20 August 2017

AABB Standards Committee,

The AABB-THOR Working Party is resubmitting its request to modify standard 5.15.1 to permit the use of low titer group O whole blood in massively bleeding patients whose ABO group might not be known. The proposal includes a background information document that provides a detailed rationale for suggesting this modification. The document reviews the historical use of whole blood, the high incidence of preventable civlian deaths per year in the US due to hemorrhage, a detailed discussion of the serological safety of low titer whole blood incuding the latest observations from civilian recipients of 3&4 units of this product, and the potential benefits of using low titer group O whole blood to improve outcomes for patients with hemorrhagic shock. The background document also addresses the lack of consistency between the standards regarding minor incompatible plasma transfusion in plasma and platelets and that in whole blood.

To address the concern that there is not widespread interest in transfusing low titer whole blood in massively bleeding civilian recipients, the working party assembled a petition that was signed by 214 thought leaders in transfusion medicine, surgery, critical care, and emergency medicine from 24 countries. By signing the petition, these thought leaders expressd their interest and support of the use of low titer group O whole blood for massively bleeding patients whose ABO group might not be known. The petition has been signed by leaders in the transfusion medicine community including, amongst many others: Jim AuBuchon, Neil Blumberg, Michael Busch, Robertson Davenport, Larry Dumont, Jose Cancelas-Perez, Cassandra Josephson, Louis Katz, Harvey Klein, Jeff McCullough, Paul Ness, Adrian Newland, Mary Oneill, John Roback, Beth Shaz, Christopher Silliman, Simon Stanworth, Ronald Strauss, Marie Steiner, Darrell Triulzi, and Jonathan Wallis. This proposal to modify standard 5.15.1 is also endorsed by the following blood collectors: American Red Cross Biomedical Services, BloodWorks Northwest, Mississippi Valley Regional Blood Center, New York Blood Center, and by the UT Health San Antonio Trauma Center and the Eastern Association for the Surgery of Trauma. Their letters of support are attached.

Respectfully,

Philip C. Spinella, MD, FCCM Co-Chair, AABB-THOR Working Party Co-Chair, THOR Network Professor, Department of Pediatrics Washington University in St Louis, St Louis, MO

Mark Yazer, MD Co-Chair, AABB-THOR Working Party Professor of Pathology, University of Pittsburgh Medical Director, RBC serology reference laboratory, Centralized Transfusion Service Associate Medical Director, Centralized Transfusion Service Adjunct Professor of Clinical Immunology, University of Southern Denmark

Executive Summary of Background Document

The AABB/THOR working party (WP) is suggesting that the AABB Standards Committee modify standard 5.15.1 to permit the use of low titer, group O whole blood (WB) in all massively bleeding patients regardless of their ABO group. Improved resuscitation strategies are needed for patients with life-threatening hemorrhage since there are approximately 30,000 preventable deaths after injury per year in the US, with 25,000 of these occurring prehospital. Data indicates that reconstituted whole blood in a 1:1:1unit ration reduces death from hemorrhage. Prehospital use of blood products within 30 min of injury also improves survival mortality is increased by 5% for every minute that initiating transfusion is delayed. Low titer group O whole blood has advantages over reconstituted whole blood as highlighted below. More than 210 experts from 24 countries have signed the WP's petition to support the modification of standard 5.15.1 to permit the use of low titer, group O WB in massively bleeding patients.

Benefits of Low Titer Group O Whole Blood Compared to Blood Components for Hemorrhagic Shock

Efficacy

- The cold stored platelets provide improved hemostasis compared to room temperature platelets
- More concentrated product that contains less anticoagulants and additive solution than an equal amount of components

Safety

- Reduced risk of hemolysis from the low titer minor incompatible plasma compared to the risk from untitered minor incompatible plasma or platelets
- Reduced risk of bacterial contamination compared to room temperature stored platelets
- Impressive safety record with over 1 million units transfused in combat and civilian settings

Logistic

- Increased access to platelets for both pre-hospital and early in-hospital resuscitations
- Simplifies and accelerates the provision of all blood components needed to treat hemorrhagic shock

Joint AABB-THOR Working Party Petition

The following individuals endorse the following statement:

"Do you agree that AABB standards should allow for uncrossmatched, low titer, group O WB to be used in the resuscitation of massively bleeding patients whose ABO group might not be known at the time of WB transfusion?"

