Passenger Lymphocyte Syndrome (case presentation)

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Case history

- 24year Female
- Known Patient with Wilsons Disease
- DBD donor Liver Transplantation done on 15/08/2016
- Indication acute on chronic liver failure following Wilsons Disease.

Case history

- Haemoglobin level immediate post OP 76g/L
- Improved to 124g/L at POD 6
- Gradually declined thereafter 70g/L at POD 12

- At POD 10 patient developed signs and symptoms suggestive of acute graft rejection laboratory tests and imaging studies confirmed the same
- Methyl Prednisolone Pulse Therapy started

Case History

- Cause for drop in Haemoglobin level ?

Date	15th Aug (imm PO)	21st Aug (POD 6)	27th Aug (POD 12)	29th Aug (POD 14)
Hb level (g/L)	**76**	**124**	**70**	**80**

LDH	↑ 566	(<240IU/L)
Con Bilirubin	↑ 151	(<4umol/L)
Haptoglobin	↓ <0.1	(0.8-2.2g/L)

- Haemolytic causes
  - Acute or delayed haemolytic transfusion reactions
  - Autoimmune haemolysis
  - MAHA
  - Drug induced haemolysis

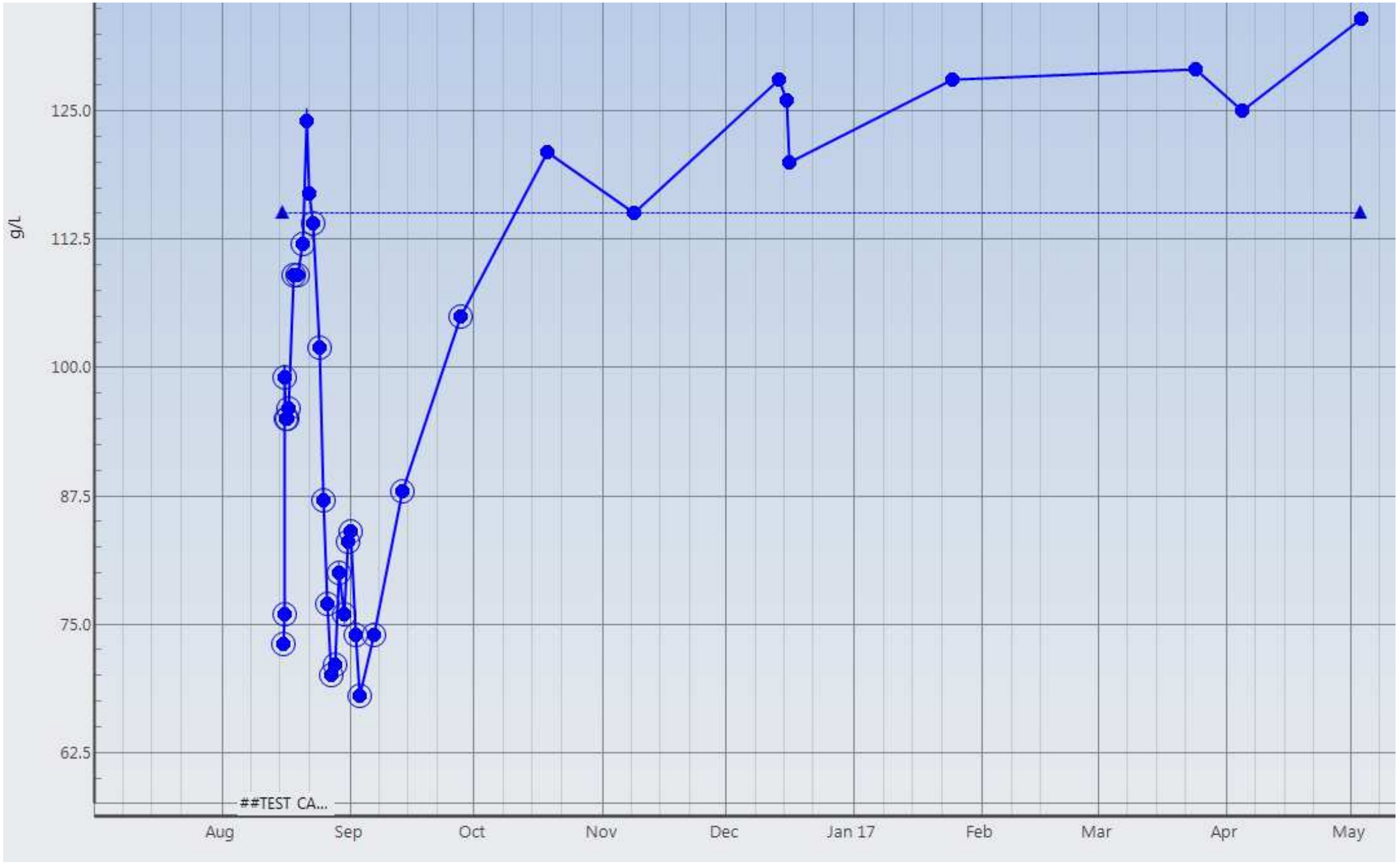
Findings of the transfusion laboratory

	Pre Transplant	Post-Transplant
Antibody screening	Negative	Positive
Antibody detected	None	Anti D
DAT	-	**+4** with IgG specificity
Eluate from DAT positive cells	-	Anti D

