

Inhibitor Eradication in Haemophilia: a European Survey

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Introduction and Objectives

Inhibitors are still a major treatment complication in haemophilia. Eradication by Immune Tolerance Induction (ITI) is the ultimate goal. However, there is still a lack of consensus concerning which regimen, dose and type of factor concentrate to use, as well as the role of immunosuppression. The aim of this study was to explore the current clinical practice in patients with haemophilia A after the publication of the I-TI-study [1] as well as the current management of poor risk patients, patients with haemophilia B and those with mild/moderate forms.

Methods

The European Haemophilia Therapy Standardisation Board (EHTSB) undertook a survey among participating Haemophilia Centres regarding the current (June 2012) and previous (January 2002-May 2012) ITI approaches and compared these to a previous published survey in 2006 [2]. Inhibitor titres were classified as very high (VHT; >200 BU/mL), high (HT; 5-200 BU/mL) and low (LT; <5 BU/mL).

Results

Details of the patient populations of the 16 participating centres from 13 European countries (Germany, Greece, Italy, Netherlands, Norway, Poland, Portugal, Slovakia, Spain, Sweden, Switzerland, Turkey, UK) are shown in **Table 1**. In severe haemophilia A most of the newly developed inhibitors were diagnosed in young patients <20 years (82%); in mild haemophilia A 85% of inhibitors were diagnosed at an age > 20 years. Of the 134 patients with a current inhibitor at time of the survey, 26 were ITI failures, 75 had never been on ITI and 33 had on-going ITI. The **current** treatments for HT inhibitors were in 46% a high dose regimen with up to 200 IU/kg/d (**Figure 1**), compared to 36% in the **period from 2002 to 2012** (**Figure 2**). In 32% of the cases with VHT inhibitors immunosuppression (IS) was added. From 2002 to 2012, low dose ITI with < 50IU/kg/d was used in 42% of LT inhibitor patients and 28% of HT inhibitor patients, whereas 82% of VHT patients were treated with >200 IU/kg/d and/or additional IS. Compared to the survey of 2006, no major difference could be seen between the two surveys. Success rates were highest in LT inhibitors (85%) and lowest (28%) in poor risk patients with VHT inhibitors (**Figure 3-5**). Treatment regimens of the 8 patients with mild/moderate haemophilia A are shown in **Figure 6**; 5 achieved complete remission. Three of 6 patients with haemophilia B achieved complete remission, 2 of whom were treated with IS (**Figure 7**). **Figure 8** shows the current first-line approach used in each centre to eradicate new inhibitors.

Table 1: Patient population and new inhibitors diagnosed between 2002 and 2012 of 16 centres of 13 countries

| Diagnosis | Numbers of patients (children < 20 y) followed | Number of patients who developed a new inhibitor between 2002 and 2012 |
|------------------------|--|--|
| Haemophilia A severe | 1558 (553) | 119 |
| Haemophilia A moderate | 408 (120) | 11 |
| Haemophilia A mild | 1503 (335) | 13 |
| Haemophilia B severe | 269 (93) | 7 |
| Haemophilia B mod/mild | 468 (107) | 1 |