1. Sasha D Adams, MD

UT Health, Houston. Asst Professor Surgery 6431 Fannin Street, MSB 4.282. Houston, TX 77030 sasha.d.adams@uth.tmc.edu

2. Jason Acker, BSc MSc MBA PhD

Senior Research Scientist - Canadian Blood Services Professor - Laboratory Medicine and Pathology, University of Alberta acker@blood.ca

3. Louis Alarcon, MD, FACS, FCCM

Professor of Surgery and CCM Medical Director, Trauma Surgery University of Pittsburgh School of Medicine F-1264, UPMC-Presbyterian 200 Lothrop St. Pittsburgh, PA 15213 412-647-1158 alarconl@upmc.edu

4. Shubha Allard MD FRCP FRCPath

Consultant Haematologist Barts Health NHS Trust and NHS Blood and Transplant shubha.allard@nhsbt.nhs.uk

5. Arwa Z. Al-Riyami, BS.c, MD, FRCPC

Senior Consultant Hematopathologist Department of Haematology, Sultan Qaboos University Hospital PO Box 38, PC 123, Muscat, Oman arwa.alriyami@gmail.com

6. Torunn Oveland Apelseth, MD, PhD

Senior Consultant Department of immunology and transfusion medicine Haukeland University Hospital, N-5021 Bergen, Norway torunn.oveland.apelseth@helse-bergen.no

7. James P. AuBuchon, MD Bloodworks 921 Terry Ave, Seattle, WA 98104 jima@bloodworksnw.org

8. Sylvain Ausset MD

Professor & Chair of anaesthesia & intensive care HIA Percy. 92140 Clamart. France sylvain.ausset@gmail.com

9. Ivar Austlid, MD

Anaesthesiologist Consultant Nordre Hauglandshella 31, 5314 Kjærrgarden, Norway iaust@live.com

10. Andrew N. Beckett, CD MD FRCS(C) FACS

Assistant Professor of Surgery, McGill University LTC, Royal Canadian Army Medical Corps Montreal General Hospital Andrew.beckett@mcgill.ca

11. Rachel Beddard, MD

Medical Director, BioBridge Global 6211 IH10 West, San Antonio, Texas 78201 rachel.beddard@biobridgeglobal.org

12. Alec C. Beekley, MD

Professor of Surgery, Sidney Kimmel Medical College at Thomas Jefferson University 1100 Walnut Street, Philadelphia, PA 19107 alec.beekley@jefferson.edu

13. LTC Carmen Bell

Deputy for Operations US Armed services blood procurement office

14. SGT Vincent Bennell

4 Pages Close, Wymondham, Norfolk, NR18 0TU vmbennell@yahoo.co.uk

15. Olle Berséus, MD, PhD

Specialist in Transfusion Medicine FoU Department, Örebro University Hospital, Örebro, Sweden. Consultant in transfusion Medicine to the Swedish Armed Forces. Örtenlundsv. 7, 702 30 Örebro, Sweden berseus@telia.com

16. Marsha Bertholf, M.D.

Medical Director Gulf Coast Regional Blood Center mbertholf@giveblood.org

17. Kenneth A. Bertram, MD PhD FACP

Principal Assistant for Acquisition US Army Medical Research and Materiel Command Ft Detrick, MD 21702 kenneth.a.bertram.civ@mail.mil

18. Per Olav Berve, MD

Consultant anaesthesist Oslo University Hospital, air amb div Lysgata 14, 1482 Nittedal poberve@gmail.com

19. Charlene Bierl, MD, PhD

Director of the Clinical Laboratory Cooper University Hospital Camden, NJ 08103 bierl-charlene@CooperHealth.edu

