

## Dental treatment of children with severe combined immunodeficiency

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### Abstract

*The prolonged survival of children having primary and secondary immunodeficiencies will require many of these youngsters to seek the attention of dentists. Two children with severe combined immunodeficiency (SCID), a disease with profound abnormalities of both cellular and humoral immunity, are presented to illustrate how dental and oral lesions cause major difficulties in clinical management. The first child developed extensive carious lesions requiring repair. The second developed multiple oral and gingival infections which ultimately led to his demise. The purpose of this report is to focus attention on the dental problems these children can experience and the extraordinary precautions required in their treatment.*

Severe combined immunodeficiency (SCID) is a congenital disease, characterized by profound deficiencies in both humoral and cellular immune function. The clinical course is characterized by recurrent, life-threatening infections which, until recently, culminated in a rapidly fatal course. Most children are ill by three months of age, frequently with diarrhea, failure to thrive, thrush, and sinopulmonary infection. In earlier reports, the mean age at the time of death was 6.8 months, however, advances in therapy have increased the life expectancy of these children.<sup>1</sup> Nevertheless, most still die during infancy. Inheritance may be autosomal recessive or x-linked recessive, although sporadic cases also have been reported. In one variant of this disease, a missing enzyme, adenine deaminase (ADA), leads to the accumulation of metabolic by-products which are toxic to the immune system.<sup>2</sup>

Laboratory tests demonstrate major abnormalities in humoral and cellular immunity. Lymphopenia (<1500/cm) is usually present and enumeration of T-cells (cellular) and B-cells (humoral) are often very low. Serum immunoglobulins are invariably low, with antibody function and response to antigenic challenge absent or poor. Delayed hypersensitivity skin tests are abnormal

and in vitro tests of cellular function as measured by response to phytohemagglutinin (PHA), antigens, or allogenic cells are diminished or absent. Mediator release from lymphocytes are usually absent.

The treatment of SCID has not been satisfactory. Increased survival has been achieved by relative isolation of these individuals along with the frequent use of broad spectrum antibiotics. Gamma globulin or plasma transfusions are given to augment humoral immunity. However, correction of cellular dysfunction has been more difficult. Successful immunoreconstitution with long-term survival has been achieved with bone marrow transplantation from histocompatible siblings. Only limited success has been achieved by transplantation of bone marrow from siblings not entirely histocompatible, from nonsibling donors, transplants with fetal tissue (thymus or liver), or cultured thymus epithelium. In cases where SCID is due to the lack of an enzyme, adenine deaminase, replacement therapy with frequent red blood cell transfusions (which provide the lacking enzyme) partially can ameliorate the immunodeficiency.<sup>3</sup>

### Case Reports

#### Case 1

A 3-year, 11-month-old white female had severe, recurrent infections beginning at 3 months of age. An immunologic workup during her first life-threatening infection, which was complicated by shock and renal failure, was consistent with a diagnosis of SCID associated with adenine deaminase deficiency (Table 1). After many life-threatening illnesses during infancy, she fortunately has not had any acute, disseminated infections during the past 18 months. Her growth has been retarded severely (less than the fifth percentile for height and weight) because of chronic disease. To protect her from increased exposure to infection, she has been kept in relative isolation except for immediate family. Since four months of age, she has received monthly packed red blood cell transfusions and since age three years, this

**Table 1.** Immunologic Studies in Case 1

	3 Months of Age	49 Months of Age
Total Lymphocytes	480/mm <sup>3</sup> (3,000–5,000)	650/mm <sup>3</sup> (2,000–5,000)
T-cells (%)	1%	13%
N-65–80%		
B-cells (%)	20%	6%
N-10–20%		
Quantitative Immunoglobulins (*in mg/dl)	IgG-92 (142–930) IgM-30 (16–125) IgA-9 (5–64)	IgG-507 (615–1530) IgM-36 (37–425) IgA-100 (42–238)
Phytohemagglutinin stimulation	No response	No response

has been supplemented by monthly plasma infusions to provide antibodies. Additionally, she has received cultured thymus epithelial transplants on five separate occasions, which have not resulted in any significant change in her immune function.

She came to a pedodontist complaining of pain in her teeth, particularly during mastication. Oral and radiographic examinations revealed several severely decayed primary teeth. Because of the extensive carious lesions, the proximity of decay to the pulp, and the need for strict medical supervision, admission to the University of Nebraska Medical Center was scheduled.

