.

Postoperative pain control

For postoperative pain monitoring a visual-analogue scale (VAS) was used. Pain in infants was assessed in most cases by the mother using a VAS. In two cases, the infant CRIES scoring system (21) was combined with mother’s assessment of the infant’s discomfort using the VAS.

To control pain during the early postoperative period, a multimodal approach was used. Non-steroidal anti-inflammatory drugs were administered with tramadol through continuous IV infusion. Suppositories were not used. If needed, sedatives were also administered. Patients showed normal respiration and reported feeling no pain. For prevention of postoperative nausea and vomiting (PONV), metoclopramide or dexamethasone was used.

Statistical methods

Descriptive statistics, including median and range for the number of surgical procedures, were used. Frequencies of complications were presented as absolute values and percentages. For not normal distributions of variables, the Kruskal-Wallis test was used to test the significance of pre- and post-intervention outcomes.

RESULTS

The sample consisted of 53 (31 male and 22 female) children with EB from 7 different countries who underwent a total of 220 sessions of general anesthesia. Fifty-one of the 53 chil-

| Type of surgical procedure | Total number of procedures performed | Performed before PCC, No. (% of total) | Performed after PCC, No. (% of total) |
|----------------------------|-------------------------------------|----------------------------------------|----------------------------------------|
| Repair of syndactyly       | 39                                  | 14 (36)                                | 25 (64)                                |
| Dilatation of esophageal strictures | 42                                  | 11 (26)                                | 31 (74)                                |
| Tooth repair                | 20                                  | 4 (20)                                 | 16 (80)                                |
| Tumor excision              | 10                                  | 1 (10)                                 | 9 (90)                                 |
| Circumcision                | 11                                  | 2 (18)                                 | 9 (82)                                 |
| PEG implantation*           | 4                                   | 1 (25)                                 | 3 (75)                                 |
| Plastic reconstructive surgery | 112                                | 25 (22)                                | 87 (78)                                |
| Body mapping                | 133                                 | 19 (14)                                | 114 (86)                               |
| Formation of hand mold      | 23                                  | 9 (39)                                 | 14 (61)                                |
| Change of dressing          | 149                                 | 27 (18)                                | 122 (82)                               |
| Wound tending               | 147                                 | 30 (20)                                | 117 (80)                               |
| Biopsy of suspect skin changes | 10                                  | 1 (10)                                 | 9 (90)                                 |
| Contracture release         | 24                                  | 4 (17)                                 | 20 (83)                                |
| Ear/neck reconstructive surgery | 16                                  | 2 (13)                                 | 14 (87)                                |
| Emergency                   | 3                                   | 0 (0)                                  | 3 (100)                                |

*PEG – percutaneous endoscopic gastrostomy.
Children underwent several sessions of anesthesia several times in a relatively short period. Eleven children (21%) had EB simplex, 3 (6%) junctional EB, and 39 (73%) dystrophic EB.

The median age at the first surgery was 10 years (range 1-19). Across all surgeries, the median age was 13 years (range 1-23). The median number of anesthesia administrations per patient was 3 (range 1-14).

Fifteen different surgical procedures were carried out 743 times (Table 1). Between April 1999 and December 2004, 150 surgical procedures were performed during 83 sessions of general anesthesia on a total of 39 patients. After the introduction of PCC in January 2005, 593 surgical procedures were performed during 137 sessions of general anesthesia on 48 patients. The median number of procedures before PCC was introduced was 2 (range 1-5), compared with 4 (range 3-7) afterwards (P < 0.001). Over the entire study period, the median number of procedures carried out during a single session of anesthesia was 3 (range 1-7).

Development and frequency of 19 different complications were noted (Table 2). Complications occurred in all 53 patients. Over the entire period, the median number of complications per session of anesthesia was 2 (range 0-10). The median number of complications per session of anesthesia increased after the introduction of PCC from 2 (range 0-10) to 3 (range 0-10) (P = 0.027). In contrast, the median number of complications per surgical procedure decreased from 1 (range 0-10) to 0.6 (range 0-2.5) after the introduction of PCC (P < 0.001) (Figure 1). The number of complications per patient was significantly lower before (median 2, range 1-20) than after (median 3, range 1-26) the introduction of PCC (P < 0.001).

PCC lengthened each anesthesia session from 65 minutes (range 35-655) to 95 minutes (range 50-405) (P < 0.001). The median number of surgical procedures per 10 minutes of anesthesia increased from 0.3 (range 0.0-0.6) to 0.4 (range 0.1-0.9) (P < 0.001), without a change in the median number of complications per 10 minutes: 0.3 (range 0-1.3) vs 0.3 (range 0-0.9) (P = 0.56).