20. Geir Bjerkan, MD, PHD

St. Olavs University Hospital and Norwegian Armed Forces, Joint Medical Services Dalhaugveien 53, 7020 Trondheim gbjerkan@hotmail.com

21. Christopher Bjerkvig, MD

Norwegian Special Forces Medical Service Christopherbjerkvig@me.com

22. Neil Blumberg, MD

Professor of Laboratory Medicine Director of Transfusion Medicine / Blood Bank University of Rochester Medical Center Neil_Blumberg@urmc.rochester.edu

23. COL Milos Bohonek, MD, PhD

Military University Hospital Prague, Czech Republic U Vojenske nemocnice 1200, 16902 Prague, Czech Republic milos.bohonek@uvn.cz

24. Matthew A. Borgman, MD, FCCM, CHSE

Chief, Pediatric Critical Care Services Medical Director, BAMC Simulation Center Associate Professor of Pediatrics, Uniformed Services University Brooke Army Medical Center MCHE-ZDP/PICU 3551 Roger Brooke Dr. JBSA Ft. Sam Houston, TX 78234 matthew.a.borgman.mil@mail.mil

- LT COL Matt Boylan, FRCEM RAMC Consultant Advisor PHEM (British Army) RCDM, Birmingham. UK m.boylan@nhs.net
- 26. Marshall Keith Brown, DO FAAFP; A. Prof UNMC, Medical Director Alpha Medical Inc. 401 E 8th St Ste 214-953, Sioux Falls SD 57103 drkeithbrown@gmail.com

27. Michael P. Busch, MD, Ph.D.

Director, Blood Systems Research Institute Senior Vice President, Blood Systems Professor of Laboratory Medicine, UCSF mbusch@bloodsystems.org

28. Becky Butler Cap, MBA

Chief Operating Officer, South Texas Blood and Tissue Center 6211 IH 10 West, San Antonio, TX 78201 becky.cap@gencure.org

29. Frank K. Butler, MD

CAPT MC USN (ret) Chairman, Committee on TCCC Chief, Prehospital Trauma Care, Joint Trauma System Adjunct Professor of Military and Emergency Medicine Uniformed Services University of the Health Sciences 4575 Lavallet LnPensacola, Florida 32504 fkb064@yahoo.com

30. David Callaway, MD

Director, Division of Operational and Disaster Medicine Associate Professor, Emergency Medicine Department of Emergency Medicine, Carolinas Medical Center 1528 Dilworth Rd, Charlotte, NC 28203 dcallawa@gmail.com

31. Jose Cancelas-Perez, MD

Director, Research Division and Medical Director for Cell Therapies, Hoxworth Blood Center Deputy Director, Hoxworth Blood Center Leader, Stem Cell Program Incumbent, Beatrice C. Lampkin Endowment for Stem Cell and Hematotherapy Cincinnati Children's Jose.Cancelas@cchmc.org

32. Jeremy W. Cannon, MD, SM

Associate Professor of Surgery, University of Pennsylvania

51 N. 39th Street, MOB 120 Philadelphia, PA 19104 jeremy.cannon@uphs.upenn.edu

33. COL Andrew P. Cap, MD, PhD, FACP

Medical Corps, US Army Chief, Blood Research, US Army Institute of Surgical Research Medical Director, Akeroyd Blood Donor Center Associate Professor of Medicine, Uniformed Services University Program Director, Clinical Research Fellowship Deputy Hematology-Oncology Consultant to the Surgeon General Staff Hematologist-Oncologist, San Antonio Military Medical Center andrew.p.cap.mil@mail.mil

34. D. Joe Chaffin, MD

VP/Chief Medical Officer LifeStream Blood Bank, San Bernardino, CA Creator and Editor, BBGuy.org joe.chaffin@bbguy.org

35. Jill M Cholette, MD

Associate Professor of Pediatrics University of Rochester Rochester NY Jill_Cholette@URMC.Rochester.edu

