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□ Case Report □

Autoimmune Hemolytic Anemia in Children

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The purpose of this study was to review the clinical, hematological, immunological features and treatment responsiveness in children with autoimmune hemolytic anemia (AHA). Eight children with AHA and positive Coombs' test was evaluated. Seven patients presented with acute onset of symptoms and histories of infection. One case was diagnosed as Evans syndrome, one as a chromosomal anomaly, and one case was combined with the Guillain-Barré syndrome. Among 8 the patients, 4 exhibited warm antibodies and the remainder had cold antibodies. The patients were given washed packed red blood cells, prednisolone or immunosuppressive drugs (6-MP or cyclophosphamide). Five patients responded well to transfusion and/or prednisolone, one patient died and one patient showed no response in 5 months of follow up.

Key Words: Autoimmune hemolytic anemia (AHA), Evans syndrome, Guillain-Barré syndrome, warm antibody, cold antibody, Coombs' test

The two essential features of immune hemolytic disease are (1) a shortened red cell survival rate in vivo and the rapid regeneration of red cells, and (2) evidence of an immune response directed toward autologous red cells, most frequently demonstrated by a positive direct antiglobulin reaction (Coombs' test) (Zuelzer *et al.* 1970; Packman and Leddy 1983).

During this century clinicians have experienced many cases of AHA, but despite the frequency of AHA in children, it has prompted very few studies. Our purpose is to describe the clinical, hematologic, immunologic features, and the responsiveness to treatment in children with AHA with brief review of the literatures.

MATERIAL AND METHODS

Eight children with AHA who were admitted to the Pediatric Department of Yonsei University College of Medicine from 1975 through 1985 were studied retrospectively. Routine hematologic tests, bone marrow studies, immuno-hematologic tests, and chromosome studies were performed by standard procedures.

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RESULTS

The patients included 5 male and 3 female whose ages at the onset of the disease ranged from 5 months to 14 4/12 years. Seven patients had an acute onset of disease followed by fever or symptoms of URI (Table 2).

Initial clinical manifestations showed pallor, hepatomegaly, fever, dark colored urine, splenomegaly, jaundice, abdominal pain, dizziness, lethargy, arthralgia and petechiae (Fig. 1).

Associated disorders were as follows. One patient presented with hepatitis B and CMV infection, one patient with sepsis and bacterial endocarditis due to Staphylococcus aureus, one patient with Guillain Barré Syndrome, and chromosomal anomaly [46XY/47XY + 21/92XXYY (19:5:3)] was found in one patient (Table 3).

Laboratory data are listed in Table 4. Most children were moderately to severely anemic, and the reticulocyte count was often inappropriately low despite the marked anemia. Half of the patients had reticulocyte counts of less than 5%. Half of the patients exhibited thrombocytopenia and one of these displayed Evans syndrome. Hemoglobinuria was noticed in 4 patients and 3 of them had warm type autoantibodies.

Decreased levels of C3 and C4 were present in one patient, hemoglobinuria in 3 patients, hyperbilirubinemia in 4 patients, and 2 patients had increased transaminase levels.

Table 1. Profile of Patients

Case No.	Age (years)	Sex	Prodromal Sx.	Associated Conditions	Hepato / Splenomegaly	Treatment	Remarks
1	6	M	Fever Diarrhea Pallor	Acute gastro-enteritis	− / −	Transfusion Steroid 6-MP	Expired Thrombocytopenia T.bil: 4.2 mg% SGPT: 60 IU/L Hemoglobinuria
2	7	M	Fever Abdo. pain Pallor	URI	+ / +	Transfusion Steroid	Recovered 46XY/47XY+21/ 92XXYY (19:5:3) T.bil: 1.8 mg%
3	11	F	Fever, Pallor Headache Dizziness Abdo. pain	Hepatitis B CMV infection Mycoplasma infection	+ / −	Transfusion Steroid Cytoxan	Recovered Decrease C_3 C_4 Thrombocytopenia
4	14 4/12	F	Fever	S. aureus sepsis Bact. endocarditis	− / −	Transfusion Steroid	Recovered Thrombocytopenia
5	5/12	M	Icteric skin Vomiting, Pallor Dark colored urine	URI Acute gastro-enteritis	+ / +	Transfusion Steroid	Recovered T.bil: 4.3 mg% SGPT: 145 IU/L
6	10/12	F	Lethargy Dark colored urine Pallor	URI	+ / +	Transfusion	Recovered Hemoglobinuria
7	1	M	Fever Dark colored urine Pallor		+ / −	Transfusion	Not recovered Hemoglobinuria T.bil: 4.2 mg% SGPT: 60 IU/L
8	10	M	Icteric skin Petechiae Arthralgia	URI Guillain-Barré SD	+ / −	Transfusion Steroid	Recovered Thrombocytopenia Hemoglobinuria Proteinuria