Blood Group	**Patient** **B Rh D positive**	**Donor** **B Rh D negative**

Management

- **“Passenger lymphocyte syndrome”** was considered as the reason for haemolysis
- Recommended to transfuse **B Rh D negative** red cells if further red cell transfusions required
- Patient was already on methyl prednisolone pulse therapy
- Haemoglobin level improved without further transfusions.


g/L
125.0
112.5
100.0
87.5
75.0
62.5
##TEST CA...
Aug
Sep
Oct
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Dec
Jan 17
Feb
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Apr
May

Passenger Lymphocyte Syndrome (PLS)

- **Definition**

  The PLS refers to the clinical phenomenon of alloimmune haemolysis resulting from the antibodies produced by viable donor B lymphocytes “passenger lymphocytes” in a primary or secondary immune response against the recipient’s red blood cell antigens

- **History**

  •The appearance of unexpected antibodies of A and B specificity in recipients of kidney allografts from ABO minor mismatched donors was first reported in the early 1980s.

  •Then, more than 100 cases involving liver, kidney, pancreas, spleen, heart, lung, and heart-lung were published in 1991.

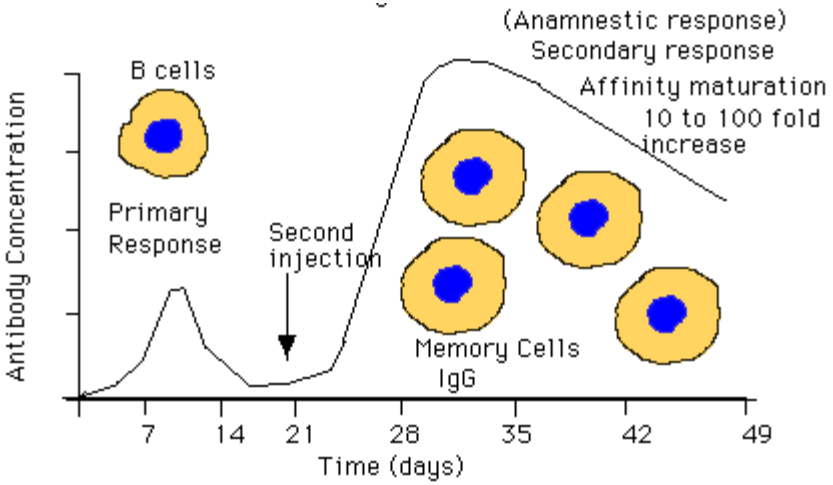
Passenger Lymphocyte Syndrome (PLS)