36. Joan Cid, MD, PhD

Apheresis & Cellular Therapy Unit Department of Hemotherapy and Hemostasis, ICMHO Hospital Clínic Villarroel 170 08036 Barcelona (Catalonia, Spain) jcid@clinic.cat

37. Franklyn Cladis, MD FAAP

Associate Professor of Anesthesiology Program Director, Pediatric Anesthesiology Fellowship The Children's Hospital of Pittsburgh of UPMC CladFP@UPMC.EDU

38. Claudia S. Cohn, MD, PhD

Associate Professor Medical Director, Blood Bank Associate Head of Clinical Laboratories University of Minnesota cscohn@umn.edu

- Brian Cornelius DNP CRNA NRP University Health-Shreveport
 1541 Kings Hwy Shreveport LA 71103 Brian.cornelius@uhsystem.com
- LTC Jason B. Corley Deputy Director, Army Blood Program jason.b.corley.mil@mail.mil
- 41. Brian Cornelius, DNP CRNA NRP University Health
 9422 Milbank Dr Shreveport, LA 71115 Brian.cornelius@uhsystem.com

42. Bryan A. Cotton, MD, MPH

Professor of Surgery and The John B Holmes Professor of Clinical Sciences Director, Surgical Critical Care, Acute Care Surgery and Trauma Fellowships Department of Surgery and The Center for Translational Injury Research McGovern Medical School at The University of Texas Health Science Center Houston, Texas Bryan.A.Cotton@uth.tmc.edu

43. Jon B. Christensen, APA-C, HMO, FAWM, DiMM

Chief of Medical Training for International Special Training Centre/ OIC of NATO Special Operations Combat Medic course. CMR 445 Box GD. ISTC APO, AE 09046 Medchief@istc-sof.org

44. Melissa Cushing, MD

Associate Professor/Weill Cornell Medicine/NewYork-Presbyterian Hospital 525 East 68th St, Box 251, Blood Bank,NY, NY 10065 mec2013@med.cornell.edu

45. Robertson D. Davenport, MD

Professor of Pathology Director, Transfusion Medicine University Hospital 2G332/5054 1500 E. Medical Center Dr. Ann Arbor, MI 48109-5054 rddvnprt@umich.edu

46. Vincenzo De Angelis, MD

Director Transfusion Medicine Dept. Azienda Sanitaria Universitaria Integrata S. Maria della Misericordia" - UDINE P.le S. Maria della Misericordia, 15 - 33100 UDINE (Italy) M vincenzo.deangelis@asuiud.sanita.fvg.it

47. Meghan Delaney, DO

Chief, Pathology & Laboratory Medicine Children's National Health System 111 Michigan Ave NW Washington DC, 20010 mdelaney2@childrensnational.org

48. Gregory A Denomme, PhD, FCSMLS(D)

Senior Investigator, Blood Research Institute Senior Director, Immunohematology and Innovation BloodCenter of Wisconsin 638 N 18th Street PO Box 2178 Milwaukee, WI 53201-2178 Gregory.Denomme@BCW.edu

49. Marc De Pasquale, BS

18D Special Forces Medic Paramedic NREMT Deployment Medicine International mxdxpx@yahoo.com

50. Allan Doctor, MD

Washington University in St. Louis / Professor of Pediatrics and Biochemistry Campus Box 8208 / 660 S Euclid Street / Saint Louis, MO / 63108 doctor@wustl.edu

51. Thomas Dolven, MD

Consultant in Anesthesia and Intensive Care Kalfarveien 108A, 5022 Bergen, Norway thomasdolven@gmail.com

52. Heidi Doughty, MD MBA FRCP FRCPath Consultant in Transfusion Medicine NHS Blood and Transplant UK

53. Leilani Doyle, BSc MSc MD

Associate Professor University of Ottawa, Royal Canadian Medical Corp Anesthesiologist 411 Ravenhill Ave Unit C K2A0J7 Idoyle@Ottawahospital.on.ca

