To sum up, an adequate therapeutic effect can be obtained in the large majority of patients with cryoprecipitates. Their essential drawbacks are lacking in purified, highly concentrated AHF preparations. The availability of such products is particularly desirable for the treatment of patients with inhibitors to factor VIII. It is anticipated that the highly concentrated factor-VIII preparations will progressively replace the cryoprecipitates if the problems of hepatitis transmission and production costs can be solved.

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Can Hemophilic Patients Be Adequately Maintained with Cryoprecipitates? Or Is it Desirable or Even Necessary to Manufacture and Administer Highly Concentrated AHF Products?

ROSEMARY BIGGS: There is no doubt that haemophilic patients can be treated adequately with cryoprecipitate. The material compares well in purification and potency of the administered dose with many other concentrates made by large-scale fractionation procedures. The cryoprecipitate method has provided a most welcome increase in the amounts of material available to treat haemophilic patients in many countries and has revolutionised the life of these patients.

The great advantage of availability should not, however, hide the disadvantages in the use of cryoprecipitate. The material is often presented in plastic bags, the contents of 10–25 of which may need to be pooled before a dose can be administered. Considerable skill is required to prevent contamination. It must be stored and transported deep frozen. The potency of the dose cannot be known before administration.

The freeze-dried concentrate can already be prepared at two convenient potencies: high potency and medium potency [NEWMAN *et al.*, 1971]. The activity of the dose material is known. It is easy to make up and administer. It does not require to be deep frozen for storage and transport and thus may be available to be carried about in the patient's ordinary luggage. The manufacture on a large scale can be planned to conserve all other blood components, indeed the conservation of all useful blood components is necessarily a large-scale process. No protein chemist engaged in large-scale fractionation would deliberately chose cryoprecipitate as a final product when a much more convenient freeze material is easier to prepare, as part of the whole procedure. At present, the freeze-dried material is very scarce; but were it as available as cryoprecipitate, most physicians would undoubtedly prefer to use the freeze-dried concentrate.

When the expense of the two preparations is considered, the advantage of cryoprecipitate lies in the fact that it can be made in existing transfusion centres without large additions of expensive apparatus and buildings. It is, however, not cheap or economical to make cryoprecipitate when the process is considered from the point of view of the country as a whole. The large-scale fractionation process must entail high initial capital expenditure, but might in the end prove less expensive due to economy in total staff required and to the conservation of all useful products.

There are two dangers in the use of plasma components in the treatment of haemophilia:

1. Serum hepatitis.
2. The development of antibodies in the haemophilic patient which destroy infused factor VIII.

Serum Hepatitis

Both cryoprecipitate and human dried concentrate may contain the hepatitis-associated antigen (HAA). The probability of a particular preparation containing the antigen (and thus being potentially infective) will depend on the number of donations contributing to a pool of material used to treat the patient. The dried concentrate is often made from large pools of normal plasma; thus the danger of transmitting jaundice to the patient is theoretically larger than if cryoprecipitate is used when the number of donations contributing to a dose is relatively small.

This difference points an advantage to the use of cryoprecipitate. But there is much still to be learnt about the infectivity of samples containing HAA. In large pools it is possible that the presence of antibody or excess of normal γ-globulin might inactivate HAA contributed by one donor to a pool of say, 100 donors. Haemophilic patients seem in any case to have a low incidence of clinical jaundice considering the amounts of material infused. There is at present in England no evidence to suggest a particularly high incidence of jaundice in patients who receive the dried factor-VIII concentrate rather than cryoprecipitate.

The Development of Antibodies to Factor VIII

In England about 5% of severely affected haemophilic patients develop antibodies. The amount of material (concentrate, cryoprecipitate or plasma) given to the patient seems to have little influence on the incidence of antibody. Some patients develop antibody after one or two doses of plasma or concentrate and some fail to produce antibody after years of regular treatment with cryoprecipitate or concentrate. We do not know whether or not complete withdrawal of treatment would eliminate the antibody problem though it must be supposed that this would be the case. However, the beneficial effects of treatment are so great that such withdrawal of treatment is impossible. Since there seems to be no correlation of antibody with the type of treatment, the danger of antibody formation is not a criterion for selection between cryoprecipitate and dried concentrate.