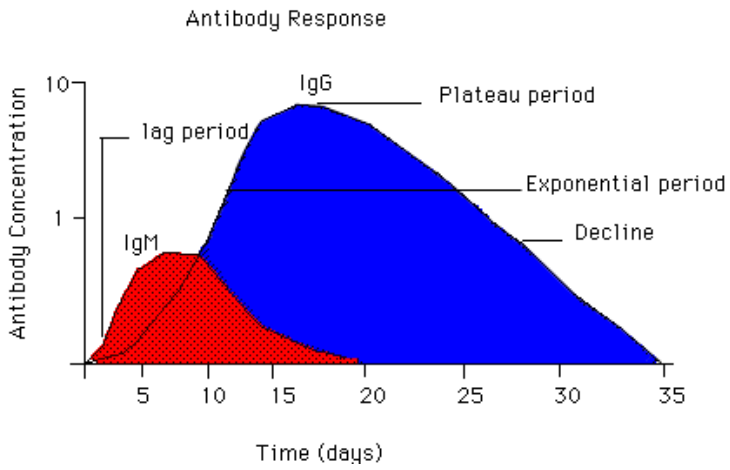
- PLS can occur after
  - Solid organ transplant
  - Stem cell transplant
  - Administration of B cell rich cellular therapeutic infusions
- PLS most often seen in solid organ transplantation with minor ABO mismatch
  - Donor Group O / Recipient Group A,
- Also reported with other blood group systems like Rh, K, Fy, Kidd
  - Donor lacks recipient’s antigens
  - Donor can form antibodies against recipient’s red blood cell antigens

Passenger Lymphocyte Syndrome (PLS)

- Pathophysiology
  - PLS can be considered as a type of graft vs host disease
  - Viable donor lymphocytes passively transferred to the recipient
  - Immunocompetent donor memory B lymphocytes produce antibodies in a secondary immune response against the recipient’s red cells.
  - The massive red cells destruction is thought to be complement-mediated

Primary and secondary immune response





http://222.197.192.76/jpkc/swjcjs/biosite/files/immunology/abproduction.html

Passenger Lymphocyte Syndrome (PLS)

- Pathophysiology
  - PLS is heterogeneous,
    - Donor B-lymphocytes are detected in recipients but antibody production is either delayed or is never detectable
    - Both donor B-lymphocytes and antibody are detected but haemolysis may not occur
  - The triggers for antibody production and haemolysis is still incompletely understood.

PLS – risk factors

- Donor B-lymphocytes stimulation after transfer
  - Through infections
  - Relative recipient T-lymphocyte inhibition (increased specific immunosuppression such as depleting antibodies, ATG)

Table 2: Risk factors for PLS

Risk factors
• Blood group O to A transfer • Possible sensitizing events: Pregnancy, blood transfusions • Cyclosporin use • Infection in the immediate posttransplantation period

Nadarajah et al. American Journal of Transplantation 2013; 13: 1594–1600

PLS – Clinical course

- PLS is a self-limiting condition
- Often overlooked as a potential cause of post transplantation anaemia
- Most reported cases of PLS after liver transplant resolve within 3 weeks (median, 20 days), yet positive DAT reportedly persist for over 1 year. ***(Gniadek et al. Transfusion 2017;57;1262–1266)***

PLS – Clinical course

- As donor B-lymphocytes fail to self renew, or tolerance of graft lymphoid tissue towards the recipient antigen develops, haemolysis ceases as antibody production declines

- However, cases of PLS occurring up to 182 days after the start of haemolysis have been reported implying that once transferred and stimulated, B- lymphocytes or plasma cells are capable of sustained new antibody production

(***Nadarajah et al. American Journal of Transplantation 2013; 13: 1594–1600)***

PLS - Solid organ transplantation

- PLS following solid organ transplantation has been reported to be;
  - 09% for kidney transplants
  - 29% for liver transplants
  - 70% for heart-lung transplants

    Nadarajah et al. American Journal of Transplantation 2013; 13: 1594–1600

- These differences are likely to reflect the amount of lymphoid tissue implanted with the corresponding organ transplant

PLS - liver transplantation

- Biochemical PLS in liver transplantation is 30%–40%.
- In almost all the cases (68–100%) the antibodies are directed against Rh blood group antigens
- Only 30–40% of these antibodies led to immune haemolysis

(Maxime Audet et al. Clinical & Developmental Immunology 2008; ID 715769)

