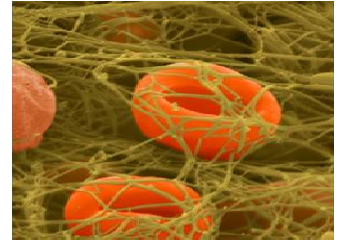


EPIDEMIOLOGY OF HEMOPHILIA IN MAHARASHTRA AND IMPLICATIONS FOR PUBLIC HEALTH SERVICES



Summary of research studies conducted at the
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Background

Hemophilia is an inherited abnormality of hemostasis. Clinically, Hemophilia manifests as frequent bleeding episodes occurring primarily in the weight carrying joints and in soft tissues. The severity of the disorder is dependent on residual coagulation factor activity. Hemophilia A and B are common coagulation disorders occurring due to dysfunctional or deficient clotting factor VIII and IX respectively. Each bleeding episode is accompanied by immobilizing pain. Chronic pain and fear of the disorder has severe psychological consequences on patients and parents¹. Due to high treatment costs, patients receive suboptimal treatment as families are unable to purchase clotting factor concentrate². Progressive crippling disability is a characteristic of chronic under treatment³. As clotting factor concentrate is limited in availability, any major hemorrhagic episode (such as intracranial hemorrhage) can result in death⁴. The unpredictable nature of the disorder disrupts family life, resulting in a very poor quality of life of patients and their families⁵.

The prevalence of Hemophilia is dependent on new births (incident cases) and survival of patients⁶. Although Hemophilia is an inherited disorder, 30% of cases arise spontaneously without any prior history of the disorder in the family. Hemophilia cases are also added to the population through births in parents with a family history of Hemophilia. Increasing survival of patients results in increasing population prevalence of the disorder and increasing health service demands for treatment. Retrospective genetic counselling is the method of prevention of Hemophilia⁷. Parents planning a next pregnancy can be referred for prenatal diagnosis, whilst sisters of the patient and other maternal relatives can be tested and empowered with the knowledge of whether they are a carrier of the defective gene or not. Extreme sensitivity is required in the counselling process, in order to prevent the stigmatization of female relatives of the patient.

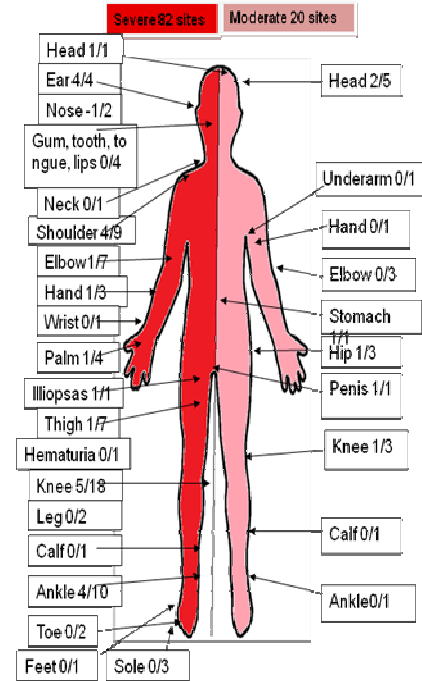


Fig. 1 Sites and number of bleeding episodes treated in patients with hemophilia

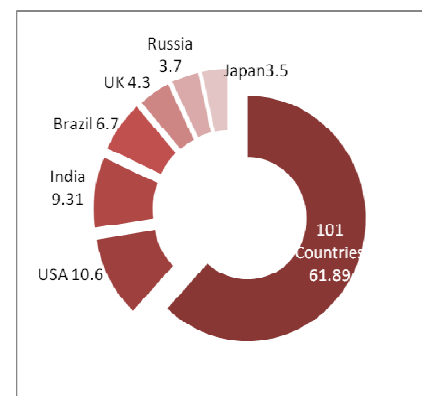


Fig.2 Despite rampant under-diagnosis, India harbours ten percent global patients with Hemophilia

Public health context

Hemophilia provides a difficult challenge to the public health system. The management of the disorder is extremely expensive. However, not providing treatment is a violation of the right to life of patients. Thus, a public health service for Hemophilia has to be constructed with extreme care, balancing the humanitarian aspects with the current realities of the health indicators of the country.