Conclusion

Cryoprecipitate can be used for the control or prevention of bleeding in haemophilic patients. In my opinion it is a valuable interim therapeutic material which has obvious disadvantages when comparison is made with a good freeze-dried concentrate. Cryoprecipitate as now usually presented is time-consuming and tiresome to make up and administer to the patient; its factor-VIII activity is not known before the dose is administered and the preparation of cryoprecipitate is not integrated with a comprehensive fractionation procedure designed to conserve all other useful blood components. The

use of relatively small numbers of donors to prepare each dose, a theoretical advantage in the use of cryoprecipitate, has not been proved to be beneficial in reducing the risk of serum hepatitis. The advantages in the use of concentrate are convenience, reliability and economy in the conservation of blood products. These advantages suggest that, despite large capital outlay, plans should be made to make the freeze-dried concentrate available on the scale required to meet all the needs of the haemophilic population.

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K. M. BRINKHOUS and A. E. WAGG: The development of methods of concentration and purification of antihemophilic factor (AHF) has made the effective control of hemophilic bleeding a reality, without significant hypervolemia. The therapeutic value is similar for both types of concentrates, cryoprecipitate and high-potency AHF concentrate, in that effectiveness is directly related to potency. From the standpoint of hemostasis, the total AHF units (1 unit equals 1 ml average normal plasma) of each injected infusion is most important, regardless of the type of preparation. There are specific advantages and disadvantages to the use of each type of concentrate.

Cryoprecipitated AHF can be readily prepared from single units of fresh plasma by any appropriately equipped blood bank and is widely available. The cryoprecipitate must be stored in a freezer, a drawback to its use in home transfusion programs. The primary disadvantage of cryoprecipitate, however, is the variable recovery of AHF from individual units of plasma. There is variation in the original plasma AHF in the donor and there is variable partition of AHF from plasma to plasma between the precipitate and the supernatant. In our experience, each bag of cryoprecipitate contains, on the average, 75–100 units of AHF but we have encountered bags which contained only about 50 units of AHF, and at times up to 125 units. The potency of the product often varies between blood banks. When many bags of cryoprecipitate are administered in a short period, the 'law of averages' may compensate for this disadvantage of variable potency.

Commercial lyophilized preparations are of three main types, the fraction I-0, cryoprecipitate, and high potency glycine-precipitated materials. Our experience has been with the latter two products. Commercial lyophilized cryoprecipitates, being pre-assayed, overcome the two major disadvantages of the blood bank-produced cryoprecipitate, need of freezer storage and variable potency. The high-potency lyophilized AHF possesses these same advantages, plus being of higher concentration. In our experience, the concentration is about 600·% for cryoprecipitate (average normal plasma = 100%) and 3,000·% for high-potency concentrates. The higher concentration of the latter permits injection by syringe and very rapid normalization of AHF levels. This higher concentration and syringe

injections of the high-potency material are also favorable attributes for home transfusion programs and for prophylactic management, particularly while the patient is travelling. One of the most advantageous uses of the high-potency material has been in the treatment of intractable bleeding in patients with circulating anticoagulant to AHF. The high-potency preparation has replaced the high-potency animal materials which we have used for catastrophic bleeding in the past. Since both types of commercially produced concentrates are prepared from pools of plasma, they pose a theoretically greater risk of serum hepatitis transmission. Resolution of the many questions concerning the HAA and institution of donor screening programs may help to reduce this risk.

Economic aspects also present problems in the treatment of hemophilia. In the USA the cost of cryoprecipitated AHF from blood banks varies greatly from one area to another. Comparison based on AHF units provided by each bag shows costs from less than half to more than double the cost of lyophilized preparations. The total annual costs to patients in our area is slightly lower if the lyophilized preparations are used, unless the costs of cryoprecipitate are partly subsidized.

Our treatment programs reflect a consideration of all the factors discussed, including availability of the preparations. Cryoprecipitate is used for outpatient and much inpatient replacement therapy. The majority of the patients practicing home transfusion programs use cryoprecipitate. The high-potency precipitate is used for excursions and where frozen storage is a problem. The high-potency AHF is used for situations where massive doses and carefully controlled plasma levels are required (catastrophic bleeding, major surgery, and inhibitor hemophilia). There is a place for both cryoprecipitated AHF and high-potency AHF in the treatment of hemophilia today. If the hepatitis problem is completely overcome and if large amounts of high-potency material can be produced continuously and economically in a standardized way, it is our belief that high-potency concentrates could well become first choice in most therapeutic situations in the future. There is much more progress that must be made before this becomes a reality.