PLS in liver transplantation **exceptional cases**

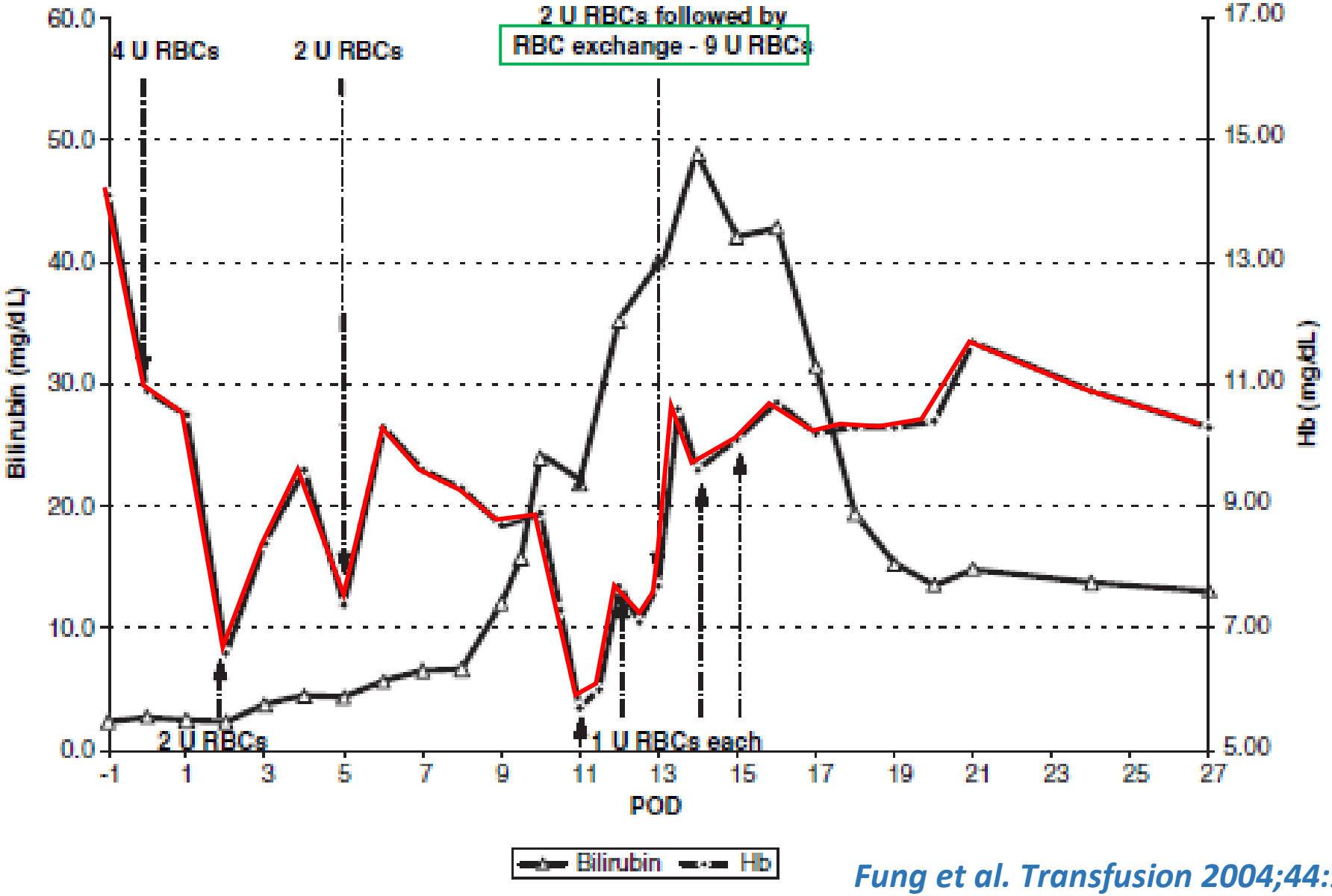
Fung et al. Transfusion 2004;44:1635-1639

- Male 50y ESLD 2^{ry} to hepatitis C–induced cirrhosis underwent liver transplantation.
  - blood group Patient O Rh+ / Donor O Rh negative female
- procedure occurred without any immediate perioperative complications
- Developed severe anaemia with hyperbilirubinemia requiring increasing RBC transfusion support
  - 2U group O Rh+ RBC on POD 2
  - 2U group O Rh+ RBC on POD 5
  - Hb level transient increase, Gradually declined 5.7g/dl on POD 11