Over the entire study period, the median number of hospitalization days was 1 (range 1-4). The number of hospitalization days per session of anesthesia was not significantly

| Complication type                    | Overall | Before PCC | After PPC |
|-------------------------------------|---------|------------|-----------|
|                                     | % per No. anesthesia sessions (n = 220) | % per No. surgical procedures (n = 743) | % per No. anesthesia sessions (n = 83) | % per No. surgical procedures (n = 150) | % per No. anesthesia sessions (n = 137) |
| Drop in RBC count                   | 63 29 8 | 21 25 14  | 42 30  |
| New head and neck bullae            | 59 27 8 | 17 20 11  | 42 31  |
| Oropharyngeal bullae                | 14 6 2  | 7 8 5    | 7 5    |
| New skin injuries                   | 50 23 7 | 16 19 11  | 34 24  |
| PONV                                | 59 27 8 | 17 20 11  | 42 31  |
| Pain requiring treatment            | 104 47 14 | 31 37 21 | 73 33  |
| Teeth damaged                       | 14 5 2  | 4 5 3    | 8 6    |
| Conjunctival erosions               | 4 2 1 | 1 1 1    | 3 2    |
| SpO2 ≤ 90%                          | 43 20 6 | 13 16 9  | 30 22  |
| Multiple intubation attempts        | 20 9 3  | 7 8 5    | 13 9    |
| Laryngospasm                        | 6 3 1  | 1 1 1    | 5 4    |
| Aspiration                          | 3 1 0.4 | 0 0 0    | 3 2    |
| Arrhythm                            | 32 15 4 | 11 13 7  | 21 15  |
| Hypotension                         | 54 25 7 | 21 25 14 | 33 24  |
| Delay awakening                     | 6 3 1  | 2 2 1    | 4 3    |
| Mechanical ventilation              | 3 1 0.4 | 1 1 1    | 2 1    |
| Allergic reaction                   | 3 1 0.4 | 1 1 1    | 2 1    |
| Hypothermia                         | 26 35 3 | 9 11 6  | 17 12  |
| Swelling of IV line insertion       | 48 22 6 | 19 23 13 | 29 21  |

*Abbreviations: RBC – red blood cells; PONV – post-operative nausea and vomiting; SpO2 – pulse oxymeter oxygen saturation; IV – intravenous.
different before (median 1, range 1-4) and after (median 1, range 1-3) the introduction of PCC \((P=0.169)\). In contrast, the number of hospitalization days per surgical procedure was significantly higher before (median 1, range 0.75-1.75) than after (median 0.3, range 0.2-3) the introduction of PCC \((P<0.001)\) (Figure 2).

**DISCUSSION**

This study was designed to investigate the impact of carrying out multiple surgical procedures during a single session of general anesthesia in the treatment of children with EB. Our results show that after the introduction of PCC, anesthesia sessions became longer and the number of surgical procedures during one session increased. Although the absolute number of complications increased, the rate of complications per 10 minutes of anesthesia did not change. The overall length of hospital stay did not change, but the number of hospitalizations decreased significantly.

Although most surgical procedures on adult patients can be performed under local or regional anesthesia, other criteria apply to children with EB. The disease makes children more vulnerable and less tolerant, so even minor and trivial operations such as dressing changes, body mapping, and formation of hand molds are performed under general anesthesia.

During the study period, 15 different surgical procedures were performed and the occurrence of 19 complications was recorded. The frequency and number of complications in our study differ from previously published results (18-20,22). Iohom et al (1) reported their 20-year experience with anesthesia for children with EB. Fifty-six anesthesia sessions (54 general and 2 local) were performed for 58 procedures in 10 children. Two complications related to anesthesia occurred 10 times (PONV, 7; new bullae, 3). We observed a far higher rate of complications: complications arose in 209 of 220 anesthesia sessions, despite the application of preventive measures. This can be explained by the fact that development of typical complications for patients with EB (new head and neck bullae and/or new oropharyngeal bullae) were reported together with adverse events associated with anesthesia (intubation, reaction to medications used in the anesthesia, irregular heart-beat, changes in blood pressure, pain and nausea, and
vomiting) and with complications related to surgery (drop in red blood cells, hypothermia).

Patients with EB are most vulnerable during the intubation period and it is the time when most complications appear. Our study showed that after the introduction of PCC there was an increase in the number of surgical procedures involving the oral cavity (dilatation of esophageal strictures, teeth repair) for which patients should be intubated (19,1,23). Surgeon and anesthesiologist share the same workspace which increases the chance of complications. This may explain the higher number of complications per anesthesia session after the introduction of PCC. Higher number of complications however did not influence duration of hospital stay.