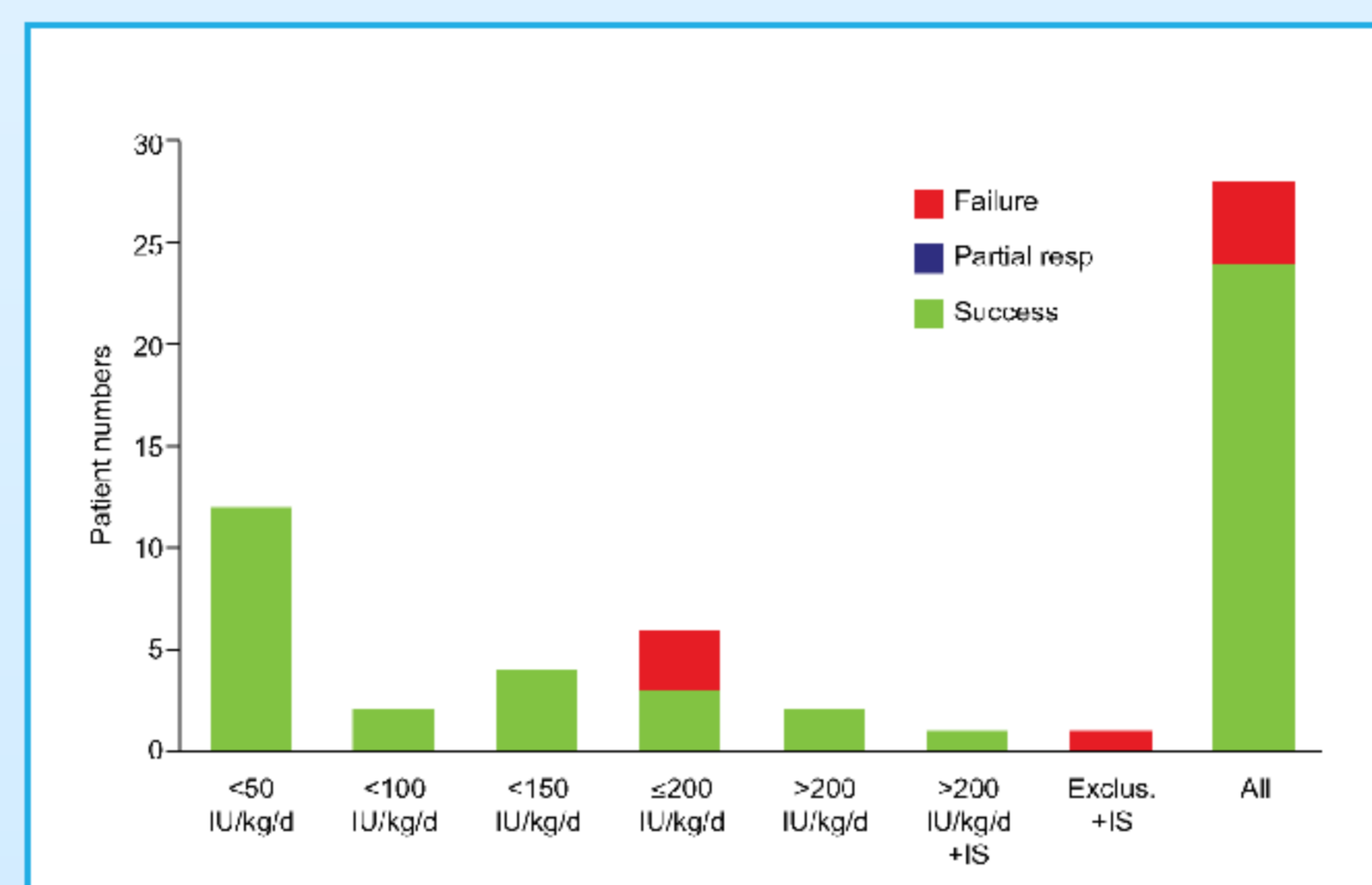


Figure 3: Success rates of ITI in severe Haemophilia A with low titre inhibitors (< 5BU)