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A. H. F. Britten: Cryoprecipitates can effectively elevate factor VIII to any desired level [2, 4]. They have been used without complication in routine emergency treatment, major surgery [1, 2], long-term prophylaxis [3] and for home treatment of hemophilia A [5]. Furthermore, there is no technique of concentrating factor VIII which is less costly than cryoprecipitation, none which fits more easily into the routine of any type of transfusion service, and none which produces a higher total recovery of the original factor VIII. So the answer to the first question is 'yes'.

There are, however, certain drawbacks to cryoprecipitates which can be eliminated by other factor VIII preparations:

1. Frozen storage. This limits the capacity for stockpiling reserve supplies, is inconvenient for home use, and prohibitively awkward for travelling. Lyophilization eliminates this problem. Cryoprecipitate itself can be freeze-dried.

2. Febrile and allergic reactions. These are very rare with the more purified preparations of factor VIII.

3. Factor-VIII content of individual cryoprecipitates *unpredictable.* This problem is in part overcome by pooling many cryoprecipitates for one infusion and perhaps by deliberately erring on the side of overdosage, but it is certainly more satisfactory to use a material whose factor-VIII content has already been assayed. This problem may be more theoretical than practical; true precision in dosage is a Utopian goal unlikely ever to be achieved.

4. Relatively low concentration of factor VIII. In general, the factor-VIII content is 5–10 times concentrated in cryoprecipitate. This is ample for all routine situations, but occasional hemophiliacs with *inhibitors* can be saved by infusion of massive doses of factor-VIII, thus overwhelming the inhibitor (antibody) with a factor-VIII (antigen) excess, allowing at least transient normalization of coagulation. This extravagant manœuvre is still controversial; but there are certainly some situations in patients with inhibitors where the required volume of cryoprecipitate is prohibitive while the relatively small volume of a 'superconcentrate' permits adequate dosage.

In summary, *frozen cryoprecipitate* can provide almost all the needs of patients with hemophilia A. There are many additional conveniences to *lyophilized* preparations. *High-potency* materials are rarely needed but may be essential to overwhelm inhibitors.

Finally, what is perhaps the worst drawback of cryoprecipitate must be mentioned. 50% or more of the original factor VIII is lost during preparation. This figure is better than for any other factor-VIII preparation, but represents a serious loss of a valuable blood resource. Cryoprecipitate is not the final answer to hemophilia. The search for a more efficient technique must be pursued.

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KATHARINE M. DORMANDY: Until the technique of extracting cryoprecipitate from a closed plastic blood-bag system was discovered by POOL and SHANNON in 1965, shortage of AHF concentrate was the main factor limiting adequate treatment of haemophilia. The availability of AHF concentrates, resulting from these developments, has revolutionised the lives of many haemophiliacs throughout the world.

Cryoprecipitate is entirely satisfactory for the treatment of all types of haemophilic haemorrhage, provided that the patient has no inhibitor to factor-VIII. Any level of factor VIII can be achieved and maintained. For the treatment of spontaneous haemorrhages, such as *joint bleeds*, a single outpatient infusion, aiming to raise the patient's factor-VIII level to between 15 and 20%, is often all that is required; for *deep muscle haematomata* where higher levels of around 40% are desirable, this can be achieved and, if necessary, maintained; for *surgery* and in cases of dangerous haemorrhage, such as a retroperitoneal haematoma, the factor-VIII level can be rapidly raised to, and even above, the normal range without overloading the circulation. It can be maintained above the baseline level of 40% throughout the necessary healing period of 2–3 weeks (or as long as is required). DJERASSI *et al.* [1965], SIMSON *et al.* [1966], DORMANDY K. M. [1968], and MAZZA *et al.* [1970] may be quoted more or less at random from the vast literature on this subject, to illustrate these points.