Table 2. Clinical characteristics

Age at onset	(years)
Mean ± SD	6.32 ± 5.26
Range	0.32 − 14.33
Mode of onset	(cases)
Abrupt	7
Insidious	1

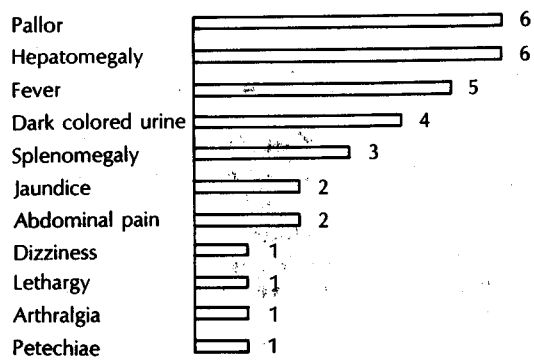

Fig. 1. *Initial Clinical Manifestations.*

In general, peripheral blood smears revealed spherocytosis in all patients, and anisocytosis, poikilocytosis, and polychromasia were also noted.

Bone marrow examinations were done in 6 patients and all of them showed erythroid hyperplasia. Megaloblastic changes had occured in one patient and increased megakaryocytes were noted in two patients.

Hematologic findings revealed hematocrit of greater than 20 percent in 3 patients, 15 to 19 percent in 3 patients, and less than 10 percent in one patient. Three patients had reticulocyte counts above 10 percent while the count in 3 patients was below

5 percent (Table 5).

The direct Coombs' test was positive in 6 patients. Two of them had specific IgG and C3 reactions, and one of them had only an elution Coombs' reaction. Among these 8 patients 4 exhibited cold antibodies as outlined in Table 6.

Table 7 notes the therapy given to these children. All of the patients received washed packed red blood

Table 3. Associated disorders

	Cases
Prodromic acute infections	8
CMV infections, Mycoplasma infection, Hepatitis B	1
Staphylococcal sepsis, Bacterial endocarditis	1
Guillain-Barré Syndrome	1

Table 5. Hemogram at the time of diagnosis

	No. of patients
Hematocrit (%)	
Less than 10	1
10-14	0
15-19	3
Over 20	4
Reticulocyte(%)	
Less than 5	4
5 - 9	1
Over 10	3
Spherocytosis	8
Thrombocytopenia (below 100,000/mm^3)	4
Hemoglobinuria	4

Table 4. Hematologic findings at the time of diagnosis

Case No.	Age (years)	Hb/Hct (g/dl)	Reti. (%)	WBC (/mm^3)	Platelet (/mm^3)	Periphral* blood finding	Bone marrow finding	Coombs' test
1	6	5.7/16.4	18.5	10,600	68,000	Anisocytosis Poikilocytosis	Erythroid hyperplasia Increased megakaryocyte	Indirect Cold Ab
2	7	6.0/19.0	0.3	3,200	211,000	Hypochromic Normocytic	Erythroid hyperplasia Megaloblastic change	Direct IgG C' Cold Ab
3	11	7.5/22.9	7.1	25,300	99,000	Polychromic Macrocytic	Erythroid hyperplasia	Direct Cold Ab
4	14 4/12	9.3/27.8	0.3	7,700	62,000	Polychromic	Erythroid hyperplasia	Direct IgG, C' Cold Ab
5	5/12	2.9/ 7.6	10.8	49,600	512,000	Polychromic Anisocytosis Poikilocytosis	–	Direct
6	10/12	5.1/14.1	3.2	24,400	966,000	Hypochromic Poikilocytosis	–	Direct IgG Indirect
7	1	7.7/22.0	3.7	8,900	116,000	Polychromic Poikilocytosis Anisocytosis	Erythroid hyperplasia	Direct Elusion
8	10	8.3/24.5	4.6	8,900	60,000	Polychromic Anisocytosis Poikilocytosis	Erythroid hyperplasia Increased megakaryocyte	Direct

*: All cases have spherocytosis

cells without any significant transfusion reactions. Six of them received the corticosteroid, prednisolone in a daily dose of 1-2 mg/kg. The dosage was usually decreased after 2 weeks and stopped within 2 months.