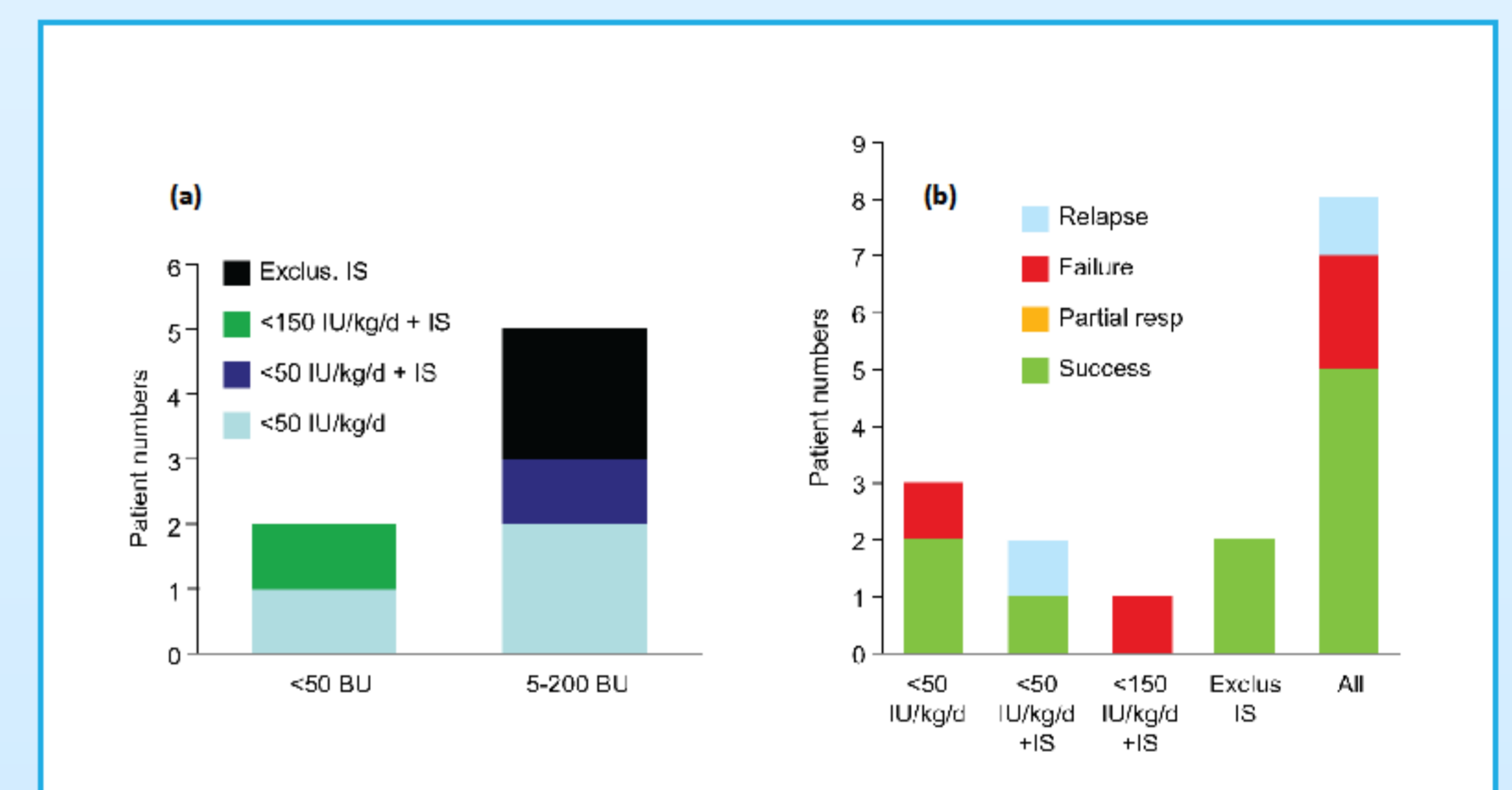


Figure 6: Treatment regimens in patients with mild/moderate haemophilia A (a) and success rates (b)