One week prior to admission, oral nystatin (liquid suspension 300,000 units three times daily) was begun to control oral candidal organisms. She was admitted to protective isolation two days prior to her dental surgery so that antibody replacement therapy (plasma transfusions) could be initiated and surveillance bacterial cultures could be obtained. Physical examination revealed a small, chronically ill child with no evidence of active infection except for mild rhinorrhea. There was no oral thrush. Cultures of the oral pharynx and gingiva revealed alpha hemolytic streptococci and *Streptococcus pneumoniae*. Bacterial cultures of the skin and ear canals grew out *Staphylococcus epidermatis*. *E. coli* were cultured from the rectum. Urine cultures grew *E. coli* with a colony count greater than 100,000 colonies/mm<sup>3</sup>. On the basis of these cultures, ampicillin (150 mg/kg/day) and gentamicin (7.5 mg/kg/day) were started. The patient also continued to receive nystatin (300,000 units) three times a day for control of oral fungal organisms. Transfusion of 200 cc of irradiated, fresh frozen plasma (15 cc/kg) was given for three days: the day before, the day of, and the day after dental surgery.

Dental instruments and materials were sent to the hospital sterile services for gas sterilization. The dental cart was disassembled to permit placement into the gas sterilizing apparatus. All liquid and paste medicaments

were in new, unopened containers to minimize vaporization during sterilization. Because of the low vapor point of mercury, preproportioned amalgam capsules could not be sterilized. Preparation for dental procedures under general anesthesia included: surgical scrub, sterile gowns, gloves, and masks for the pedodontic team; isolation of the oral cavity, throat pack, oral prophylaxis and debridement, mouth prop, and rubber dam isolation. The teeth were restored with silver amalgam and composite restorative materials. The maxillary right and left second primary molars had large carious lesions with involvement of the dental pulp. These teeth were extracted and pressure hemostasis was achieved with sterile gauze. The patient tolerated the procedure well and returned to protective isolation in the recovery room in good condition.

Postoperatively, the patient continued to receive amoxicillin (125 mg) three times a day (for the urinary tract infection) and nystatin (300,000 units) three times a day for the remainder of her hospital course. Six days postoperatively the patient received a transfusion of irradiated, fresh frozen plasma and irradiated packed red blood cells as part of her monthly replacement therapy for SCID with adenine deaminase deficiency. Normal healing of the extraction sites took place and the patient was dismissed from the hospital in good condition one week after dental surgery. The parent and patient received instructions about oral hygiene procedures and preventative dental measures which included 1.1 mg of sodium fluoride drops (to supplement the patient's drinking water which contained 0.4 ppm of fluoride), brushing with a fluoride toothpaste, flossing, and the use of a fluoride mouth rinse. At her six-month recall appointment, she was doing well with no new clinical or radiographic lesions present.

## Case 2

A two-year-old white male had a past history of fever, failure to thrive and recurrent staphylococcal infections since one month of age. An immunologic workup performed at the Children's Memorial Hospital (Chicago) at one year of age revealed profound defects in both humoral and cellular immune function. A diagnosis of SCID was made and the child was treated with gamma globulin injections every four weeks along with bactrim (1/2 tsp BID).

The patient did well until age two years, when he developed persistent fever and erythematous, indurated macules over the right ankle, the arms, and face. A skin biopsy revealed chronic panniculitis. Small, shallow ulcers with erythematous borders were seen on the palate. The oral ulcers were cream-colored and surrounded by an erythematous halo. The ulcerations also were noted on the tip of the tongue and pharynx. Dicloxicillin, methicillin, ampicillin, and gentamicin were utilized in different antibiotic regimens. Glyoxide was utilized to

debride the oral lesions and hydrocortisone acetate<sup>a</sup> was applied to the lesion before meals. Medicated cream<sup>b</sup> also was applied to the lips. The patient's poor appetite was thought to be secondary to the painful oral lesions, and nasogastric feeding was instituted.

The patient's oral hygiene was very poor with dental plaque on all surfaces of the teeth. Marginal gingivitis was observed all around the teeth and was markedly worse in the maxillary and mandibular anterior tissue. No obvious carious lesions were detected. Cultures of the mouth ulcers grew out alpha hemolytic streptococci and Neisseria colonies. *Staphylococcus aureus* was cultured from the purulent nasal discharge. Gentian violet and glyoxide were applied to the oral lesions. After one week, the oral lesions improved considerably on a regimen of oral saline rinses and additional parenteral gamma globulin. Peripheral hyperalimentation was started to improve the patient's nutritional status prior to thymus epithelial transplantation.

One week after a thymic epithelium transplant, the patient again was examined by the dental service. In addition to severe gingival disease, a large, shallow, plaque-covered ulcer was noted on the hard and soft palate which extended to the posterior pharyngeal wall. Cultures of the lesion grew *Staphylococcus aureus*, haemophilus and Neisseria organisms. Viral and fungal cultures were negative. Dicloxicillin (125 mg q 6h po) was initiated. Dental radiographs were within normal limits.