Table 6. Results of Coombs' test

	No. of Patients
Positive direct Coombs' test	7
IgG Coombs' only	1
Mixed IgG & C_3 Coombs'	2
Elusion Coombs' only	1
Broad spectrum Coombs' (specific reagents not used)	3
Positive indirect Coombs' test	2
Positive cold antibody	4

Table 7. Treatment of patients in this series

Treatment	No. of Patients	No. of Responders
Transfusion alone	2	1
Transfusion plus corticosteroids	6	5
Immunosuppressive Agents*	2	1

*: Immunosuppressive agents used in conjunction with transfusion and corticosteroids.

Cyclophospamide was administered to one patient but was dicontinued due to hemorrhagic cystitis, and in another patient with thrombocytopenia (Evans syndrome), 6-MP was used and despite its transient effect, the patient eventually died due to intracranial hemorrhage. The prognosis was usually good; 5 patients recovered within 3 months, one patient with positive cold antibodies and thrombocytopenia recovered within 4 months, one patient with warm antibodies showed no signs of recovery within 5 months of follow up, and one patient with Evans syndrome died of intracranial hemorrhage 6 months after diagnosis.

Figure 2 outlines the course of one patient with cold antibody type hemolytic anemia. Initially there was an unfavorable response, in spite of transfusion, glucocorticoid and immunosuppressive therapy, but eventually the patient demonstrated normal hemoglobin and reticulocyte counts.

Figure 3 reviews the course of one patient with warm antibody type hemolytic anemia. It reveals a favorable response to transfusion and glucocorticoid therapy, and all thematologic findings reached normal levels within 20 days of treatment.

DISCUSSION

The annual incidence of AHA is estimated to be one per 75,000 or 80,000 population (Pirofsky 1975;

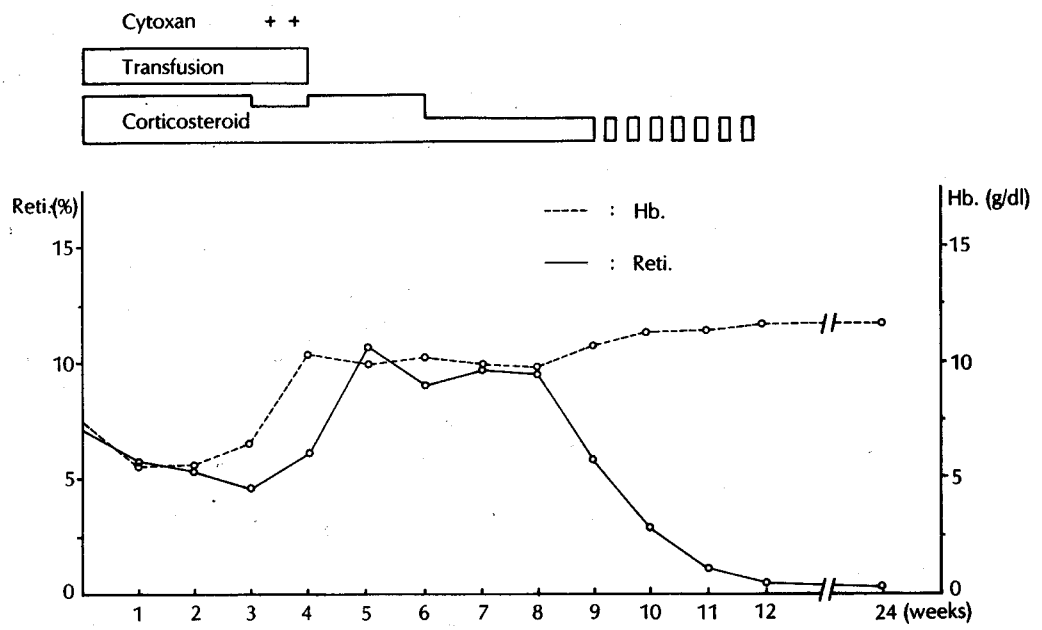

Fig. 2. Changes in the Hemoglobin and Reticulocyte counts during therapy in a Case of Cold Antibody type Hemolytic Anemia.