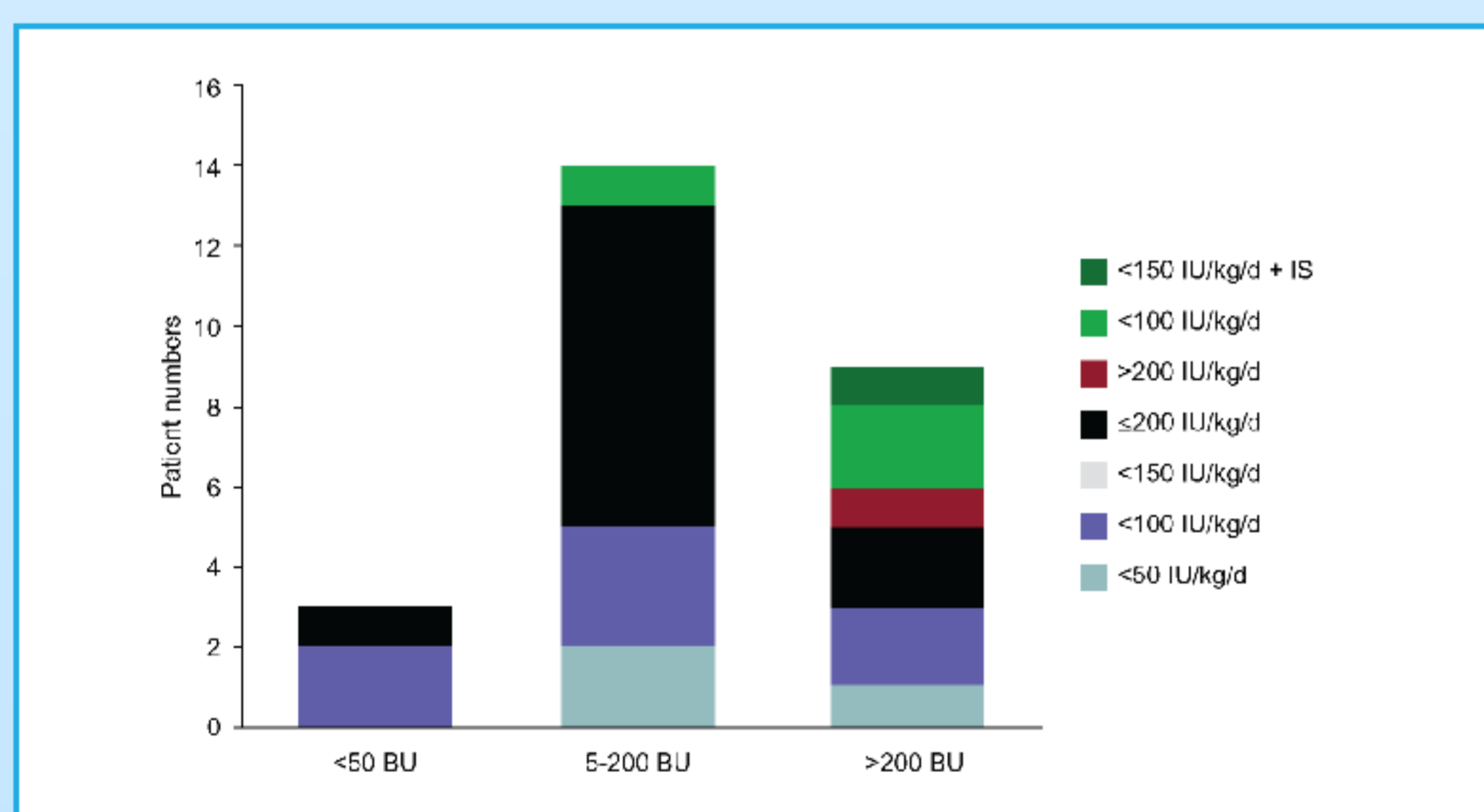


Figure 1: Current ITI treatments for severe haemophilia (n=26)
IS = Immunosuppression