An incisional biopsy of the lesion on the palate was obtained, which revealed nonkeratinized, squamous epithelium with irregular extension into the dermis, consisting of moderately dense fibrous tissue with few inflammatory cells (lymphocytes). No atypical cells or inclusions were noted. Specialized studies failed to show evidence of any organisms. The microscopic examination was consistent with the diagnosis of chronic inflammation. *Staphylococcus aureus* was cultured from a bullous impetiginous lesion on the lip. Over the next two months, the patient was treated with trimethoprim and sulfamethoxazole<sup>c</sup> orally and irradiated fresh frozen plasma. A fungal infection was suspected after the appearance of a gummy exudate from the mouth. Nystatin was used since no pseudohyphae was seen (no mucosal invasion). Despite aggressive therapy, the child's condition continued to deteriorate and therapy was changed to intravenous amphotericin. Four days later, the patient had a respiratory arrest and died.

## Discussion

Dental treatment of patients with severe combined immunodeficiency previously has not been reported in

the dental or medical literature, probably because the disease is rare and most affected children die within the first few years of life. As a result, little attention is focused on the dental or oral care of these youngsters. However, as patients survive longer, dental care becomes a major consideration in the well-being of these children. Because of extreme susceptibility to infection, these children require far greater precautions during dental treatment than would be necessary with other conditions which reduce immunity such as renal transplantation,<sup>3</sup> leukemia,<sup>4</sup> and other malignancies,<sup>5,6</sup> or other secondary immunosuppressed states.<sup>7,8</sup> What ordinarily would be a relatively minor procedure is fraught with danger because of the patient's markedly compromised immune system. Unlike the skin, the mouth is impossible to keep sterile—thus dental manipulation could lead to bacteremia and sepsis.<sup>4,9</sup> Greenburg<sup>10</sup> recommends that patients with decreased T-cell function be treated with topical antifungal therapy prior to dental treatment in order to minimize the risk of systemic fungal infections. He also suggests culturing the mouth to determine the oral flora prior to initiation of antibiotic therapy, since these children are susceptible to fungi and opportunistic bacteria.<sup>10</sup>

Children with B-cell deficiencies usually are treated with gamma globulin injections (0.7 cc/kg) or plasma infusions (15 cc/kg) on a monthly basis. Additional gamma globulin or plasma should be given if dental treatment is to be performed. Appropriate antibiotics directed against oral bacteria should be given prior to dental treatment and probably should be continued for a day or two following treatment. Prolonged use of prophylactic antibiotics generally is not warranted since it carries the risk of superinfection with resistant organisms. During the dental procedure, care must be taken to minimize trauma and excessive manipulation of oral tissues, which would enhance hematogenous bacterial seeding. Patients with SCID are not considered good candidates for pulpotomy or pulpectomy procedures because, even though the possibility of failure may be slight, if failure did occur, the resultant apical or inter-radicular infection could result in abscess formation. This would serve as a nidus of infection which could be fatal. Therefore, extraction should be the treatment of choice when the pulp is cariously involved.

Robertson et al.<sup>11</sup> have suggested that young immunodeficient patients do not have an increased incidence of gingival inflammation, early periodontal destruction, or dental caries as compared to immunocompetent patients of similar age and oral hygiene. However, Patient 2, had poor oral hygiene accompanied by severe gingival problems and oral lesions. Microorganisms entering through these lesions more than likely led to his death. Patient 1 had many cavities and a thinner than normal layer of enamel, but no other abnormalities of the teeth, gums, pharynx, or oral mucosa. In contrast to Robertson, Cole et al.<sup>11</sup> found that patients with immunoglobulin

<sup>a</sup> Orabase: Hoyt Laboratories, Division of Colgate-Palmolive Co., Norwood, Mass. 02062.

<sup>b</sup> Carmex: Carma Lab Inc., Franklin, Wis. 53132.

<sup>c</sup> Bactrim: Roche Laboratories, Division of Hoffman-La Roche, Inc., Nutley, N.J. 07110.

dysfunction do have an increased susceptibility to dental caries and that these individuals seem to harbor *Streptococcus mutans* in greater quantities than normal individuals. Cole also found that *S. mutans* comprised a greater proportion of the pit and fissure flora than that of the smooth surface. The caries found in Patient 1 were of the pit and fissure variety except for those on the labial and lingual surfaces of the maxillary cuspids. Also, the extent of her carious lesions could have been elevated due to the fact that she lived in a rural area where the fluoride content of the drinking water was suboptimal (0.4 ppm).

Treatment of dental problems in children with primary immunodeficiencies will become more prevalent in the future as more of these children survive due to medical advances in treating their diseases. Bacteremia or fungemia from dental caries or periodontal problems potentially could be fatal. Therefore, physicians and dentists must be on the alert for caries and periodontal disease in children with SCID.

### Summary

The care of children with SCID requires a multifaceted team approach. Dentists will play an increasingly important role in the overall care of these children. The prevention of dental caries and periodontal disease is imperative because of the high risk of infection and the potential risks involved in their dental treatment.

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## Quotable Quotes

Even if it were possible, most American women would not want to choose their children's gender, report Anne Pebley and Charles Westoff of Princeton University. Of 3,400 women surveyed, 59% disapproved of gender preselection. Most of those who approved said they would probably want a male first-born child.

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