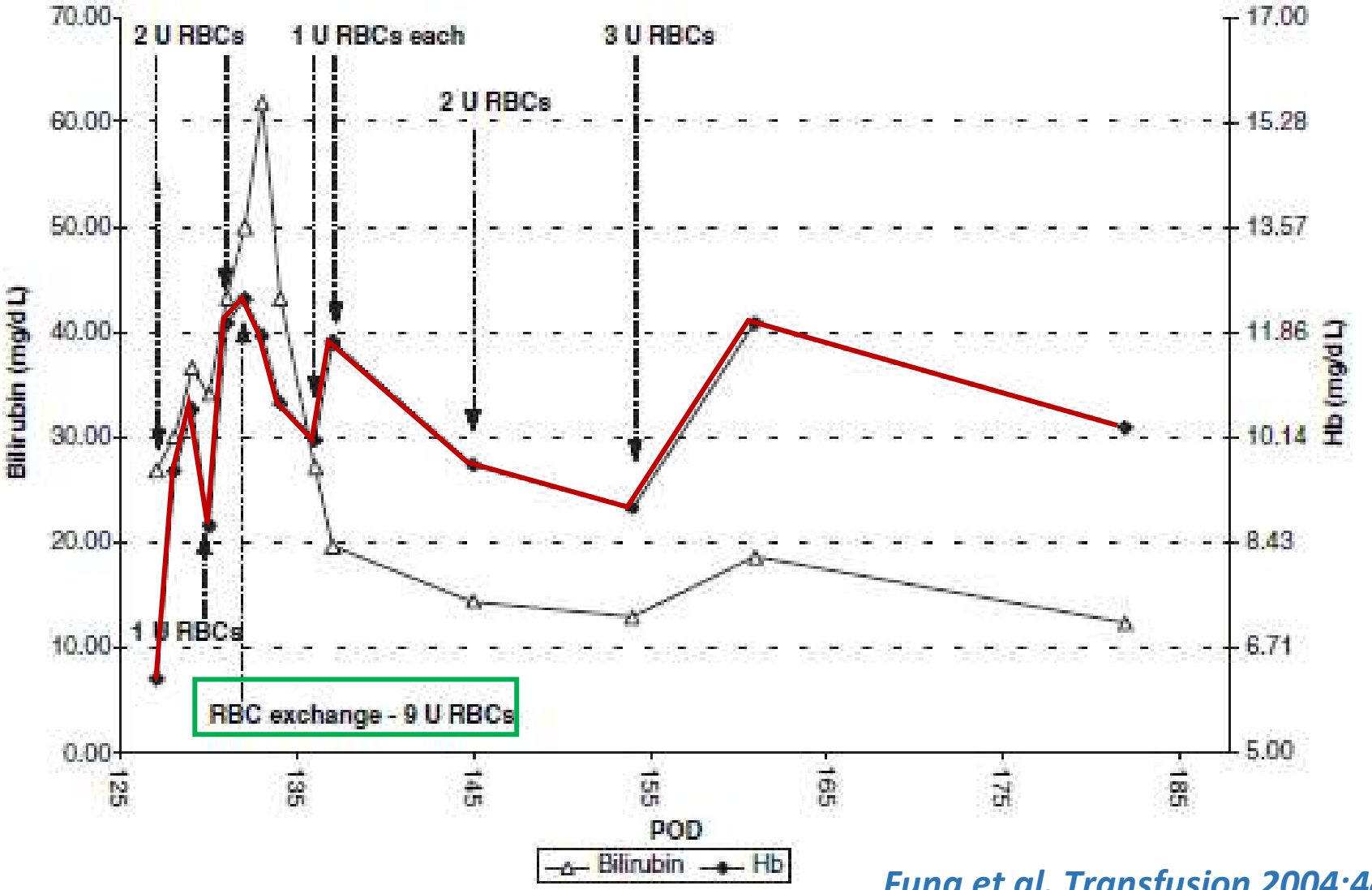
PLS in liver transplantation exceptional cases

Fung et al. Transfusion 2004;44:1635-1639

- Patient had no prior transfusion history
  - His antibody screens were negative until POD 11,
  - At POD 11 demonstrated the presence of anti-D and anti-K
  - The **DAT was positive** (4+ IgG; no C3d binding detected)
  - The elution showing **anti-D** only
- The medical records of the organ were reviewed.
  - The donor was found to have antibodies against D, C, and K.
  - The donor was C–, E–, and K– (rr, Kell neg)