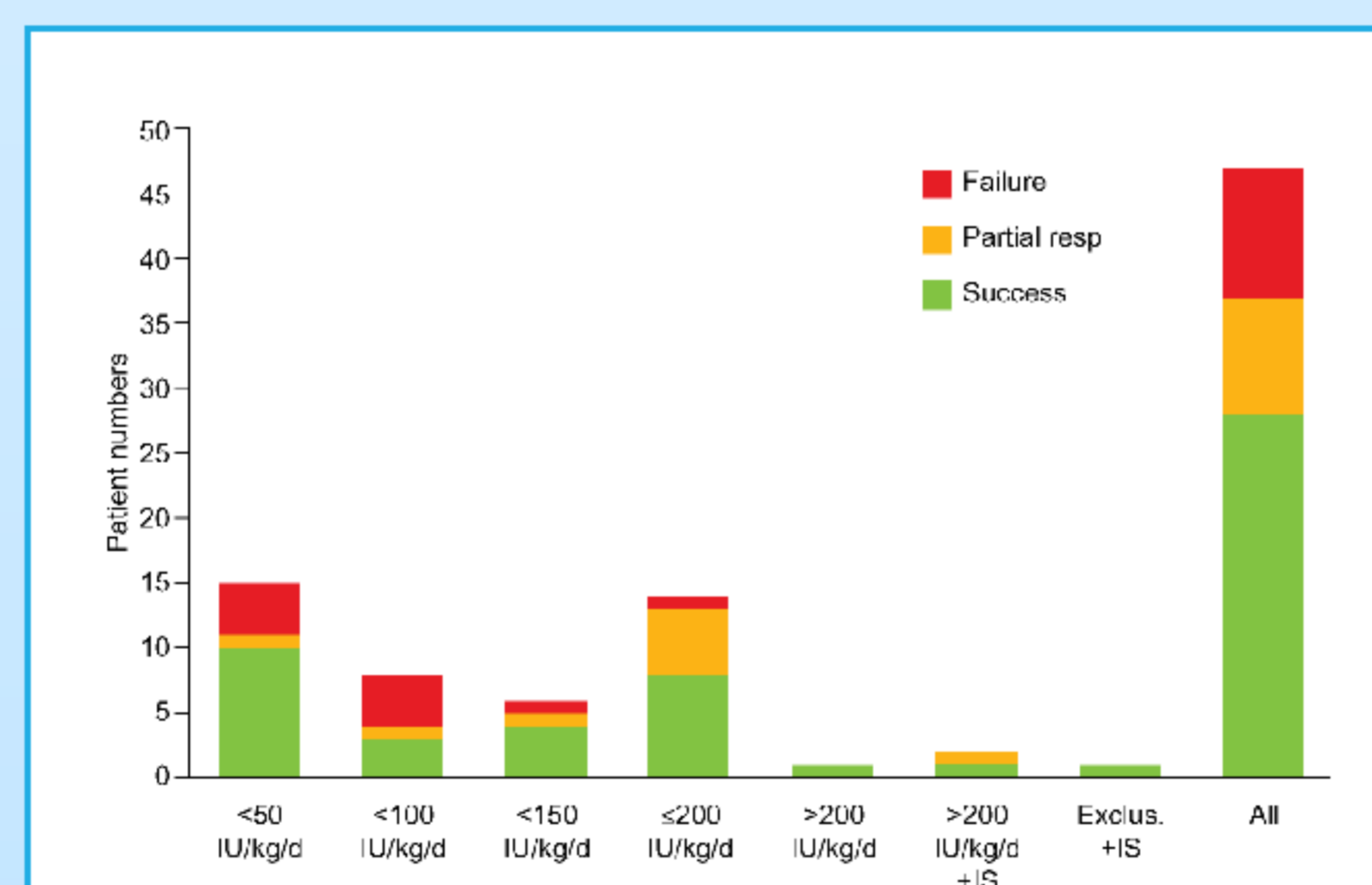


Figure 4: Success rates of ITI in severe Haemophilia A with high titre inhibitors (5-200 BU)