Background to this research

At the School of Health Sciences of the University of Pune, Hemophilia has been used as a disease model to understand the evidence required for development of contextual, relevant and low cost services for birth defects including genetic disorders in the public health system. The Hemophilia study has been ongoing for over a period of sixteen years, and includes a twenty year surveillance of Hemophilia in the state of Maharashtra, as well as various epidemiological studies.

Methodologies

The methodology of the studies from which the data has been accrued, has been either published^{2-4,8-11} in peer reviewed, international journals, or are in the process of communication for publication¹²⁻¹⁸. All these studies have been conducted as a part of post-graduate or doctoral courses of the public health teaching programme of the University of Pune.

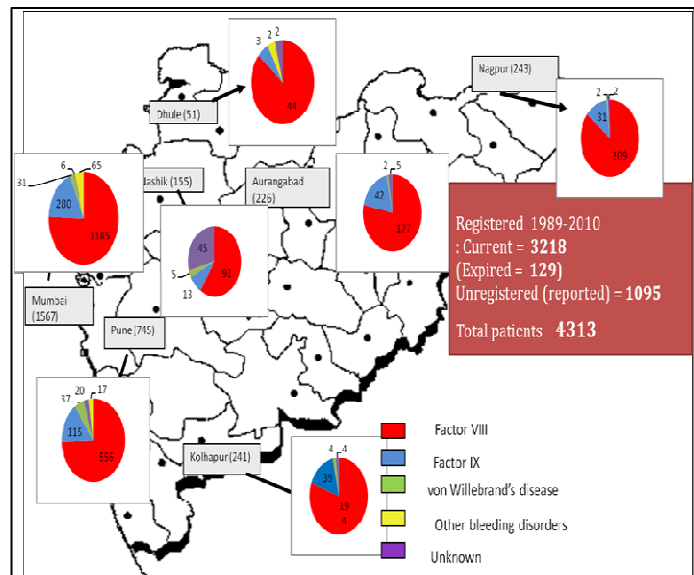


Fig. 3 Distribution of patients with bleeding disorders in the state of Maharashtra from 1989 -2010

Results

- 1.1 Till 2010, over 4000 patients can be identified from records.
- 1.2 During the last ten years, on an average nearly 200 new patients have registered each year, with nearly 50% of these being cases of severe Hemophilia.
- 1.3 The current number of patients represent the tip of the iceberg, as they represents only 30% of the estimated number of cases. If all cases are detected, the state would have 11237 patients with hemophilia

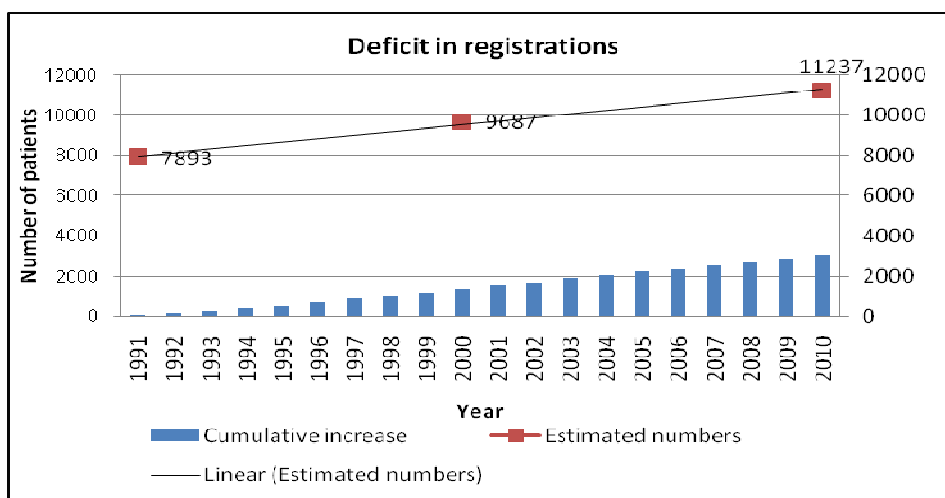


Fig. 4: Average annual registration from 1991-2010. During the last ten years, on an average nearly 200 new patients have registered each year.

- 1.4 The registration of female patients with bleeding disorders (von Willebrand's disease) and patients with rare factor deficiencies are increasing, suggesting increasing medical recognition of these rare disorders.

