Combating Transfusion transmitted infections in thalassemia-Current Indian scenario

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Introduction

- Safety of the blood supply is a subject of great concern for all recipients.
- Since the starting of blood transfusion scientifically in the early 1940s, various transfusion associated problems have come to the forefront.
Serious Allergic Reactions (Anaphylaxis)
• However, TTI was first observed in the process of blood transfusion in the late 1940s.

• Till early 1970s, blood bank personnel were only concentrating on a few blood borne infections like syphilis and serum hepatitis by “Australia antigens”.

• In the last 40 years, we have noted that numerous viral, bacterial and parasitic infectious agents are involved as hurdles in blood safety to patients.
• There are even some infections which have been proved to be transfusion transmitted and we, transfusion workers, were not aware of these infections.
• The general public may be idealistic in their belief that risk-free blood products are achievable in today's world.

• In fact, the threat of infectious agents entering the blood supply is not static and may evolve as new pathogens emerge or as old ones change their epidemiological pattern.
Magnitude of TTIs

- The magnitude of the TTI varies from country to country
- The problem of TTI is directly proportional to the prevalence of the infection in the blood donor community.
- The reports point to prevalence of ~2% of viral diseases in the blood donor population
- There is a risk of 1–2 per 1000 recipients receiving contaminated blood with viral, bacterial or parasitic agents.

Shyamala V. Transfusion transmitted infections in thalassaemics: need for reappraisal of blood screening strategy in India. Transfusion Medicine 2014;24:79–88
• Majority of the problems are due to prevalence of asymptomatic carriers in the society, as well as, blood donations during the window period of infections.
• While in the past, the risk of TTI was accepted by patients and physicians as unavoidable, a low-risk blood supply is expected today.
Why thalassemics?

- Direct estimation of risks associated with blood screening protocol—study rate of infection prospectively in recipients
- Low prevalence of TTI and occasional transfusion makes impractical
- Alternative is to analyse among repeat recipients
- They reflect the blood safety status
• TTIs mainly occur in patients who are dependent on blood transfusion like thalassemia
• TTI are still major concerns in developing countries where paradoxically thalassemia is most common.
• Worldwide, there are more than 60,000 births annually of serious forms of thalassemia.

Widespread throughout the Mediterranean region, Africa, the Middle East, the Indian subcontinent and South East Asia.

• Thalassemia is one of the major public health problems in India with an estimated incidence of 2 per 1,000 births and a carrier frequency of 3-4% (1).
• The general incidence of thalassemia trait in India varies between 3 and 17%.
• It is estimated that there are about 65,000-67,000 beta-thalassemia patients in India with around 9,000-10,000 cases being added every year (2).

Appropriate and regular red cell transfusion remains the main treatment of choice for patients with thalassemia major.

<table>
<thead>
<tr>
<th>Age in years</th>
<th>No. of cases</th>
<th>Average body weight (kg)</th>
<th>Average blood requirement ml/kg/year</th>
</tr>
</thead>
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<tr>
<td>1-5</td>
<td>57</td>
<td>13.8</td>
<td>110.0</td>
</tr>
<tr>
<td>6-10</td>
<td>48</td>
<td>20.3</td>
<td>150.0</td>
</tr>
<tr>
<td>11-15</td>
<td>19</td>
<td>31.5</td>
<td>180.0</td>
</tr>
</tbody>
</table>

- Worldwide thalassemia patients exhibit 0.3-5.7% HBsAg and 4.4-85.4% HCV positivity (1).

- The incidence of hepatitis and HIV infections in Indian pediatric patients with thalassemia is high due to high prevalence of hepatitis and HIV in the general population (2).

- Positivity rate correlated with the number of transfusions, with 8% prevalence for <50 transfusions, 23% for 51-100 and 42% for >100 transfusions (3).

Prevalence studies have found that common infections occurring in thalassemic patients are Hepatitis C (2.2%-44%), followed by Hepatitis B (1.2%-7.4%) and HIV (0%-9%) (1,2).

Choudhury et al. on multi-transfused thalassemia patients reported the seropositivity for HIV varying from 0.5% to 3.8% (3).

