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Current status of the treatment of Argentine Hemorrhagic Fever

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Argentine Hemorrhagic Fever (AHF) is a severe disease caused by Junin virus (JV), one of the four arenaviruses pathogenic for man. The illness is characterized by hematologic, vascular, renal, and neurologic alterations, with a 15–20% mortality [8]. The treatment of AHF consists in the administration of immune plasma. A controlled therapeutic study has proved that when given within the first 8 days of illness the mortality is reduced to less than 3% [10].

Until a few years ago, complement fixation and indirect immunofluorescence were the only serological criteria used to select the immune plasma donors. With these methods, the range of titers of antibodies against JV is very narrow, and the empirical treatment was transfusion of a fixed volume of immune plasma to each patient (500 ml). The introduction of a test to measure neutralizing antibodies (NAb) revealed wide variations in the titers of different persons who have had AHF. A retrospective study demonstrated a higher mortality in cases that had been treated with lower doses of NAb against JV, and it was decided to define the therapeutic dose of immune plasma on the basis of the amount of NAb to be given to each patient. As a result of a prospective study, a dose of no less than 3,000 therapeutic units of NAb against JV per kg of body weight (TU/kg) is recommended [4]. This study is still in progress, and the results observed between 1982 and 1984 are presented in Table 1.

A controlled study revealed that 8–10% of the cases of AHF treated with immune plasma develop a late neurologic syndrome (LNS) [10]. This association has been confirmed by additional studies conducted between 1973 and 1981, in 797 cases of AHF. Of these, 464 were treated with immune plasma and the remaining 333 did not receive this form of treatment. There were 40 cases of LNS, all in patients that had been treated with immune plasma. No cases were observed among untreated patients. The neurological manifestations of the LNS differ from those seen during the acute period of AHF. The LNS appears in convalescence, after an interval free of symptoms, and is generally benign and self-limited. Changes are regularly detected in the cerebrospinal fluid; these include a moderate increase in the number of cells and the presence of antibodies against JV. The primary humoral response is also different in patients with LNS. In this respect, in cases of AHF that were not treated with immune plasma, the

Table 1. Evaluation of the dose of virus-neutralizing antibody effective in the treatment of Argentine Hemorrhagic Fever (prospective study)

Outcome	TU/kg[a]		
	1,000–2,000	2,000–3,000	> 3,000
Death	2	1	1
Improvement	22	39	123
Mortality	8.3%	2.5%	0.8%

[a]Therapeutic units as defined in [4]

serological conversion was detected between days 11 and 15, and the highest titers of NAb were reached between days 20 and 25, with a geometric mean titer ($\overline{XG}$) of 2,153. In 13 patients without LNS who had been treated with immune plasma, the serological conversion was detected between days 11 and 25, with highest titers between days 35 and 50, and with a $\overline{XG}$ of 871. However, in 17 cases with LNS the seroconversion was later, reaching highest titers between days 45 and 90, but with a $\overline{XG}$ of 3,695. This $\overline{XG}$ is significantly higher than the $\overline{XG}$ of the patients without LNS ($P < 0.01$). These findings suggest an immunological mechanism in the pathogenesis of the LNS and also support the hypothesis of persistence of antigenic determinants of JV in the central nervous system. Nevertheless, several other mechanisms should be considered. No correlation has so far been demonstrated between the dose of specific NAb given to patients with LNS and the day of evolution on which immune plasma was transfused.

During the acute period of AHF the bone marrow is affected, resulting in moderate to severe leukopenia and thrombocytopenia, and superimposed bacterial and mycotic infections are frequent [8]. It has been shown that JV has a definite lymphotropism [5], while other studies suggest a direct viral action in the pathogenesis of AHF [9, 3]. It has also been shown that JV is associated with the circulating lymphomononuclear cells of patients with AHF [1]. Preliminary observations revealed alterations in the cells involved in the immune response during the acute period of AHF [2]. These have recently been confirmed by means of mitogen stimulation assays, using concanavalin A, phytohemagglutinin, and pokeweed mitogen and measuring the mitogenic response by the incorporation of radiolabelled thymidine. In 12 patients with AHF, a depressed response for the three mitogens was found previous to the transfusion of immune plasma ($P < 0.05$). Interestingly, 72 h after treatment, there was a significant change in the mitogenic response ($P < 0.05$), with a tendency to decreasing values in early convalescence, as shown in Fig. 1. This clearly indicates that treatment with immune plasma also results in modulation of the cellular immune response. In addition, alterations in the subpopulations of T lymphocytes were found in six patients studied during the 1985 epidemic. In the acute period there was a decrease in the proportion of T helpers with an increase of T repressors, resulting in a low T_4/T_8 ratio. These changes reverted in early convalescence when the values were found within normal limits.

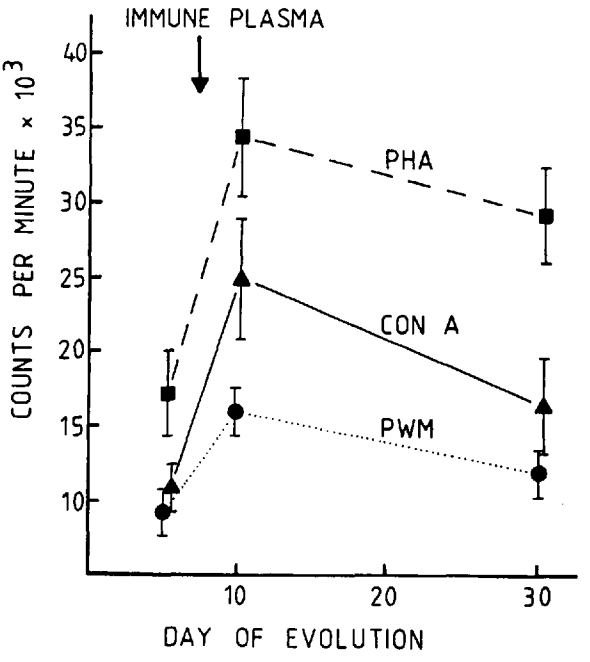

Fig. 1. Mitogen stimulation assays in 12 cases with Argentine Hemorrhagic Fever before and after treatment with immune plasma and on day 30. Means and standard errors of the net counts per minute are plotted. Means and standard errors for controls were concanavalin A, 29,310 ± 1,964; phytohemagglutinin, 44,807 ± 3,284; pokeweed mitogen, 16,608 ± 799

The beneficial effect of the transfusion of immune plasma is attributable to the specific action of the NAb against JV. Viremia is present throughout the acute febrile period of AHF and is neutralized after treatment [10].

To explore the role of other mechanisms that operate in the control of viral infections, the levels of circulating interferon (IFN) were studied. Very high titers of IFNα are present in serum taken during the acute period of AHF. After the administration of immune plasma, the levels of circulating IFN drop drastically. Interestingly, an association between IFN titers and fever, chills, and lumbar pain was found [6]. In this respect, it is worth mentioning that the majority of signs and symptoms seen in AHF have also been observed in patients receiving exogenous IFN for the treatment of malignant diseases. Recently, a correlation between IFN levels and the evolution of AHF was observed, the titers of IFN being significantly higher in fatal cases than in survivors [7]. These studies clearly suggest that no beneficial effect should be expected from the treatment of AHF with IFNα.

At present, the treatment of AHF consists in the administration of immune plasma. A therapeutic dose has been defined and is based on the amount of specific antibodies per kg of body weight. In spite of certain risks and limitations, the transfusion of immune plasma is an effective treatment to reduce the lethality of AHF.

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