2.0 Clinical and demographic characteristics of patients

- 2.1** Majority of the registered patients have severe Hemophilia A (85%). Patients with severe Hemophilia B are smaller in number (15%).
- 2.2** The age distribution of patients show that 22% ,29% and 22% patients are in the first, second and third decades of life. 26% patients are above 30 years of age. The latter patients are predominantly those with severe Hemophilia indicating increased survival of these patients.
- 2.3** The annual bleeding frequency of patients with severe Hemophilia A ranges from 2 bleeding episodes in a year to as many as 31 bleeding episodes per year. The median value suggest that a patient with severe Hemophilia A may bleed as frequently as 11 times a year².
- 2.4** For patients with moderate Hemophilia A, the annual bleeding frequency ranges from 5 bleeding episodes in a year to as many as 12 bleeding episodes per year. The median value suggests that a patient with moderate Hemophilia A may bleed as frequently as 10 times a year².
- 2.5** Patients with Hemophilia are clinically variable. While some patients with severe Hemophilia may bleed infrequently, some patients with moderate Hemophilia may have clinical characteristics of patients with severe Hemophilia².
- 2.6** Majority of patients are resident in urban areas. However, patients with rural residence constitute 29% of the total patients. Registration of patients from rural areas has shown an increase over the twenty years from 1991 to 2010.

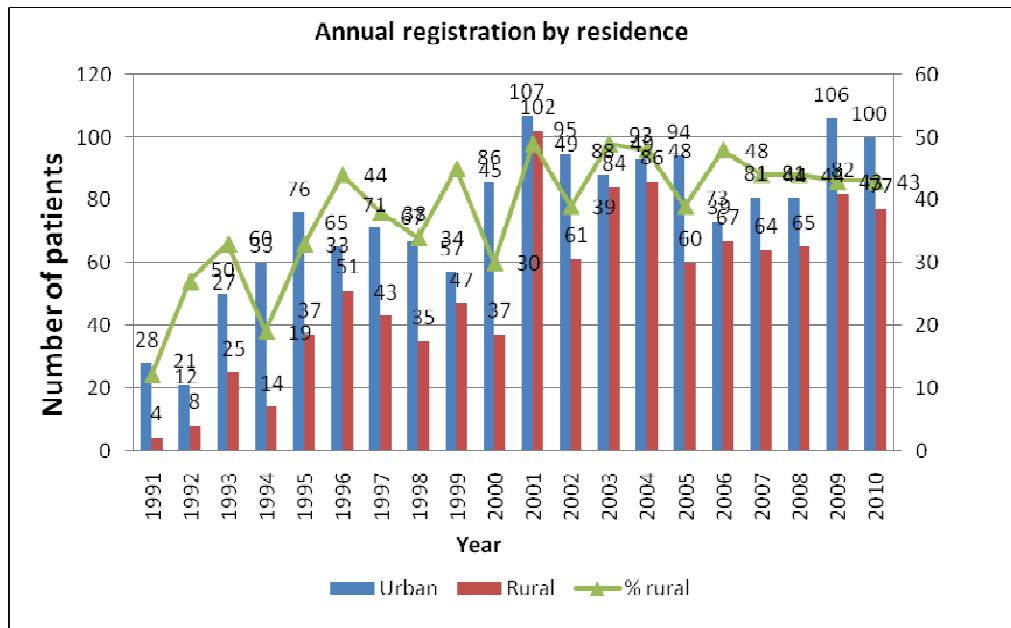


Fig. 5 Registration of patients from rural areas has increased from 1991-2010

3.0 Orthopaedic morbidity

3.1 Orthopaedic complications are rampant in patients with Hemophilia. In a study conducted across the country, only 9 out of 149 patients were found to be free of disability³.

3.2 The extent of disability is proportional to age. The number of affected joints increased progressively with age, so that by the age of 25 years, mobility of all patients were affected³.

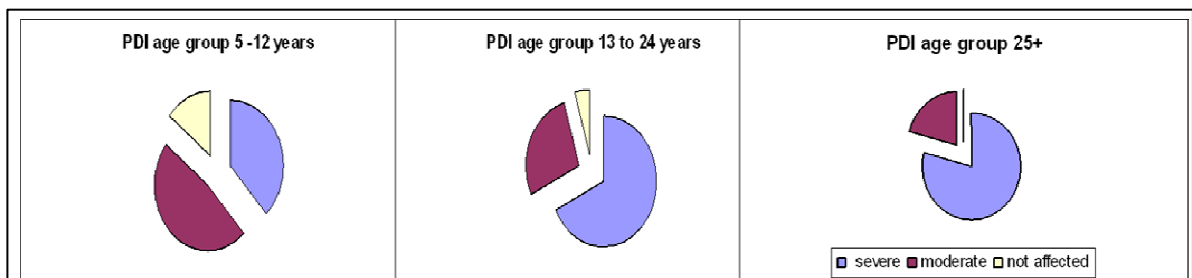


Fig. 6 Progressive increase in disability with age in patients with severe Hemophilia

3.3

The target joint (that is the joint that is repeatedly affected in a patient) was most frequently the knee joint (39%)².