54. Larry J. Dumont, MBA, PhD

Associate Director and Senior Investigator Blood Systems Research Institute – Denver c/o Bonfils Blood Ctr. 717 Yosemite Street Denver, CO 80230Office: 303-363-2401 Idumont@bloodsystems.org

55. Nancy M. Dunbar, MD

Associate Professor Geisel School of Medicine Department of Pathology and Laboratory Medicine Department of Medicine Medical Director, Blood Bank Associate Medical Director, Transfusion Medicine Service Nancy.M.Dunbar@hitchcock.org

56. David Duncan, MD

Medical Director: CALSTAR Air Ambulance, Medical Director: CAL FIRE 6952 Kayo Drive, Penryn, CA 95663 daveduncanmd@gmail.com

57. Richard P. Dutton, MD MBA

Chief Quality Officer, US Anesthesia Partners Dallas, TX Richard.dutton@usap.com

58. Torsten Eken, MD PhD

Consultant anaesthesiologist, Oslo University Hosiptal, and Researcher in traumatology University of Oslo Oslo University Hospital Ullevål, Dept. of anaesthesiology PO Box 4956 Nydalen, NO-0424 Oslo, Norway torsten.eken@medisin.uio.no

59. Håkon Eliassen

Norwegian Special Forces Medical Service Norway hskogran@hotmail.com

60. CAPT Roland Fahie

Director, US Armed Services Blood Procurement Office

61. Andrew D. Fisher, MPAS, PA-C

PA-C, US Army Reserve, Major andrewdfisher@icloud.com

62. G. Michael Fitzpatrick, PhD, COL (Ret.) USA

President Director Clinical Research and Development, Cellphire Inc. 9430 Key West Ave Suite 204 Rockville. MD 20850 mfitzpatrick@cellphire.com

63. Steven M. Frank, MD

Director PBM Program / Johns Hopkins / Professor 1800 Orleans Street, Zayed 6208, Baltimore, MD 21287 sfrank3@jhmi.edu

64. Alan I. Frankfurt, MD Anesthesiologist

7626 Caillet Street F7040@aol.com

65. Barbara A. Gaines, MD

Professor of Surgery University of Pittsburgh School of Medicine Director, Trauma and Injury Prevention Clinical Director, Division of General and Thoracic Surgery Program Director, Pediatric Surgery Training Program Children's Hospital of Pittsburgh of UPMC gainesba@upmc.edu

66. Pr. Olivier Garraud, MD PhD

Senior Consultant International Affairs INTS - Institut National de la Transfusion Sanguine 6 rue Alexandre-Cabanel - 75739 PARIS cedex 15 - France ogarraud@ints.fr

67. Eric A. Gehrie, MD

Assistant Professor, Pathology Johns Hopkins University Associate Director, Transfusion Medicine Johns Hopkins Hospital egehrie1@jhmi.edu

68. Karen Giordano KGiordano@cerus.com

69. Melissa Givens, MD MPH

Associate Professor Department of Military and Emergency Medicine, Uniformed Services University 4117 Jones Bridge Road, Chevy Chase MD melissa.givens@usuhs.edu

70. Jacob Glaser, MD

Critical Care and Trauma Surgeon, Naval Medical Research Unit San Antonio 3503 Puesta De Sol San Antonio TX 78261 jacob.glaser1@gmail.com

71. COL Elon Glassberg, MD

Professor of Surgery IDF medical corps headquarters, Israel edoc11@gmail.com

 72. Sherry Glenn, CLS(ASCP)SBB Major
311 Foxglove Path, San Antonio, TX 78245 Sherry.d.glenn.mil@mail.mil

73. Ruchika Goel, MD MPH

New York Presbyterian Hospital, Weill Cornell Medicine, Assistant Medical Director of TM/CT, Assitant professor 525 East 68th Street, M-014, New York Presbyterian Weill Cornell. ruchikagoel1@gmail.com