Home treatment with cryoprecipitate is also a practical proposition. At least four Haemophilia Centres in England have patients on this regime: one such patient, who was reported by BELLINGHAM *et al.* in 1967, has successfully administered cryoprecipitate to himself at weekly intervals for the past five years. At the Royal Free Hospital, eight patients use cryoprecipitate on a home treatment basis. None of these experienced any particular problems, once the patient himself or a close relative had become proficient in the technique of making up the dose and administering it through a butterfly needle. Supplies of cryoprecipitate are collected by patients from the Haemophilia Centre, transported in cardice and stored in a deep freezer at home. Published reports from the USA, where cryoprecipitate has been successfully used for home treatment for some time include those of RABINER and TELFER [1970] and LAZERSON, J. [1971].

The advantages of cryoprecipitate in comparison with the highly concentrated freeze-dried materials are as follows: the preparation, which is quick and simple, can be carried out on a small scale and in a hospital laboratory as well as on a large scale in a blood transfusion centre; blood economy is achieved, for the red cells and other blood components can still be used. Other advantages include the fact that on administration there are no significant side effects and the danger of serum hepatitis is less because the donor pool is so much smaller.

The disadvantages of cryoprecipitate include the variation in activity between the different packs and the inconvenience of having to store the concentrate at a minimum temperature of −25°C. The variation in activity means that laboratory control of treatment is essential, especially if surgery is to be performed safely. The need to store cryoprecipitate at −25°C makes it impractical for patients who travel, for those who live in places with an unreliable electricity supply, or where there is no deep freezer. This latter problem can be overcome by the use of lyophylised cryoprecipitate. Dr. A. F. H. BRITTEN, in a personal communication (1970), reports the success of a home treatment programme in which this is used.

In the treatment of patients with high titre factor-VIII inhibitors, very high doses of concentrated material are required. Since the number of units of factor VIII per bag of

cryoprecipitate varies according to the exact method of preparation, as does the total volume in which it is administered, the figures here can be only approximate. On the assumption then that there are 100–150 units of factor VIII per bag, each in a final volume of 10–15 ml, an average concentration of 10 units factor VIII/ml cryoprecipitate can be expected. Fifty bags therefore will give a maximum dose of approximately 7,500 units factor VIII and 100 bags 15,000 units, the volumes of the doses being 750 ml and 1,500 ml, respectively. Although it is quite feasible to use cryoprecipitate in this way (especially if the patient is plasmapheresed to lower the inhibitor titre), more concentrated AHF products are called for when this size of dose is indicated, especially if repeated doses are required.

For all these reasons it is very important to continue to manufacture the highly concentrated AHF products and hope that improved methods of fractionation will eventually bring down the cost. If the danger of hepatitis could be overcome, and if the cost were less, most patients and physicians would, I think, choose to use the highly concentrated products. Apart from this, there is always the hope that the more intensive the research carried out on the various fractions the greater will be the chance of increasing our knowledge about the basic chemistry of factor VIII.

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J. van der Meer. An ideal AHF preparation has to meet the following requirements: (1) method of preparation resulting in high yield of AHF and little loss of other useful plasma proteins, (2) high purity, (3) high recovery *in vivo*, (4) no side effects, (5) high stability and (6) low cost. At this moment it is impossible to attain all these goals at the same time, so reasonable compromises have to be sought.

POOL's original cryoprecipitate procedure can easily be carried out by any blood bank at low cost and with relatively high yield (about 50%). The purity is low and the material contains a rather high concentration of fibrinogen. Serious side effects, however, have rarely been encountered. Major drawbacks are the wide variability of AHF concentration in the material and the lack of stability at 4°C.

The Central Laboratory of The Netherlands Red Cross Blood Transfusion Service has modified the procedure as follows: plasma of four Au-negative donors is pooled and the cryoprecipitated material is freeze-dried. This four-donor cryoprecipitate has permitted major surgery in several cases without any side effects. The material may be stored in a refrigerator at the patient's house.

Theoretically, highly concentrated AHF products have to be preferred because of their high purity and stability. The large-scale production of high-potency material, however, is a much more complicated process than cryoprecipitation, while the yield of AHF is lower. Some preparations appear to have a very high disappearance rate *in vivo* [1].

Considering the total need for AHF products in a given population, in this way a considerable amount of AHF is lost, while there is an increasing demand: several patients are awaiting orthopedic surgery and much more patients ought to be helped by prophylactic treatment than is possible nowadays.