Use of a laryngeal mask as an alternative to intubation was not considered for several reasons: it would reduce the already small workspace available for delicate procedures such as esophageal dilatation and tooth repair; most anesthesia sessions for syndactyly repair lasted longer than two hours, which is a contraindication for laryngeal mask; and the anesthesiologist on our team was well-trained in fiber optic intubation.

Although introduction of PCC led to a greater number of complications, this increase did not significantly prolong hospital stay. At the same time, PCC reduced the number of hospitalizations due to the smaller number of sessions of general anesthesia. The 593 surgical procedures that were carried out in the post-PCC group during 137 sessions of general anesthesia and 137 hospitalizations would have required, in the pre-PCC approach, 2.4-fold more hospitalizations, with the associated risks and costs. A reduction in the number of hospitalizations, without any decrease in health services, translates into improved quality of life for children with EB, since it means less stress and distortion of established routines.

Although this study used a relatively large sample, there are some important limitations. The main ones are the retrospective study design and insufficient data about the influence of patient age, co-morbidity, and the severity of complications. In addition, we examined only short-term perioperative complications. Patients were discharged from hospital when these complications were considered no longer life-threatening to patients. Although we did not perform longer-term follow-up, we were nevertheless able to show satisfactory results for standard EB findings, such as anemia and positive skin microbiological culture. Our patients were discharged with the recommendation that they continue outpatient supervision and treatment with a competent pediatrician and dermatologist. During the study period, discharged patients did not report any problems related to recently performed surgical procedures that would have required re-hospitalization.

Our results suggest that PCC is effective at reducing the exposure of patients with EB to the risks of general anesthesia. This approach requires the involvement of multidisciplinary teams to plan, prepare, and coordinate treatment for each patient.

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Declaration of authorship MKI gave the idea for the concept, was the principal investigator and coordinator of research, and performed processing and interpretation of results. JK conducted data analysis and interpretation, read and corrected the draft of the manuscript and read and approved the final version of the manuscript. IB was included in the study. JS made substantial contribution to the concept and design of study, data analysis, and interpretation of the results, and drafted and revised the manuscript. She also read and approved the final version of the manuscript. AK was included in study and was a part of the team. VMK was completely involved in writing the manuscript with suggestions and corrections.

Competing interests All authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare: no support from any organization for the submitted work; no financial relationships with any organizations that might have an interest in the submitted work in the previous 3 years; no other relationships or activities that could appear to have influenced the submitted work.

References

1. Iohom G, Lyons B. Anaesthesia for children with epidermolysis bullosa: A review of 20 years’ experience. Eur J Anaesthesiol. 2001;18:745-54. Medline:11580781
2. Fine JD. General cutaneous manifestations. In: Fine JD, Hniter H. Life with epidermolysis bullosa (EB): etiology, diagnosis, multidisciplinary care and therapy. Wien: Springer-Verlag; 2009. p.99-106.
3. Holbrook KA. Extracutaneous epithelial involvement in inherited epidermolysis bullosa. Arch Dermatol. 1988;124:726-31. Medline:3284471 doi:10.1001/archderm.124.5.726
4. Fine JD, Eady RA, Bauer EA, Briggaman RA, Bruckner-Tuderman L, Cristiano A, et al. Revised classification system for inherited epidermolysis bullosa: Report of the Second International Consensus Meeting on diagnosis and classification of epidermolysis bullosa. J Am Acad Dermatol. 2000;42:1051-66. Medline:10827412 doi:10.1016/s0190-9622(00)90302-5
5. Fox T. Notes on unusual or rare forms of skin disease. no.4 Congenital ulceration of the skin (two cases) with pemphigus eruption and arrest of development generally. Lancet. 1879;1:766-7. doi:10.1016/s0140-6736(02)46295-2
6 Pulkkinen L, Uitto J. Hemidesmosomal variants of epidermolysis bullosa. Mutations in the alpha6beta4 integrin and the 180-kD bullous pemphigoid antigen/type XVII collagen genes. Exp Derm. 1998;7:46-64. Medline:98533744 doi:10.1111/j.1600-0625.1998.tb00304.x

7 Fine JD, Eady RA, Bauer EA, Bauer JW, Bruckner-Tuderman L, Heagerty A, et al. The classification of inherited epidermolysis bullosa (EB): Report of the Third International Consensus Meeting on Diagnosis and Classification of EB. J Am Acad Dermatol. 2008;58:931-50. Medline:18374450 doi:10.1016/j.jaad.2008.02.004

8 Fine JD. Epidemiology of inherited epidermolysis Bullosa. In: Fine JD, Hintner H. Life with epidermolysis bullosa (EB): etiology, diagnosis, multidisciplinary care and therapy. Wien: Springer-Verlag; 2009. p.25-9.