74. Samantha Gomez Ngamsuntikul, MD Associate Medical Director 6211 IH 10 W, San Antonio TX 78201 samantha.ngamsuntikul@biobridgeglobal.org

75. Richard Gonzales, MS

Director, TerumoBCT, COL, US Army , MT(ASCP)SBB 440 Devine Road, Olmos Park, TX 78212 Richard.gonzales@terumobct.com

76. Dr Laura Green, MBBS, MD(Res), FRCP, FRCPath Barts Health NHS Trust and NHS Blood and Transplant, London, United Kingdom laura.green@bartshealth.nhs.uk

77. Ronald I. Gross, MD, FACS

Chief, Division of Trauma, Acute Care Surgery & Surgical Critical Care Baystate Medical Center 759 Chestnut Street, Springfield, MA 01199

ronald.gross@baystatehealth

78. James Richard Gruenewald APA-C, MPAS

Deputy Regiment Surgeon/160th Special Operations Aviation Regiment (Abn)/Captain 1149 North Ja Tate Drive Clarksville, TN 37043 jimmygruenewald@gmail.com

79. Mark W. Hall, MD

Chief, Division of Critical Care Medicine, Nationwide Children's Hospital Nationwide Children's Hospital, 700 Children's Drive, Columbus, OH. 43205 Mark.Hall@nationwidechildrens.org

80. Judith Hannon, MD FRCPC

Medical Officer, Canadian Blood Services, Edmonton, Alberta, Canada

Clinical Professor, University of Alberta, Edmonton, Alberta, Canada 8249-114 Street, Edmonton, Alberta, Canada, T6G 2R8 judy.hannon@blood.ca

81. Sheila J. Hanson, MD, MS

Associate Professor of Pediatrics Associate Director, PICU Children's Hospital of Wisconsin shanson@mcw.edu

82. Sarah K Harm, MD, MS

Assistant Professor, Pathology Robert Larner, M.D. College of Medicine @ UVM Medical Director, Blood Bank University of Vermont Medical Center 233 MP1, 111 Colchester Ave, Burlington, VT 05401

83. John Andrew Harvin, MD

Assistant Professor, UT Health 6431 Fannin Street, MSB 4.294 Houston, TX 77030 John.Harvin@uth.tmc.edu

84. **Tor Hervig, MD** Overlege

Helse Førde HF Norway tor.audun.hervig@helse-bergen.no

85. Luis Alfredo Perez Bolde Hernandez

Lieutenant Col. Medicina Tactica Mexcio calle cantil 31 D fracc.cañada de la bufa, guadalupe Zacatecas C.P. 98613 mexico director@medtacmex.org.mx, hypermed@gmail.com

86. CDR Jonathan Hoiles, MSC, USN

Branch Head, Navy Blood Program

87. John Holcomb, MD

Professor of Surgery, UT Health, Houston TX Suite 1100, 6410 Fannin, Houston, TX, 77030 john.holcomb@uth.tmc.edu

Eirik Holmstrøm, EMT-P/Flight P/CCATT MCD AOIC-Instructor / ISTC NSOCM /CPT Passebekkv. 546, 3648 Passebekk, Norway eirik@holmy.no

89. Greggory J. Housler, MScEng, MBA Product Manager, Blood Products US Army Medical Materiel Development Activity (USAMMDA) Pharmaceutical Systems Program Management Office (PSPMO) 1430 Veterans Drive, Room 312 Fort Detrick, MD 21702-5009 greggory.j.housler.civ@mail.mil

90. Beverley J Hunt, FRCP, FRCPath, MD

Thrombosis & Haemostasis, King's College Consultant, Depts of Haematology & Pathology, Clinical Lead in Haematological Laboratories Guy's & St Thomas' NHS Foundation Trust & Viapath Westminster Bridge Road London SE1 7EH Beverley.Hunt@gstt.nhs.uk

91. Fabian Hurbin

NR-P / Lieutenant Weidstrasse 27, CH-4317 Wegenstetten, Switzerland fabian.huerbin@vtg.admin.ch