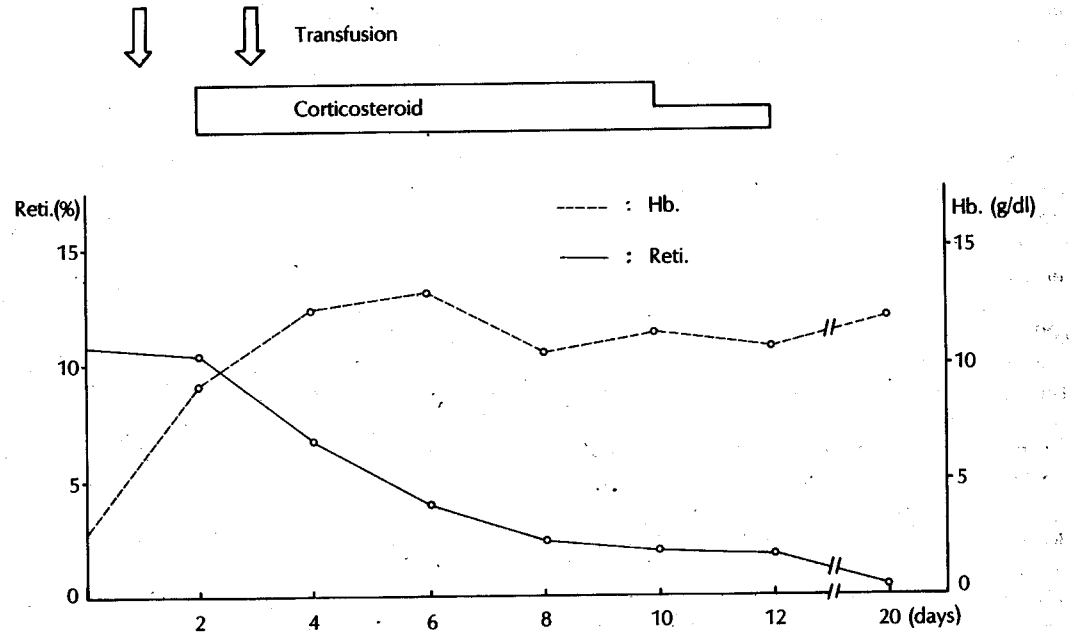

Fig. 3. Changes in the Hemoglobin and Reticulocyte counts during therapy in a Case of Warm Antibody type Hemolytic Anemia.

Packman and Leddy 1983).

AHA may be classified in 2 complementary ways where as the majority of the cases (80-90%) are mediated by warm-active autoantibodies, and the remainders are mediated by cold active autoantibodies (Packman and Leddy 1983).

Twenty to eighty percent of AHA consist of idiopathic type (Packman and Leddy 1983) with a seasonal incidence peak in the spring. AHA can occur in all age groups, but the majority of patients are over 40 years of age (Allgood and Chaplin 1967). In children the majority of patients are younger than 4 years of age (Habibi *et al.* 1974) and Laski *et al.* (1961) reported one case of AHA which occurred at 2 1/2 years of age. There is no sexual preponderance in children but the incidence is significantly high in adult females (Packman and Leddy 1983). In children the male to female ratio is 1.2 – 1.96:1 (Habibi *et al.* 1974; Buchanan *et al.* 1976).

In this study, 3 children were younger than 5 years of age, 5 were male, and 4 had warm active autoantibodies.

The etiology of AHA includes warm active autoantibodies, cold active autoantibodies, drugs, malignant tumors, infections, connective tissue disorders, and post operation state of aortic valve (Packman and Leddy 1983). In this study all cases were associated with respiratory or gastrointestinal infections, and associated infectious disorders included hepatitis B, CMV infection, mycoplasma infection or staphylococcal sepsis.