Fung et al. Transfusion 2004;44:1635-163



Fung et al. Transfusion 2004;44:1635-1639

PLS in liver transplantation exceptional cases

Fung et al. Transfusion 2004;44:1635-1639

- POD 321, the patient underwent a splenectomy.
- POD 327, started epoetin alfa
- POD 343, Hb level 15.5 g/dL & t bilirubin dropped to 6.9mg/dL
- POD 373,
  - antibody screen remained positive with 1+ reactivity against K, but not against either D or C. The DAT and eluate were negative

PLS in liver transplantation **exceptional cases**

Gniadek et al. Transfusion 2017;57;1262–1266

- 34-year-old male patient, blood group O pos
- History of hepatitis C and alcoholic hepatitis.
- Underwent a liver transplant from a group O, neg donor,
- Proceeded without intraoperative complications,
- Required 20 units of group O pos RBCs during surgery

PLS in liver transplantation exceptional cases

Gniadek et al. Transfusion 2017;57;1262–1266

- Stable until POD 5,
- Developed signs and symptoms consistent with RTI
- By POD 7, his anaemia had worsened,
- Antibody screen became weakly positive against some, but not all, Rh D+ screening and panel cells.
- A DAT was positive, and IgG anti-D was identified in eluate studies
- Switched to group O neg transfusion protocol

PLS in liver transplantation exceptional cases

Gniadek et al. Transfusion 2017;57;1262–1266

POD 10	Haptoglobin decreased to less than 6 mg/dL
POD 11	Indirect bilirubin rose to 1.7 with a total bilirubin of 3.4 mg/dL
POD 12	Erythropoietin elevated to 1025 ng/mL
POD 14	LDH peaked at 649 U/L