92. Donald H. Jenkins, MD, FACS

Professor/Clinical, Division of Trauma and Emergency Surgery Vice Chair for Quality, Department of Surgery Betty and Bob Kelso Distinguished Chair in Burn and Trauma Surgery Associate Deputy Director, Military Health Institute UT Health San Antonio 7703 Floyd Curl Drive San Antonio, TX 78229-3900 Jenkinsd4@uthscsa.edu

93. Bryon P. Jackson Sr., MD, MHA

Assistant Professor of Pathology Emory University School of Medicine Medical Director Blood and Transfusion Services Grady Memorial Hospital bryon.patrick.jackson@emory.edu

94. **Timo Jama, MD, MSc (disaster medicine)** Medical Director of EMS Keskussairaalankatu 7, 15850 Lahti, FINLAND timo.jama@phhyky.fi

Dennis Jarema, 18D RN 18D/ USSOCOM/ SSG 2103 Stonewall Farms dr dmjarema@hotmail.com

96. David Jobes, MD

Prefessor of Anesthesia and Critical Care; the Chidlren's Hospital of Philadelphia and the Perelman School of Medicine at the University of Pennsylvania the Children's Hospital of Philadelphia; 34th Civic Center Blvd; Phila. PA jobes@email.chop.edu

97. George A. Johnson, MSN

Landstuhl Regional Medical Center/212th Combat Support Hospital/LTC CMR 422, BOX 398, APO, AE 09067 george.johnson1900@gmail.com

98. Cassandra D. Josephson, MD

Professor, Pathology and Pediatrics, Emory University School of Medicine Director of Clinical Research, Center for Transfusion and Cellular Therapies Program Director, Transfusion Medicine Fellowship Medical Director, Children's Healthcare of Atlanta Blood, Tissue, and Apheresis Services, Atlanta, GA cjoseph@emory.edu

99. Shawn F. Kane, MD FAAFP, FACSM

COL, MC, MFS, DMO Commander, Special Warfare Medical Group (Airborne) Dean, Joint Special Operations Medical Training Center Family Medicine Consultant to The Surgeon General shawn.kane@socom.mil

100. Matthew S. Karafin, MD, MS

BloodCenter of Wisconsin 638 N 18th Street, Milwaukee WI 53201 matthew.karafin@bcw.edu

101. Oliver Karam, MD, PhD

Children's Hospital of Richmond at VCU 1250 E Marshall St, Richmond, VA 23298 oliver.karam@vcuhealth.org

102. Jeffry Kashuk, MD

Professor of Surgery, Tel Aviv- Sackler SOM Habarzel 11 Suite 5A TelAviv Israel Jeffrykashuk@gmail.com

103. Louis M. Katz, MD

Interim Chief Executive Officer Chief Medical Officer America's Blood Centers 725 15th St. NW, suite 700 Washington DC, 20005 Adjunct Clinical Professor University of Iowa, Carver College of Medicine, Division of Inf. Dis. Ikatz@americasblood.org

104. Sean Keenan, MD, FAAEM FAWM

US Special Operations Command USA dockeenan95@aol.com

105. Jeffrey D. Kerby, MD, PhD

Professor and Director, Acute Care Surgery, University of Alabama at Birmingham KB 120, 1720 2nd Avenue South, Birmingham, Alabama 35294-0016 jkerby@uabmc.edu

106. Harvey G. Klein, MD

Chief, Department of Transfusion Medicine Clinical Center National Institutes of Health Adjunct Professor of Medicine and Pathology The Johns Hopkins School of Medicine

107. Fredrik Koller Lund, MD EDIC

Consultant intensivist/ anesthesiologist Haukeland University Hospital, 5021 Bergen, Norway fredrik.koller.lund@gmail.com

108. Justina Kordai Ansah, MCChB, CTM, FGCPS

National Blood Service Ghana- Chief Executive Officer (C.E.O) National Blood Service Ghana GHANA kordaiansah@yahoo.com