9 Bauer JW, Rouan F, Koffer B, Reznicek GA, Kornacker I, Muss W, et al. A compound heterozygous one amino-acid insertion/nonsense mutation in the plectin gene causes epidermolysis bullosa simplex with plectin deficiency. Am J Pathol. 2001;158:617-25. Medline:11159198 doi:10.1016/S0002-9440(10)64003-5

10 Buchbinder LH, Lucky AW, Ballard E, Stanley JR, Stolar E, Tabas M, et al. Severe infantile epidermolysis bullosa simplex. Dowling-Meara type. Arch Dermatol. 1986;122:190-8. Medline:3511860 doi:10.1001/archderm.122.2.190

11 Cummins RE, Klingberg S, Wesley J, Rogers M, Zhao Y, Murrell DF. Keratin 14 point mutations at codon 119 of helix 1A resulting in different epidermolysis bullosa simplex phenotypes. J Invest Dermatol. 2001;117:1103-7. Medline:11710919 doi:10.1046/j.0022-202x.2001.01508.x

12 Pavicic Z, Kmet-Vintin P, Kansky A, Dobric I. Occurrence of hereditary bullosa epidermolyses in Croatia. Pediat Dermatol. 1990;7:108-10. Medline:2359725 doi:10.1111/j.1525-1470.1990.tb00664.x

13 Goldscheider K, Lucky AW, Mellerio JE, Palisson F, del Carmen Viruela Miranda M, Azizkhan RG. Perioperative care of patients with epidermolysis bullosa: proceedings of the 5th international symposium on epidermolysis bullosa, Santiago Chile, December 4-6, 2008. Pediatric Anesthesia. 2010;20:797-804.

14 Wu J. Deep sedation with intravenous infusion of combined propofol and ketamine during dressing changes and whirlpool bath in patients with severe epidermolysis bullosa. Paediatric Anaesthesia. 2007;17:592-6. Medline:17498025 doi:10.1111/j.1460-9592.2006.02177.x

15 Sakland M. Grading of patients for surgical procedures. Anesthesiology. 1994;2:281-4. doi:10.1097/00000542-199410050-00004

16 Menke H, John KD, Klein A, Lorenz W, Junginger T. Preoperative risk assessment with the ASA classification. A prospective study of morbidity and mortality in various ASA classes in 2,937 patients in general surgery [in German]. Chirurg. 1992;63:1029-34. Medline:1490409

17 Lubowikowski B. Surgical interventions. In: Fine JD, Hintner H. Life with epidermolysis bullosa (EB): etiology, diagnosis, multidisciplinary care and therapy. Wien: Springer-Verlag; 2009. p.246-57.

18 Ames WA, Mayou BJ, Williams KN. Anaesthetic management of epidermolysis bullosa. Br J Anaesth. 1999;82:746-51. Medline:10536554

19 Griffin RP, Mayou BJ. The anaesthetic management of patients with dystrophic epidermolysis bullosa. Anaesthesia. 1993;48:810-5. Medline:8214506 doi:10.1017/s000331090021777x

20 Boughton R, Crawford MR, Vonwiller JB. Epidermolysis bullosa – a review of 15 years’ experience, including experience with combined general and regional anaesthetic techniques. Anaest Intensive Care. 1988;16:260-4. Medline:3189735

21 Spence K, Gillies D, Harrison D, Johnston L, Nagy S. A reliable pain assessment tool for clinical assessment in the neonatal intensive care unit. J Obstet Gynecol Neonatal Nurs. 2005;34:80-6. Medline:15673649 doi:10.1111/j.1365-2044.2004.02278.x

22 Hagen R, Langenberg C. Anaesthetic management in patients with epidermolysis bullosa dystrophica. Anaesthesia. 1988;43:482-5. Medline:3407874 doi:10.1111/j.1365-2044.1988.tb06638.x

23 Lin AN, Lateef F, Kelly R, Rothsau KO, Carter DM. Anaesthetic management in epidermolysis bullosa: review of 129 anesthetic episodes in 32 patients. J Am Acad Dermatol. 1994;30:412-6. Medline:8113453 doi:10.1016/00000542-199410050-00004