In my opinion it is realistic to aim at increased production of cryoprecipitate in order to meet the demand for the first few years. Only a few centres should undertake to produce highly concentrated AHF products for treatment of patients with AHF inhibitors and for biochemical studies. Only when the production of cryoprecipitate has attained a satisfactory level one could start to produce high-potency material on a large scale.

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INGA MARIE NILSSON. Human fraction I-0 prepared by the method of BLOMBÄCK and BLOMBÄCK [1956] has been used in Sweden since 1957 in the treatment of patients with haemophilia A and von Willebrand's disease. The preparation was originally manufactured at Karolinska Institutet, Stockholm, and each batch was prepared from 1,400 ml of fresh plasma which yielded 2 doses of AHF of 100 ml each (100 ml = 1 dose of AHF). The preparation had an activity of up to 8 times that of normal plasma. Since 1967 AB Kabi has taken over the manufacture of AHF containing fraction I-0. For each batch Kabi uses about 17 l of plasma (from 84 blood donors), from which 17 bottles of 100 ml AHF concentrate are obtained. Kabi uses only frozen plasma as raw material. The use of larger batches, sterile filtration and deep freezing has resulted in a decrease of the yield. 100 ml of AHF concentrate (1 dose) has, as a rule, an activity equal to that of 250–300 ml of fresh plasma. Cryoprecipitate has hitherto been given to only a few patients

in Sweden. One unit of cryoprecipitate (from 500 ml of blood and dissolved in about 20 ml) has been reported to possess an AHF activity corresponding to that of 50–150 ml plasma, which implies that Kabi AHF and cryoprecipitate have approximately the same activity per unit of volume. In contrast with the varying AHF activity in different batches of cryoprecipitates, the activity of Kabi AHF preparations is constant.

In Sweden, we have, since 1956, given AHF containing fraction I-0 on about 25,000 occasions to control bleeding in, or in association with, surgery of all together about 400 patients with haemophilia A or with von Willebrand's disease.

Major surgical operations (gastric resection, cholecystectomy, nephrectomy, operations because of intestinal obstruction etc.) and surgical orthopaedic correction (osteotomy, synovectomy) have been performed on 45 patients and minor operations (tooth extractions, treatment of inguinal hernia) on 140 patients without serious complicating haemorrhage [Nilsson *et al.*, 1962; Nilsson, 1965; Ahlberg, 1965]. At the major operations we have maintained the AHF content between 50 and 80% during, and the first few days after, the operation. This means that with the use of the present Kabi preparation the adults required more than 2,000 ml of the AHF concentrate a day. This has created difficulties in some cases requiring also some other special fluid treatment.

Severe bleeding episodes in patients with haemophilia A and circulating anticoagulants were treated with large doses of Kabi AHF. The AHF values achieved were at most 10–20%. No surgical operations could be performed on such patients because it was not possible to raise the AHF level to acceptable level with the preparations available. In Sweden, where only Kabi AHF is used, it is highly desirable that everything should be done to raise the specific activity of this concentrate.

Cryoprecipitate can probably be used with advantage in the treatment of most bleeding episodes in haemophiliacs. But owing to the variation of the AHF yield of cryoprecipitate from one batch to another, control of the AHF content *in vivo* is desirable. Major surgery, very severe bleeding and treatment of patients with anticoagulants require a preparation with a higher specific activity than that of cryoprecipitate. It is also necessary that the *in vitro* activity of the preparation be known to facilitate exact calculation of the dose of AHF (units/kg body weight) necessary for the attainment of a certain predetermined AHF level.

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E. SHANBROM. There is no question that hemophilic patients can be adequately treated with cryoprecipitates for acute bleeding episodes. There are also adequate studies now to suggest that cryoprecipitates may be very useful in prophylaxis in selective hemophiliacs. However, there are a number of problems and theoretical considerations that must be carefully examined in the long-term, intensive use of cryoprecipitates, and they are as follows.

1. The hyperfibrinogenemia which is invariably induced with the administration of moderate amounts of cryoprecipitate may in itself induce certain complications. Hemolytic anemia has already been referred to in a number of publications, although this is not at all a well-established complication.