PLS in liver transplantation exceptional cases

Gniadek et al. Transfusion 2017;57;1262–1266

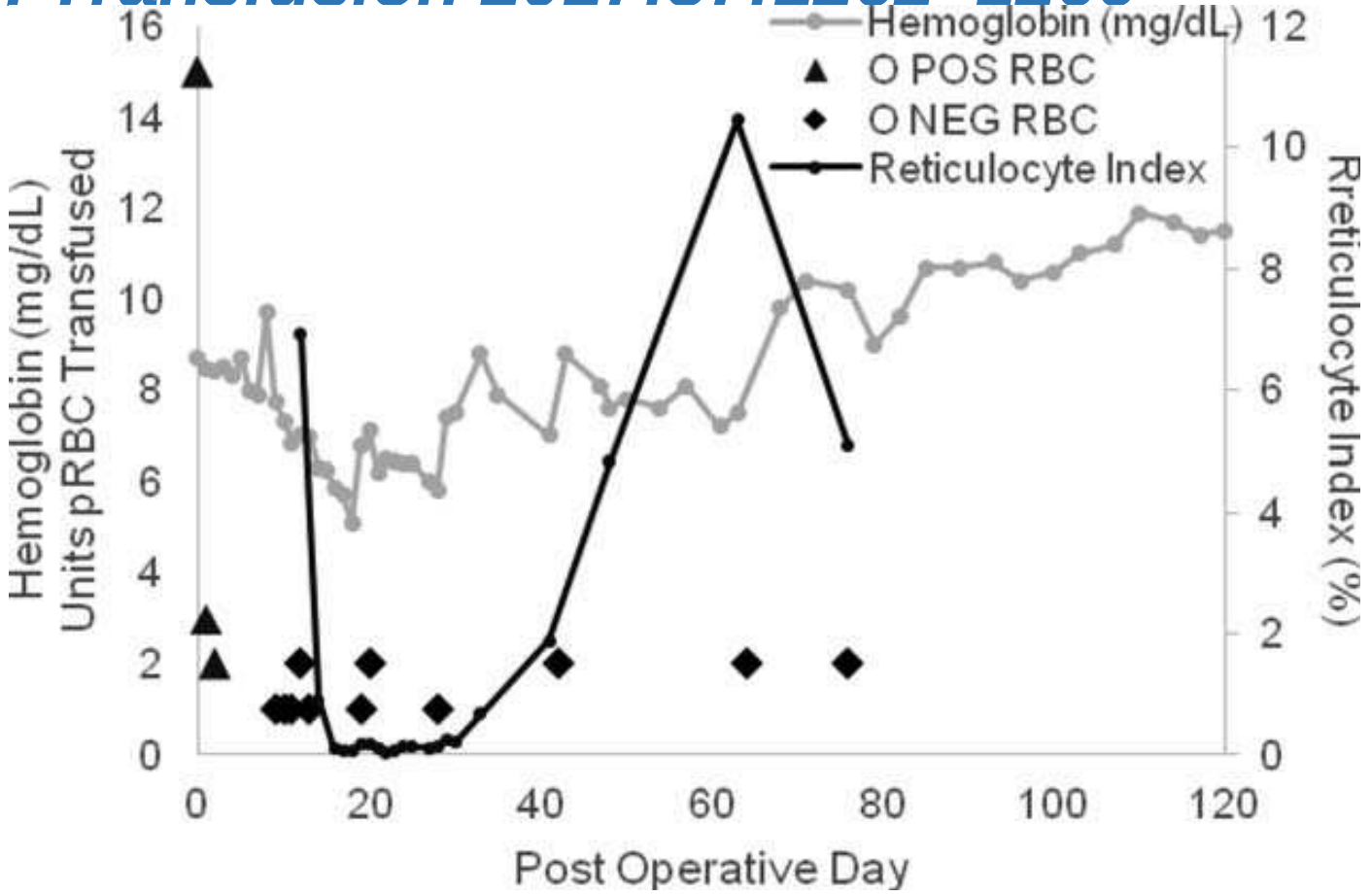
TABLE 1. Serologic test results*

POD	ABO/Rh	Antibody screen, panel	DAT	Eluate
0	O pos	Negative		
4	O pos	Negative		
7	O pos	Inconclusive	Positive (IgG only)	Anti-D
10	O pos	Anti-D		
12			Positive (IgG only)	Not tested
13	O neg	Anti-D		
20	O neg	Anti-D	Negative	
48	O neg	Anti-D		
63	O pos	Anti-D		
76	O pos	Inconclusive	Positive (IgG only)	Anti-D
168	O pos	Negative	Positive (IgG only)	Not tested
233	O pos	Negative	Positive (IgG only)	Anti-D

* The table shows blood bank serologic test results after liver transplantation.

PLS in liver transplantation exceptional cases

Gniadek et al. Transfusion 2017:57:1262–1266



reticulocyte index decreased markedly and remained suppressed until POD 33

PLS in liver transplantation exceptional cases

Gniadek et al. Transfusion 2017;57;1262–1266

- To exclude an infectious aetiology extensive infectious disease testing was performed, all were negative
  - blood and sputum cultures;
  - Histoplasma, cryptococcal, and Aspergillus (galactomannan) antigen testing
  - cytomegalovirus, Epstein-Barr virus, and HIV nucleic acid testing.
  - Preoperative serology for IgG anti-CMV indicated that the donor was negative, but the recipient was positive.
  - Parvovirus B19 nucleic acid tests of plasma and marrow were negative.