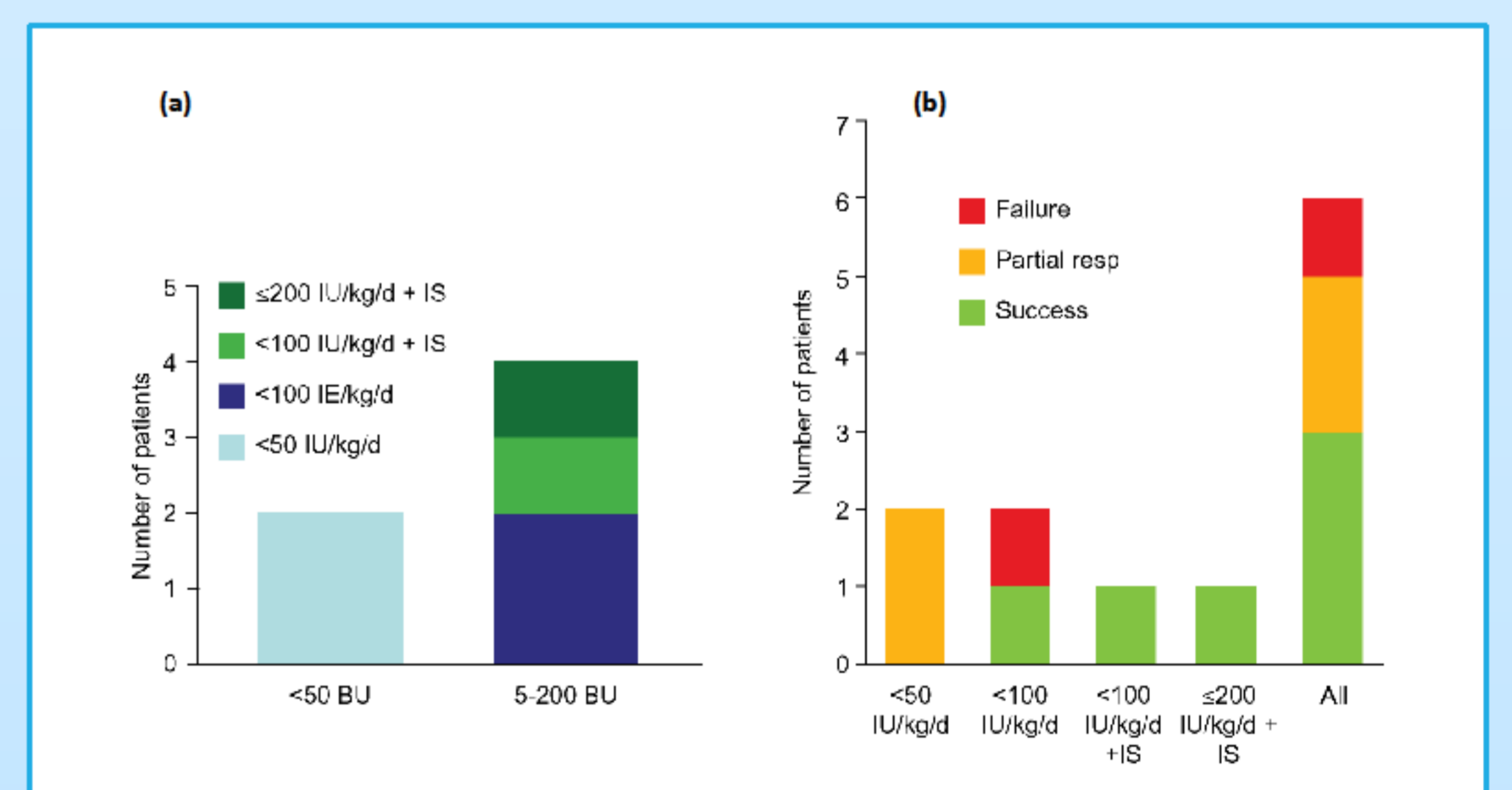


Figure 7: Treatment regimens in patients with haemophilia B (a) and success rates (b)

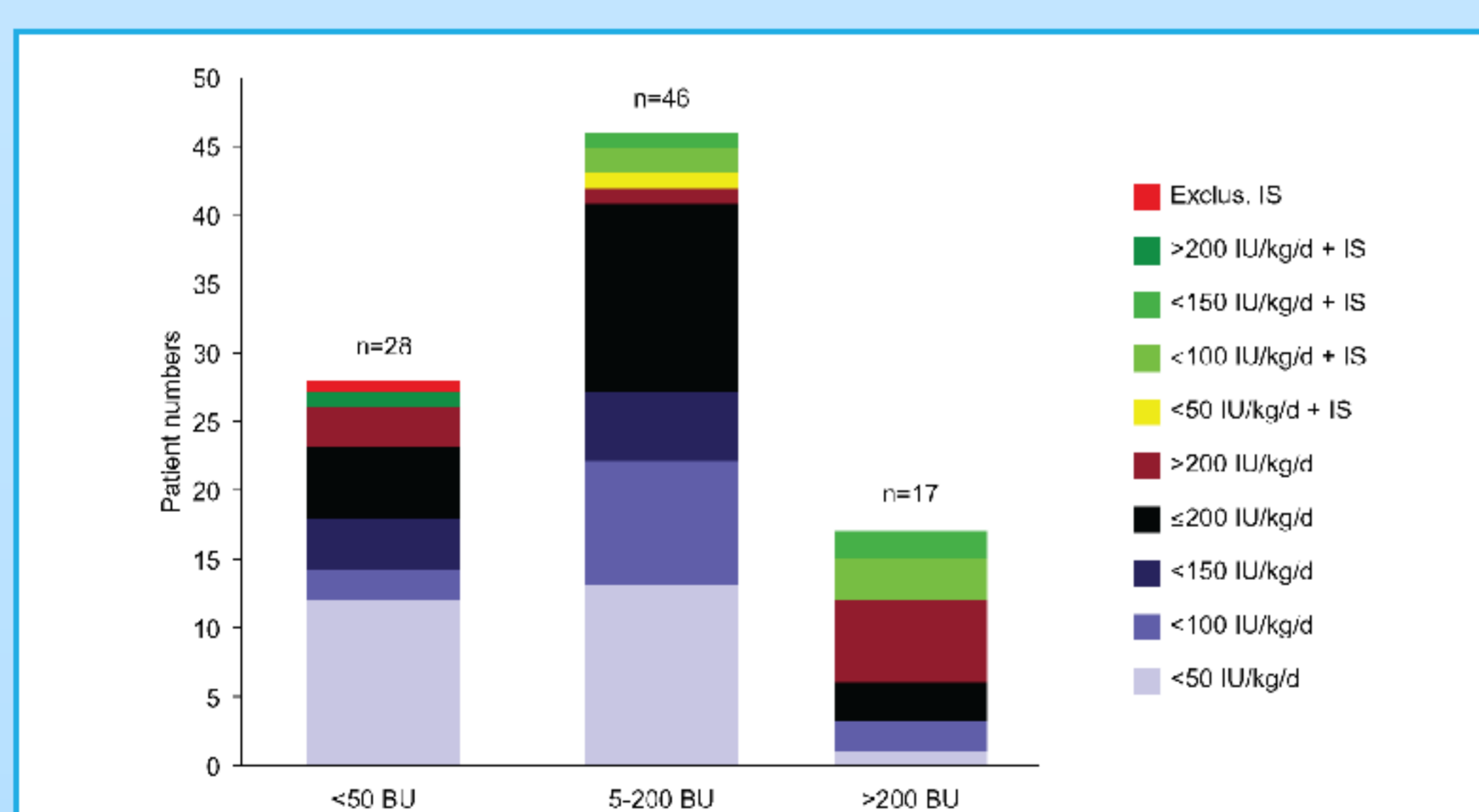


Figure 2: ITI procedures performed between Jan 2002 and Apr 2012 Severe Haemophilia A (numbers), n=91