4.0 Schooling and employment

4.1

The number of school or workdays lost due to bleeding episodes ranged from 3.1 to 35.3 per year. Studies show that 37% of 148 patients have discontinued education³.

5.0 Quality of life of parents

5.1

Knowledge about the disorder allows proper management and better coping of repeated bleeding episodes.

5.2

In a study of 167 parents of children with Hemophilia, knowledge about the salient features of Hemophilia was 52%.

5.3

In terms of practice, clotting factor concentrate was utilized for the management of 31% of 118 bleeding episodes in one study, whilst it was 25% in another study².

5.4

Management of bleeding episodes using first aid was 2% of 81 bleeding episodes in one study whilst in another study it was 34% of 113 bleeding episodes². No treatment was frequently reported.

5.5

Parents of haemophilic children were severely affected in all measures of quality of life which included physical functioning ($p=0.000$), emotional functioning ($p=0.000$), social functioning ($p=0.000$), cognitive functioning ($p=0.000$), communication ($p=0.000$), worry ($p=0.000$), daily life ($p=0.000$) and family relationships ($p=0.000$) as compared to control parents.

5.6

Quality of life of mothers was more severely affected than that of fathers ($p=0.001$).

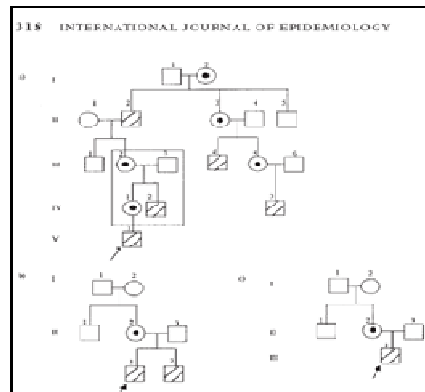
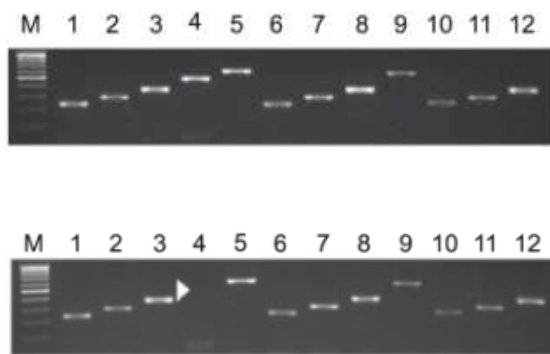


6.0 Treatment costs

- 6.1 A follow up study conducted in Pune showed that only 25% of bleeding episodes were treated with clotting factor concentrate. First aid, that is application of cold compression was the available method of treatment due to financial limitations².
- 6.2 Using an average estimate of 20 000 units of clotting factor concentrate per patient per year, 61,400,000 IU of clotting factor concentrate would be required per year for treatment of patients.
- 6.3 These estimates are generalized as clotting factor concentrate use is dependant on body weight. The estimate excludes clotting factor concentrate requirements for surgery or medical emergencies and is calculated assuming each bleeding episode will be treated with a single infusion of clotting factor concentrate
- 6.4 Using the estimated number of Hemophilia patients, patients till 2010 (11237), and the same generalizations described in the earlier statement, the annual clotting factor requirement in Maharashtra will be 224,740,000 IU.

5. Genetic characteristics

- 5.1 Family history data was available for 52% of the families. Antecedent history was present among 37% of the families.



- 5.2 Medical practitioners in the private sector are offering genetic counselling but there is no data on uptake of these services.
- 5.3 Outreach of genetic counselling can be measured indirectly from the number of haemophilic sons born to a parent. Two or more sons would indicate that genetic counselling is lacking. Twenty year trend analysis shows that the number of parents with two or more haemophilic sons has reduced over a twenty year period. After 2003, there has been no registration of families with more than three sons.