<table>
<thead>
<tr>
<th>No.</th>
<th>Author</th>
<th>Place</th>
<th>Duration</th>
<th>HIV +ve %</th>
<th>HBV +ve %</th>
<th>HCV +VE %</th>
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<tr>
<td>2</td>
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<td>2.9</td>
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<td>–</td>
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<tr>
<td>3</td>
<td>Benerjee D et al. [5]</td>
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<td>1990</td>
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<tr>
<td>4</td>
<td>Choudhary N et al. [6]</td>
<td>India</td>
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<tr>
<td>6</td>
<td>Sheyyab M et al. [8]</td>
<td>Amman, Jordan</td>
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<td>8</td>
<td>Singh H et al. [10]</td>
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<td>Kapoor C et al. [15]</td>
<td>Ouetta, India</td>
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<td>14</td>
<td>Ocak S et al. [16]</td>
<td>Turkey</td>
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<td>0</td>
<td>0.75</td>
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<table>
<thead>
<tr>
<th>Name of the study</th>
<th>No. of cases</th>
<th>Anti-HCV positivity (%)</th>
<th>Anti-HBsAg positivity (%)</th>
<th>Anti-HIV positivity (%)</th>
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<tbody>
<tr>
<td>Jain et al.[4]</td>
<td>96</td>
<td>25</td>
<td>1.04</td>
<td>1.04</td>
</tr>
<tr>
<td>Vidija et al.[5]</td>
<td>200</td>
<td>2</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Patel et al.[6]</td>
<td>81</td>
<td>16.04</td>
<td>2.46</td>
<td>1.23</td>
</tr>
<tr>
<td>Bhavsar et al.[7]</td>
<td>100</td>
<td>18</td>
<td>6</td>
<td>9</td>
</tr>
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</table>

Combating TTI

- From blood donor collection to transfusion of the recipient, there are several layers of protection of the blood supply.

Traceability, haemovigilance systems
Reporting of adverse events
National and international networks

Indication for transfusion
• Assess the need for each individual transfusion

Storage, pathogen inactivation
• Optimize storage temperature and time
  • Effective pathogen inactivation procedures that do not compromise product integrity

Screening tests
• Bacterial detection methods for platelets may detect most contaminated units
  • NAT testing combined with serology for viral infection decreases the residual risk

Processing, quality control
• Improved donor skin disinfection and diversion of the first 30ml of blood effectively reduces contamination
  • Audits and quality control assessments of the procedures during product processing ensures highest safety standards

Donor eligibility
• Careful donor selection lowers risk of dispensing blood products obtained during window period
In India, prevention of transfusion-transmissible diseases requires special and different strategies due to several factors:

- the high prevalence of replacement donors
- their specific geographical location
- climate
- genetic
- sociocultural status of the population making them vulnerable to endemic diseases.
Since the early 1960s, blood banks have aggressively pursued strategies to reduce the risks of TTI.

In particular, donor exclusion criteria, such as a history of hepatitis or transfusions in the past six months have been in place since early on.
Donor eligibility

- Careful donor selection lowers risk of dispensing blood products obtained during window period
Donor eligibility

- In India, prevalence of these viral infections in donor and patient populations is high due to the lack of regular repeat voluntary blood donations.
- India still depends mainly on replacement donors in whom the prevalence of TTI is more.
Seroprevalence and Trends in Transfusion Transmitted Infections Among Blood Donors in a University Hospital Blood Bank: A 5 Year Study

P. Pallavi · C. K. Ganesh · K. Jayashree · G. V. Manjunath

Fig. 2 Trends in the prevalence of TTI among voluntary and replacement donors
WISH TO DONATE BLOOD?
REGISTER AS VOLUNTARY BLOOD DONOR

“Hazards of Great Battles lie before us”

“Will you enrol as a blood donor?”

Here is a warning all must heed. Adequate reserves of fresh blood, plasma and serum must be available for giving transfusions to all 1944 battle casualties that need them. For this reason the Army Blood Transfusion Service calls for many thousand more blood donors of all groups. Will you help by giving a little of your blood? It is simple, painless and harmless; but the lives of our wounded depend upon it and thousands more blood donors are wanted.

THE PRIME MINISTER
HAS SAID:
(Dec. 9, 1943)

HEART HEADQUARTERS, 35, BROADHED
Bristol’s Blood Transfusion Campaign
Feb. 12th to 26th

ARMY BLOOD TRANSFUSION SERVICE
• Recruitment of safe altruistic voluntary blood donors and retention of regular blood donors
• Directed donation by a repeat regular voluntary blood donor is one of the way to mitigate TTIs in these patients.
Vaccination

- Globally the practice of vaccinating all thalassemics with HBV is being promoted, and in India it was adopted in 1990.
- Additionally, in several countries, through pediatric vaccination and vaccination of the donors, the spread of HBV is being contained.
• In India, Pediatric vaccination was initiated as a pilot project in 1996 with a phased expansion to the rest of the country and donor vaccination has not been implemented (1).

• One study reported a very low prevalence (0.75%) of HBsAg in multi-transfused β-thalassemia patients because of the efficacy of the vaccination program followed in their country (2).