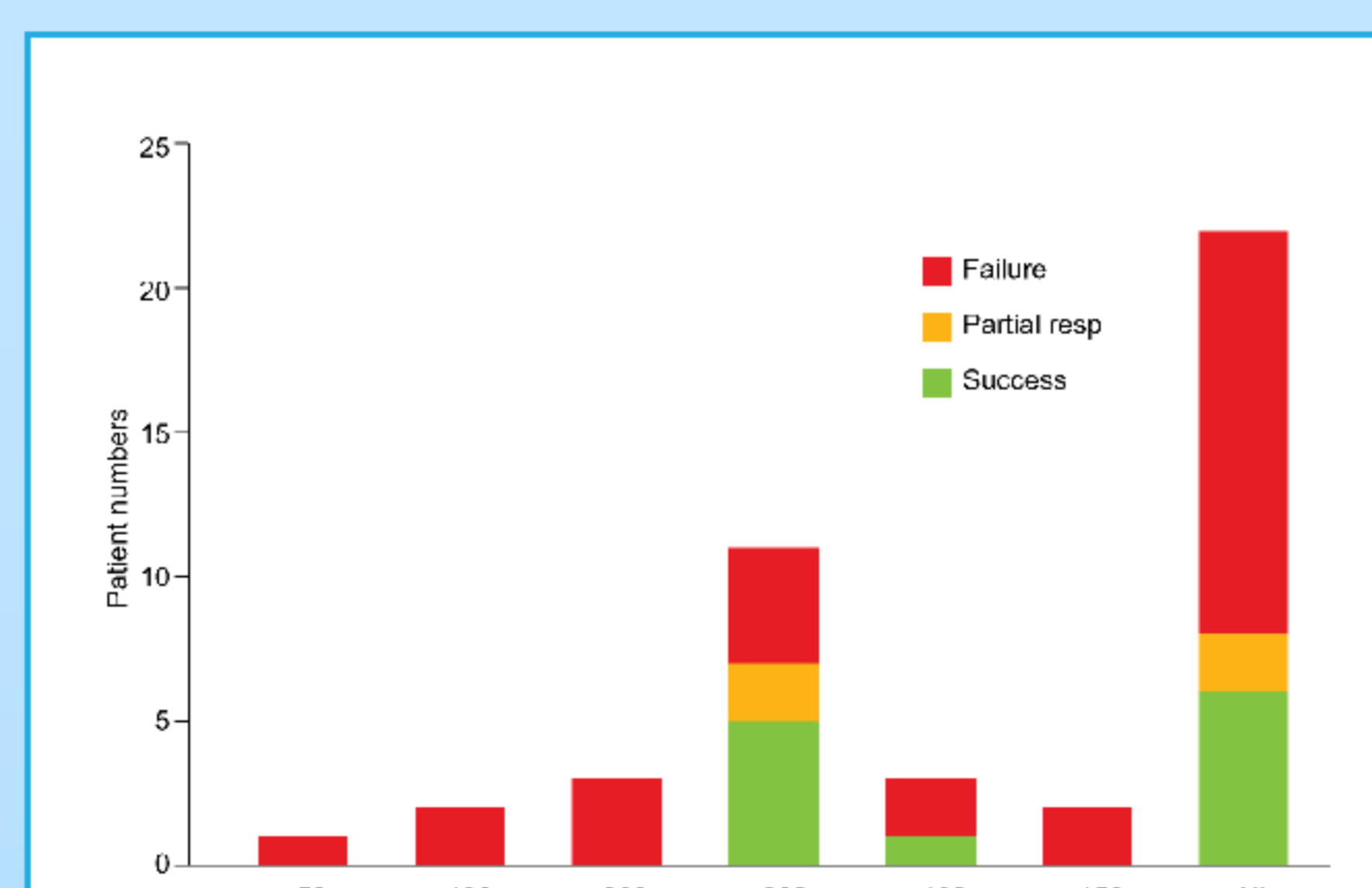


Figure 5: Success rates of ITI in severe Haemophilia A with very high titre inhibitors (> 200 BU)