Buchanan *et al.* (1976) described the acute and transient nature of AHA but Habibi *et al.* (1974) said that there were no differences between the two groups in responsiveness to treatment or prognosis.

The symptoms and physical findings vary according to the degree of hemolysis. Common manifestations of AHA include anemia, jaundice, pallor, fever, loss of appetite, fatigue, red colored urine, abdominal pain, diarrhea, dehydration, or purpura. Hemoglobinuria is rare in warm reactive AHA but frequently occurs in cold reactive AHA (Packman and Leddy 1983). Hepatomegaly or splenomegaly may occur, but Habibi *et al.* (1974) noted that hepatomegaly occured in only 12.5% of the cases.

Among the 8 presented cases here, symptoms and signs included fever in 5 cases, hemoglobinuria in 3 cases, pallor, jaundice, fatigue, hepatomegaly in 5 cases, and splenomegaly in 3 cases.

Important diagnostic features are found on examination of blood film. Hemoglobin level, reticulocytes count, red blood cells count are various according to the destination of red blood cell and ability of compensation in bone marrow. Polychromasia indicates the presence of reticulocytes, reflecting an increased rate of egress of red cells from marrow. Spherocytes are seen in patients with moderate to severe AHA and such cells are fragile in the osmotic

fragility test. Reticulocytopenia has been noted in patients with normal or hyperplastic erythroid marrow (Packman and Leddy 1983) and may also be seen in patients with marrow function compromised by an underlying disease, toxic chemicals, or nutritional deficiency. Rarely, severe immune thrombocytopenia associated with warm antibody AHA; this condition is termed Evans syndrome (Evans *et al.* 1951).

In this study spherocytosis was found in all of the patients and 6 patients had reticulocytosis. Thrombocytopenia (defined as a platelet count of less than 100,000/mm^3) was noted in 4 cases, One of which was diagnosed as Evans syndrome.

The white blood cell count is usually within normal limits, but in acute hemolysis leukocytosis can be noted and its usual level is above 30,000/mm^3 with occasional hypersegmentation (Habibi *et al.* 1974). In this study 3 patients had leukocytes above 20,000/mm^3.

Bone marrow examinations usually reveal increased activity of erythropoiesis ie. erythroid hyperplasia in about 10% (Klemperer 1978) and rarely megaloblastic changes (Willoughby *et al.* 1961). In this study all 6 biopsied cases manifestated erythroid hyperplasia, 2 cases had increased megakaryocytes, and one of them exhibited megaloblastic changes.

Serologic tests reveal positive Coombs' tests which may consist of direct, indirect or both direct and indirect Coombs' tests.

In warm antibody AHA three major patterns of direct antiglobulin reaction have been noted: (1) coating of red cells with IgG alone, (2) coating of red cells with IgG plus complement components, and (3) coating with complement components in the absence of detectable immunoglobulin. In patterns 2 and 3, the complement components usually detected are C3 and C4 (Engelfriet *et al.* 1968; Talal 1980). In most but not all patients there is a rough correlation between the strength of the antiglobulin reaction (IgG molecules per cell) and the rate of red cell destruction. IgG1 and IgG3 antibodies appear to be more effective in decreasing red cell life span than those of the IgG2 and IgG4 subclasses (Von dem Borne *et al.* 1977). The explanations for these findings is thought to reside in (1) the preferential affinity of macrophage Fc receptors for IgG1 and IgG3 subclasses, and (2) a greater complement-fixing capacity of antibodies belonging to the IgG1 or IgG3 subclasses (Yasmeen *et al.* 1973; Müller-Eberhard 1975; Ehlenberger and Nussenzweig 1977).