- Medications modified suspecting drug induced anaemia/haemolysis

PLS in liver transplantation exceptional cases

Gniadek et al. Transfusion 2017;57;1262–1266

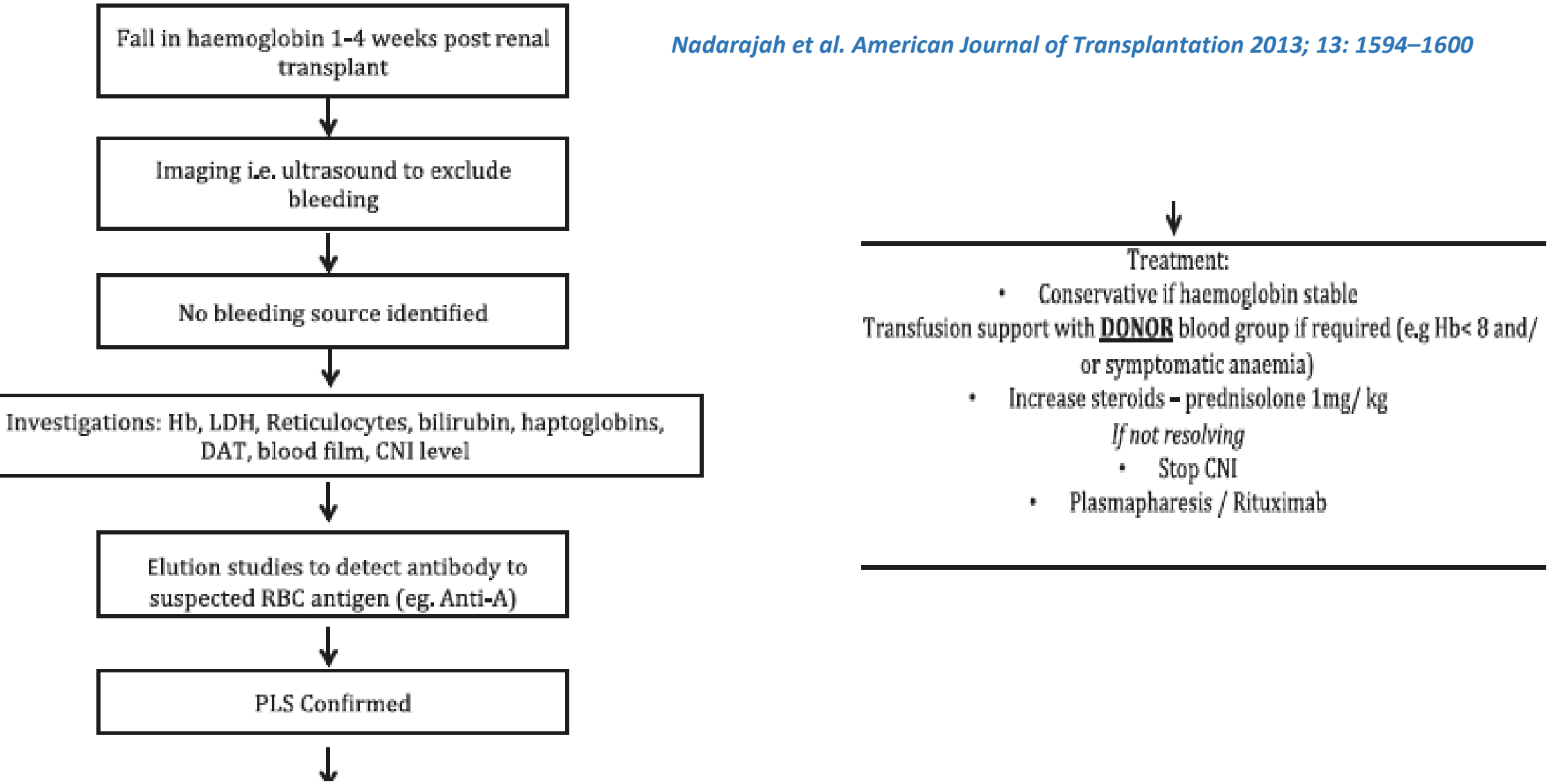
- Reticulocytopenia / anaemia /normal erythropoietin levels,
- Needed excluding an intrinsic marrow or RBC disorder.
  - Flow cytometry-based testing for PNH was unremarkable
  - A marrow biopsy revealed erythroid hyperplasia, but no signs of MDS
  - MDS FISH panel and marrow cytogenetic studies - no evidence of a myeloproliferative neoplasm or MDS
  - Prussian blue iron-stained marrow aspirate & Plasma iron studies were unremarkable
  - Other pertinent laboratory test results included normal folate and B12 levels
- It was concluded that haemolysis due to PLS together with reticulocytopenia

PLS – Worth anticipating

- Be vigilant about ABO and minor blood group incompatibilities
- Identify the risk factors
- Daily DAT starting 3 – 4 days post op aids early detection
- Use of donor-compatible RBCs prophylactically in the perioperative and immediate postoperative setting might reduce the development of graft associated immune haemolysis, but remains an untested hypothesis.

Fung et al. Transfusion 2004;44:1635-1639

Proposed algorithm for the detection and treatment of PLS.



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References

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- *Fung et al. Transfusion 2004;44:1635-1639*
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Thank you

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