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Processing-Components usage

- In India only 30% of the blood banks have component preparation facilities.
- As a result, thalassemics are provided with whole blood.
- Nearly all of the viral load in the blood is present in the plasma fraction.

Marwaha N. Whole blood and component use in resource poor settings. Biologicals 2010;38:68-71
The total viral load transfused has been shown to be directly correlated to cases of TTI.

There are reports of TTI with plasma transfusion, while PRBC and platelets from the same unit have not resulted in TTI.

Hence in all situations TTIs can be minimised through the required use of components.

Allain et al. Infectivity of blood products from donors with occult hepatitis B virus infection. Transfusion 2013;53:1405-15

Kleinman et al. Infectivity of HIV-1, Hepatitis C virus and hepatitis B virus and risk of transmission by transfusion. Transfusion 2009;49:2454-89
Leukoreduction is a known effective strategy for reducing the risk of the transmission of cell-associated viruses.

Selective leukoreduction should also be seen as an important processing step that will contribute to improving the safety of blood components especially in resource poor country like India.

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Screening tests

- Though technological advancements have led to the development of more sensitive methods to detect various infectious disease markers,
- like viral specific antigens, antibodies and nucleic acids in order to enhance the safety of blood transfusion,
- early detection of infection remains elusive goal due to the existing problem of “Window period”
- due to the limitation in the screening assays, genetic modifications in viral strains, and laboratory errors.
The residual risk of TTI transmission from screened blood depends on:

- the safety of donor population,
- sensitivity of the screening tests used,
- window-period donations,
- mutant strains.
• NACO -1987,
• licensing of blood by DCGI - 1992
• National Blood Policy-2002
• efforts have been made for making blood supply safer in India.
• Testing of blood was mandated in
  • 1989- anti-HIV
  • 1992-HBsAg
  • 2001-anti-HCV
• Depending on the category of blood bank, there is a wide range in the quality of serology assays.

• A majority of the government blood bank are provided third generation ELISA serology assay of variable quality.

• A number of blood banks that are resource and facilities constrained, and also have few donations are permitted to use rapid tests to screen which are less sensitive.

• There is an urgent need to replace rapid tests wherever feasible with sensitive tests to shorten the window period.
Table 3: Comparison of ELISA and Western blot results

<table>
<thead>
<tr>
<th>Reactive ELISA Results</th>
<th>Western Blot Results</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Reactive</td>
</tr>
<tr>
<td>3(^{rd}) generation ELISA, n = 14</td>
<td>11</td>
</tr>
<tr>
<td>4(^{th}) generation ELISA only, n = 30</td>
<td>15</td>
</tr>
<tr>
<td>Grey zone (with 4(^{th}) gen ELISA), n = 7</td>
<td>2</td>
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</tbody>
</table>

“Fourth generation” combined antigen-antibody assays can provide a single serological platform in resource constrained settings.

<table>
<thead>
<tr>
<th>RT-PCR</th>
<th>HCV antibodies</th>
<th>Combined Ag/Ab</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Positive (20)</td>
<td>Negative (19)</td>
</tr>
<tr>
<td>Positive (22)</td>
<td>18</td>
<td>4</td>
</tr>
<tr>
<td>Negative (17)</td>
<td>2</td>
<td>15</td>
</tr>
<tr>
<td>Sensitivity</td>
<td>81.8%</td>
<td></td>
</tr>
<tr>
<td>Specificity</td>
<td>88.23%</td>
<td></td>
</tr>
<tr>
<td>Accuracy</td>
<td>84.6%</td>
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</tbody>
</table>

Although less sensitive than NAT (71 % of HCV RNA positive/anti-HCV negative in window period), this assay could be a reasonable alternative when NAT cannot be used for reasons such as cost, organization, emergency or logistic difficulties.

The mean delay in detecting HCV infection between HCV-RNA and this new test was found to be 5 days, reducing the window period by an average of 37 days.

• Inspite of the mandated serology assays in India the reports for all three viral TTIs indicate the inadequacy of serology only screening in ensuring blood safety.
• Currently in India, only 7% of the 7.9 million units of annually donated blood is screened by ID-NAT testing.
• There is a lack of second tier NAT of the blood donors at pan India level (8).

Shyamala V. Transfusion transmitted infections in thalassaemias: need for reappraisal of blood screening strategy in India. Transfusion Medicine 2014;24:79–88
Why Nucleic Acid Testing? Reduction of Window Period

In the first multicentre evaluation of NAT in Indian blood donors HCV RNA yield was 1 per 12224 donors (1).

Overall in the Indian donor population the range of 1 of 301 to 1 of 1079, with >62% being HBV yields (2,3)

Nearly 70% of the HBV NAT yields are OBI cases, which being HBsAg negative by serology are currently being transfused as “safe blood”.