Cold agglutinins may be detected in normal children and in cold agglutinin AHA the serum titer is commonly 1:1,000 or higher, and may reach 1:100,000 or more. Cold agglutinins are predominantly 19 S IgM globulins. IgA or IgG cold agglutinins have been reported in a few cases (LoBuglio *et al.* 1967; Huber *et al.* 1968). The direct antiglobulin test is positive with anticomplement (anti-C3 or anti-C4) reagents, the antibody itself is not detected by antiglobulin reactions with antiserum to human immunolobulins, nor by specific anti-IgM, anti-IgA or anti-IgG. This is because the cold agglutinins, unlikely the more firmly bound complement proteins, dissociate from the red cells, eg., during the washing steps of the antiglobulin procedure. The majority of cold agglutinins are reactive with human erythrocyte antigens of the I/i system. The I antigen complex is expressed strongly on adult red cells but weakly on neonatal cord red cells. The converse is true of the i antigen complex. Cold agglutinins with anti-i specificity are found in patients with infectious mononucleosis and in some patients with lymphoma (Packman and Leddy 1983). High titer cold agglutinins usually appear symptomatic of chronic secondary cases (Habibi *et al.* 1974).

In this study the direct Coombs' test was positive in 6 patients. In 2 patients specific IgG and C3 component reactions were detected but the elution Coombs' reaction was noted only in one patient.

Treatment consists of transfusion, glucocorticoids, splenectomy, immunosuppressive drugs, and etc. (Packman and Leddy 1983).

Transfusion of red cells in AHA presents two sets of difficulties: the problem of cross-matching and the rapid in vivo destruction of transfused cells. It is nearly always impossible to find truly sero-compatible donor blood except in rare cases in which the autoantibody can be shown to have specificity for a defined blood group antigen. If such specificity cannot be defined by testing of serum or eluted autoantibodies against standard cell panels, donor red cells should be chosen on the basis of least incompatibility with the patient's serum in cross-match testing (Rosenfield and Jagathambal 1976; Neerhout 1978). It is also important to test the patients serum carefully for an alloantibody which could cause a severe hemolytic transfusion reaction against donor red cells. Once selected, approximately 20-50 cc of packed red cells should be transfused very slowly while the patient is monitored for signs of a hemolytic transfusion reaction. Thirty to sixty minutes after transfusion, if there are no complication transfuse 50 ml/m^2 of packed red cells or washed packed cells with warming (Zuelzer *et al.* 1970).

Buchanan *et al.* (1976) reported that 3 of 22 patients had been treated with transfusion alone. Glucocorticoids, first used for this disorder about 30 years ago (Dameshek *et al.* 1951), can cause dramatic cessation or a marked slowing of hemolysis in about

two-thirds of the patients. About 20 percent of treated patients with warm antibody AHA undergo complete remission. About 10 percent show minimal or no response to glucocorticoids (Engelfriet *et al.* 1968). The best responses are seen in the idiopathic cases and in those related to lupus erythematosus (Wilkinson *et al.* 1973; Dacie 1975; Pirofsky 1975). In general about 70% show a response to glucocorticoids. Glucocorticoids may influence hemolysis in warm antibody AHA by several mechanisms. Earlier investigations noted that hematologic improvement was often, though not always, accompanied by a reduction in the strength of the direct antiglobulin test (Wilkinson *et al.* 1973). The subsequent observation of a decrease in cell-bound and/or free serum autoantibody during stable glucocorticoid induced remission (Evans *et al.* 1951; Leddy and Swisher 1978) suggests that a decrease in the synthesis of autoantibody may ultimately be important in improving red cell survival. However, reduction in autoantibody synthesis cannot explain the rapid improvement seen in many patients within 24 to 72 hours after starting glucocorticoid therapy. There is substantial clinical and experimental evidence that the most important early effect of glucocorticoids is to suppress sequestration of opsonized red cells by splenic macrophages (Greendyke *et al.* 1965; LoBuglio *et al.* 1967; Huber *et al.* 1968; Kurlander *et al.* 1978). Another proposed early effect of glucocorticoid therapy may be a reduction in the binding affinity of autoantibodies for the patient's red cells (Jandl and Kaplan 1960).

The main criteria for recommending splenectomy is that; (1) no response to transfusion and/or glucocorticoids for 1-2 months, (2) severe side reaction to the use of glucocorticoids, or spleen: liver ratio with 51Cr t 1/2 was at least 2.3 (Goldberge *et al.* 1966; Allgood and Chaplin 1967). Fifty percent of patients treated with this criteria showed remission. But attempts to select responders by 51Cr red cell sequestration studies have been disapponting because of poor correlation with results of splenectomy (Tisdale *et al.* 1959; Parker *et al.* 1977; Talal 1980). Results of splenectomy vary widely, but approximately two-thirds of splenectomized patients will have partial or complete remission (Tisdale *et al.* 1959; Christensen 1973; Bowdler 1976). The relapse rate however is disappontingly high (Packman and Leddy 1983). Many patients require further glucocorticoid therapy to maintain acceptable hemoglobin levels (Tisdale *et al.* 1959; Wilkinson *et al.* 1973), although often at lower dosage than required prior to splenectomy (Christensen 1973; Chaplin and Avioli 1977).