2. In addition the excessive plasma fibrinogen may serve to activate the plasminogen-plasmin system, resulting in fibrinolysis. A number of such cases are now being recognized.

3. The hyperfibrinogenemia may possibly result in chronic renal disease either by filtration through the kidney *per se*, or as fibrinogen fragments or fibrin breakdown products.

4. The presence of trace amounts of A and B substance in cryoprecipitate is apparently adequate to stimulate isohemagglutinin when type-specific cryoprecipitate is not used.

5. Cryoprecipitate contains fair amounts of all immunoglobulins, and allergic reactions are still a problem, although less than when whole plasma is used.

6. Cryoprecipitates contain isohemagglutinins and when moderate amounts are administered hemolytic reactions are always a potential hazard, unless type-specific material is used.

7. Since the number of units of AHF present in the cryoprecipitate bag can never be determined, dosage is at best empiric and failure to control bleeding in a patient could be due to inadequate therapy, the induction of fibrinolysis, or the presence of AHF inhibitors.

8. Cryoprecipitate is usually ineffective in the emergency management of AHF inhibitors.

9. Cryoprecipitates require storage at refrigerated temperatures and are, therefore, not convenient in a mobile society.

Purified forms of AHF may obviate all of the above problems associated with cryoprecipitate. The highly purified concentrate made by Hyland Laboratories allows for immediate and convenient intravenous injection via syringe, thus making it ideal for outpatient, office or home care. Most of the immunoglobulins and pyrogens are removed by the fractionation procedure, thus eliminating febrile or allergic reactions.

There is the added theoretical advantage that if a fibrinogen-free preparation could be made available, the factor VIII could possibly be administered subcutaneously.

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K. Stampfli. Provided that the patient has no inhibitor to factor VIII, almost all hemophilic bleeding incidents can be adequately controlled with cryoprecipitates. It is possible to achieve even high levels of factor VIII in the patient's plasma and to maintain them over a period of several weeks. A number of authors have reported on the successful use of cryoprecipitates for major surgery, long-term prophylaxis and home treatment.

The principal advantages of cryoprecipitates are the following. Their preparation is relatively simple and cheap and is also suitable for small-scale production in hospitals. None of the procedures so far available for the manufacture of factor-VIII concentrates yields a higher total recovery of the activity contained in native plasma.

As compared to highly concentrated factor-VIII preparations, however, cryoprecipitates have several disadvantages. Cryoprecipitates must be stored and transported in the deep-frozen state and are therefore inconvenient for home use and for travelling. This drawback can be circumvented by the use of lyophilized preparations. In contrast to purified factor-VIII concentrates, cryoprecipitates contain small quantities of immunoglobulin aggregates which may cause febrile reactions. Their fibrinogen content may be troublesome, if cryoprecipitates have to be administered in substantial amounts (e.g. impaired solubility of the product, or activation of fibrinolysis by way of the plasminogen-plasmin system). Single unit-cryoprecipitates contain A- and B-substance, as well as isohemagglutinins, which necessitates the use of type-specific preparations. In contrast to the highly concentrated products, the factor-VIII content of the individual cryoprecipitate is unknown and variable. The relatively modest concentration of factor-VIII activity in cryoprecipitates (usually by a factor of 5 to 10 as compared to native plasma) generates the risk of circulatory overload in some patients with circulating anticoagulants, whereas a sufficient effect can still be obtained with relatively small volumes of highly concentrated AHF preparations. Finally, the superior solubility of highly concentrated AHF products, the possibility of administering them by injection, their convenient storage characteristics (not frozen, small volume), and the defined factor-VIII content, are substantial advantages for the home treatment of hemophiliacs. The importance of this form of therapy will undoubtedly increase, because the patient or his relatives can – at least in selected cases – effect it themselves, so as to minimize the clinically important delay between the onset of bleeding and the begin of treatment.

To sum up, an adequate therapeutic effect can be obtained in the large majority of patients with cryoprecipitates. Their essential drawbacks are lacking in purified, highly concentrated AHF preparations. The availability of such products is particularly desirable for the treatment of patients with inhibitors to factor VIII. It is anticipated that the highly concentrated factor-VIII preparations will progressively replace the cryoprecipitates if the problems of hepatitis transmission and production costs can be solved.

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