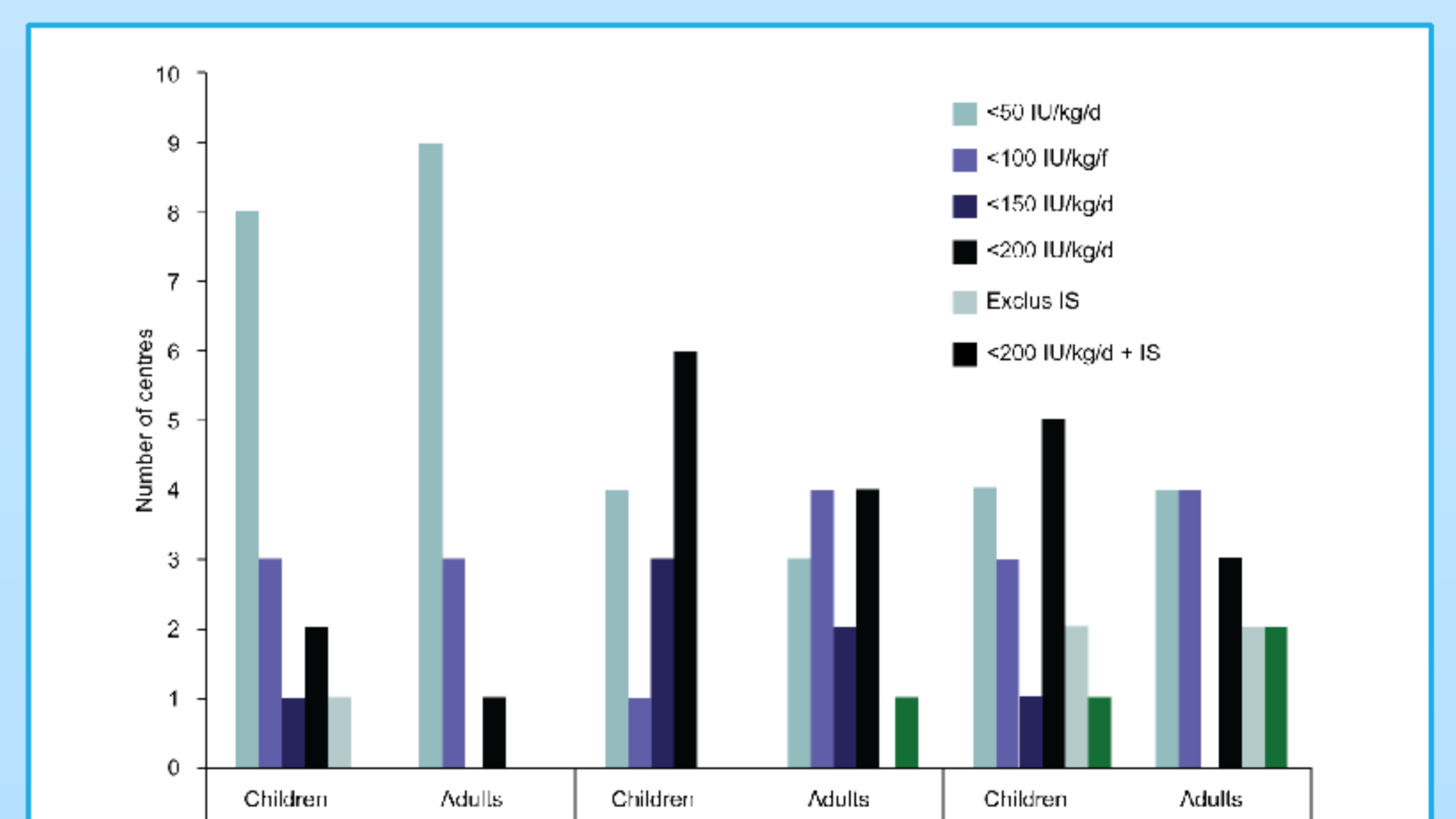


Figure 8: Current approach for inhibitor eradication for a new patient with inhibitors who appears at the centre

Conclusion

There may be a trend towards more usage of a high dose regimen in patients with high titer inhibitors. The combined use of IS is considered in some centres, in particular for mild/moderate haemophilia A, poor risk patients and haemophilia B. As expected, lower success rates in higher inhibitor titers were observed.

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Literature:

- [1] Hay *et al.* *Blood* 2012; 119: 1335-1344
[2] Astermark *et al.* *Haemophilia* 2006; 12: 363-371