3. Kumar et al. Importance of blood screening by nucleic acid testing with a repeat testing algorithm in hepatitis C and B virus high prevalence region. VoxSanguinis 2013;105:86
The revelation by individual donation (ID) NAT testing, of 1 per 310 units being serology negative-NAT reactive is alarming.

Extrapolating the serology negative NAT reactive yields, for an annual blood supply of 7.9 million units, 23,700 units or nearly 100,000 blood components are likely to be infectious.

Though the cost for ID-NAT testing is considered unaffordable for a medium development country such as India, the enormity of TTIs will place an unmanageable cost burden on the society.
• NAT is an additional though highly sensitive and significant advance in blood safety.
• There are situations where NAT is negative but serology is positive.
• Hence serology and NAT testing are complimentary tests.
• NAT testing where affordable and feasible should be introduced since the prevalence of TTIs is higher and NAT might detect more window period donations.

Neelam Marwaha, Suchet Sachdev. Current testing strategies for hepatitis C virus infection in blood donors and the way forward. World J Gastroenterol 2014; 20: 2948-54
Microarray-single platform

- Another approach is to consider microarray platforms for all potential transfusion transmissible infections or combination technologies (antibody, antigen and NAT) as one platform.

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Pathogen inactivation

- Though Pathogen reduction technology (PRT) for red cells and artificial blood alternatives can mitigate the transmission of infections, they are still in experimental phase.
- Issues - high costs, neo-antigen formation and post PRT yields
- PRT for red cells - not yet licensed.
- Attempts on-going for whole blood.
- may obviate the need for multiple PRT platforms for blood components.

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Transfusion needs—Neocytes

- As these patients depend on regular blood transfusions,
- neocytes can be transfused which survives in the circulation longer than older cells
- will reduce the total blood requirement
- lengthens the interval of transfusions
- decreasing the number of donor exposures.
- Program of super transfusion of neocytes produces a significant decrease in the rate of iron accumulation too

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Hemovigilance

• One of the most important weapons we do not use against TTI is the hemovigilance.
• Once we transfuse patients with blood and components, there is no system to follow up for any long-term post-transfusion effects.
• Procedures to quickly detect the possible spread of transmissible diseases via blood transfusion provide yet another safety layer for protecting the blood supply.
• Collaborating with public health officials by sharing surveillance data, look back/trace back policy are some of the methods that can be used.

• While medical technology and services have seen a rapid increase in progress in recent years, they have not coordinated with the development of the national health care system.
• Nationwide database like Scandinavian Donations and Transfusions (SCANDAT) database
• containing data on blood donors, blood transfusions, and transfused patients, with complete follow-up of donors and patients for a range of health outcomes can be created
• We can use this database for further studies of donor health, transfusion-associated risks, and transfusion-transmitted disease.

Reporting

- Ongoing education and up-to-date information regarding infectious agents that are potentially transmitted via blood components is necessary to promote the reporting of adverse events, an important component of TTI surveillance.
Collaboration of all parties involved in transfusion medicine, including national haemovigilance systems, is crucial for protecting a secure blood product supply from known and emerging blood-borne pathogens.
• In order to maintain the integrity, purity and adequacy of the blood supply, new donor screening assays, donor deferral, and pathogen inactivation of blood components need to be balanced against the undue loss of potential donors because of overly stringent exclusion criteria.
• Attention has to be paid to emerging viral, bacterial and parasitic agents that are similarly transmitted, and are not routinely tested.

• Changing population dynamics, increase travel and immigration may require new policies to maintain the safety of blood supply.
• The true value of diagnostics depends on assays that are early predictors of infection offering maximum blood safety.
• However, through breach in safe blood transfusion, thalassemics are confronted by new and more severe health challenges of TTIs contributing to increased mortality.
• Transforming the donor base to voluntary repeat donors is a sociological change which will take a long time to accomplish and is not an immediately implementable way to curtail this increase.
- For the immediate, implementable testing practice for maximum safety is the solution.
- The residual risk of the resulting TTIs places a serious burden on health care, finances, society and human life.
To conclude

- The goal of a safe and affordable blood supply may be reached by the coordinated optimization of each step in the transfusion chain,
- including the careful consideration of donor eligibility criteria,
- adherence to rigorous rules during donation,
- processing and storage,
- the optimal implementation of available screening tests,
- reporting of adverse events and
- finally the vigilance of prudent physicians, who evaluate the necessity of each transfusion.
Combined with the development and implementation of sensitive and affordable detection and total dependence of altruistic repeat voluntary donors, these measures can make blood transfusion a safer form of therapy even in places where the risks to date have to be considered significant.
Looking for Complete safety