Cytotoxic drugs such as cyclophosphamide, 6-mercaptopurine, azathioprine, or 6-thioguanine were first tried in AHA with the idea that they may inhibit the synthesis of autoantibodies. Though there is little direct evidence for such an effect, beneficial responses to immunosuppressive drugs may be observed in some patients who fail to respond to glucocorticoids (Skinner and Schwartz 1972; Murphy and LoBuglio 1976). The drugs of choice are cyclophosphamide 60 mg/m^2 or azathioprine 80 mg/m^2, given daily and if the drug is tolerated by the patient, it is resonable to continue treatment for up to 6 months while waiting for a response. When response occurs, the dosage may be slowly decreased. If there is no response, an alternative drug may be similary tried (Packman and Leddy 1983).

Other therapies included plasma exchange, plasmapheresis, thymectomy, heparin, or vinblastine tagging to platelet sensitized with IgG. But all of these forms of therapy should be considered experimental and reserved for those patients who have failed to respond to established forms of treatment (Wilmers and Russell 1963; Karaklis *et al.* 1964; Murphy and LoBuglio 1976; Rosenfield and Jagathambal 1976).

Among the 4 cases of warm reactive AHA in this study, 2 cases were treated with transfusion alone and one of them responded. Two cases were treated with transfusion and glucocorticoids, and they responded to treatment.

In cold reactive AHA, keeping the patient warm, particulary the extremities, provides moderately effective symptomatic relief. This may be the only measure required in patients with mild chronic hemolysis. Chlorambucil or cyclophosphamide therapy has been helpful in some patients and deserves consideration in difficult cases (Schubothe 1966; Evans *et al.* 1973; Conley *et al.* 1980). Splenectomy and glucocorticoids have generally been disappointing, although exceptions have been reported (Pisciotta 1955; McCurdy and Rath 1958; Bell *et al.* 1973). There is some experimental and clinical basis for considering very high doses of glucocorticods in severely ill patients. Plasma exchange may provide temporary amelioration of hemolysis (Logue *et al.* 1973; Taft *et al.* 1977), but no long term benefit can be expected (Rosenfield and Jagathambal 1976). Red cell should be reserved for those patients with severe anemia of rapid onset and in dager of cardiorespiratory complications. Because the reduction in serum complement levels in such cases may limit the hemolytic rate, administration of washed red cells is prefered, to avoid replenishing the hemolytic sequence (Packman and Leddy 1983).

Prognosis may be related to the reticulocyte count, age at onset and underlying diseases, but this is not widely accepted.

In warm reacting AHA, overall mortality rate has been significant (up to 46 percent) in several older series, but appears to be improving (Worlledge 1974). The actual survival at 10 years is reported to be 73% (Silverstein *et al.* 1972). In children the majority of patients exhibit an acute self-limited course and respond rapidly to glucocorticoids. Those who recover from the initial hemolytic episode have a good prognosis. The overall mortality rate is lower than in adults, ranging from 10 to 30 percent (Evans and Weiser 1957; Allgood and Chaplin 1967; Habibi *et al.* 1974; Buchanan *et al.* 1976; Zupanska *et al.* 1976). Dausset and Colombani (1959) reported that a decreased reticulocyte count, leukopenia or a negative indirect Coombs' test was related in bad prognosis. Patients with cold reactive AHA often have a relating benign course and survive for many years (Schubothe 1966; Evans *et al.* 1973; Conley *et al.* 1980). Occasionally death results from infection or severe anemia, or in the case of a secondary cold agglutinin disease from the underlying lymphoproliferative process. In general the main causes of death in AHA are pulmonary embolism, infection, severe anemia, myocardial infarction, and acute renal tubular necrosis (Packman and Leddy 1983). In this study the cause of death was intracranial hemorrhage.

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