Implications of these findings

- ✓ a. Even though there has been a change in fertility patterns in families with majority families reporting only one son with Hemophilia, the population prevalence of the disorder is increasing in the state.
- ✓ b. Till 2010, over 4000 patients with bleeding disorders and resident in Maharashtra state were diagnosed. These patients represent only 30% of estimated prevalent cases.
- ✓ c. With the development of public health services for Hemophilia, there is likely to be an increase in case detection and a demand for clotting factor concentrate.
- ✓ d. Currently due to the high cost of treatment, only a small proportion of bleeding episodes are treated with clotting factor concentrate, resulting in widespread morbidity.
- ✓ e. Psychological distress and poor quality of life is widespread in parents, primarily arising from the inability to treat the child.
- ✓ f. Out of pocket and catastrophic expenditure is widespread which is the major reason for limiting treatment to the affected child.

Suggested strategies from this evidence

Care

1. The key reality that has to be kept in mind at all times is the insufficiency of clotting factor concentrate for treatment
2. Management of Hemophilia requires specialized training, especially when clotting factor concentrate is severely limited. An expert group should be invited for training and a training module should be developed for clinicians, support staff, casualty officers who will be involved in providing Hemophilia care under treatment product- limited setting.
3. Issues of equity have to be kept in mind at the time of disbursement of clotting factor concentrate, as patients resident in nearby areas are likely to access care more frequently than patients from more remote areas.
4. Patient registration with proper address should be made compulsory in order to ensure fair disbursement of clotting factor concentrate
5. A ceiling of the amount of treatment product to be used per

**Communication,
Patient
education
and counselling**

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- patient, guided by clinical judgement has to be developed. A sufficient amount of treatment product must be kept aside for medical emergencies.
6. An essential component of training should be understanding the importance of regular auditing of clotting factor concentrate stocks, in order to ensure that supplies can be rationed out.
 7. Routine monitoring of activities should assist in developing care services for patients.
 8. As physiotherapy services require clotting factor concentrate cover, these services can be offered at cost or introduced in a second phase, in order to ensure sustainability of providing treatment product for care of routine hemorrhagic episodes.
 9. The use of first aid for controlling bleeds has to be emphasized repeatedly to patients and parents, especially those families who may need to travel distances in order to reach treatment services.
 10. Counsellors are key to provision of services. Their role can be for (a) general counselling and (b) genetic counselling.
 11. Due to the severe distress experienced by families, sensitive communication, empathy and support are integral to the medical training and training for support staff.
 12. The time of diagnosis is a time of severe emotional stress for parents. Education on the disorder, management of bleeds, understanding the danger signs that require hospitalization need to be given to parents.
 13. Repeated counselling so that parents, primarily mothers can unburden their emotions, have shown to have beneficial impact on the quality of life.
 14. A help-line assists in the process of counselling.
 15. The Hemophilia chapters across the state have been the referral point for patients diagnosed in the private sector. This organization has been at the forefront of advocacy, organizing procurement and disbursement of treatment product, referral of parents for genetic counselling and has provided psychosocial support for parents and patients.
 16. Under the mentorship of the World Federation of

collaboration

Hemophilia and twinning programmes with advanced clinical centres, several haematologists have been trained in the specialized care needed for the management of hemophilia. Hemophilia care has been fine-tuned by these specialists, as they have standardized the management of bleeding episodes using limited quantities of clotting factor concentrate.

17. One of the major contributions of these centres has been patient registrations, which provides a surveillance of Hemophilia in the state.

18. The use of the services of this NGO needs to be kept in mind.

19. Integral to the programme is the need to offer a genetic counselling service.

20. Counsellors need to be trained in order to elicit family history data with extreme sensitivity, so that the mother is not stigmatized.

Prevention

21. Referral linkages can be made with the gynaecology department for collection of sample (amniotic fluid).

22. Collaborative linkages with national institutes with a track record of providing DNA based diagnosis can be made for testing with appropriate pre and post-test counselling.

23. Female relatives of the patient are at risk of being a carrier of the hemophilia gene. An important component of prevention is to ensure that sister and female cousins of patient are tested. However, this testing has to be done with extreme sensitivity as it has ethical implications on the marriage and future of the girl.

Overall recommendations

The hematology programme can be implemented through two existing programmes:

- a) The District Early Intervention Centres that have been planned under the Rashtriya Bal Swasthya Karyaram can be used for delivery of routine patient care and**
- b) Genetic counselling services can be integrated with the antenatal care service of the NRHM-RCH II programme.**

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