109. Rosemary Kozar, MD PhD

Professor of Surgery; Shock Trauma Center; University of Maryland 22 South Green St. Maryland, MD 21201 rkozar@umm.edu

110. Robert Kramer, MD, FACS

Clinical Associate Professor of SurgeryTufts University School of Medicine Maine Medical Center 22 Bramhall St Portland Maine kramer@mmc.org

111. Oliver Kreuzer

SAR Flight Paramedic, Air Zermatt / Flight Paramedic US ARMY Reserve Heliport, 3920 Zermatt, Switzerland oliver.kreuzer@air-zermatt.ch

112. Einar K. Kristoffersen, MD, PhD

Head of Department, Professor Univ. of Bergen Department of Immunology and Transfusion Medicine, Bergen, Norway einar.kristoffersen@helse-bergen.no

113. Jens Kronborg, MD, PhD

Chief Consultant, Dep of Immunology and Transfusion Medicine, Innlandet Hospital, Norway Avd for blodbank og medisinsk biokjemi, Sykehuset Innlandet, 2629 Liullehammer, Norway kronborg@bbnett.no

114. John Lacroix, 68W

US Army/68W/CoTCCC 1111 vista Valet SATX 78216 Jlcjohn83@gmail.com

115. Sami Länkimäki

South-Osthrobothnian Health Care Districr /M.D, Chief Physician for Prehospital Care EPSHP, Ensihoitokeskus, Sami Länkimäki, Rengastie 13, 60100 Seinäjoki, Finland Sami.lankimaki@epshp.fi

116. Marcus Larsson, MD MSc

Sunderby Hospital, Norrbotten County, Sweden Havrevagen 20, 95432 Gammelstad, Sweden marcus.o.c.larsson@gmail.com

117. Fiona Lecky MB ChB,Ph D,FRCEM, FRCS

University of Sheffield and Salford Royal/Clinical Professor&Honorary Consultant CURE, HSR Section, School of Health and Related Research, University of Sheffield, Regent's Court, Regent Street, Sheffield S14DA f.e.lecky@sheffield.ac.uk

118. Parvez M. Lokhandwala, MBBS, PhD

Assistant Professor, Division of Transfusion Medicine, Johns Hopkins University School of Medicine 550 N. Broadway Building, 8th Floor, Baltimore, MD 21205 PLOKHAN1@JHMI.EDU

119. Paul Loos 18D

JSOMTC Instructor 70 West Trafalgar Court medguy21@gmail.com

120. Joseph Love, DO MS FACS

Associate Professor 6431 Fannin Street Houston texas joseph.d.love@uth.tmc.edu

121. Andrew I.R. Maas, MD, PhD

Em Professo of Neurosurgery University Hospital Antwerp Wilrijkstraat 10 2650 Edegem - Belgium andrew.maas@uza.be

122. Professor Dr. med. Marc Maegele

Klinik für Unfallchirurgie und Orthopädie Klinikum Köln-Merheim (Cologne-Merheim Medical Center) Universität Witten-Herdecke Institut für Forschung in der Operativen Medizin (IFOM) Ostmerheimerstr. 200, 51109 Köln Marc.Maegele@t-online.de

123. Kathryn Maitland

Professor Paediatrics, Imperial College, London KEMRI Wellcome Trust Research Programme, PO Box 230, Kilifi, Kenya k.maitland@imperial.ac.uk

124. Justin D. Manley, MD

Major 809 Flowering Path, Niceville, FL 32578 docmanley@gmail.com

125. COL Elizabeth Mann-Salinas, PhD, RN

US Army Institute of Surgical Research, Colonel 335 Pershing Ave San Antonio, TX 78309 Elizmann@ gmail.com

126. Prof. Noga Manny, MD

Emeritus Associate Clinical Prof. of Internal Medicine (Hematology) Hebrew University ,Jerusalem ,Israel. Emeritus Medical Director of Hadassah Medical Center Blood Banks Jerusalem ,Israel

127. Marisa B. Marques, MD

Transfusion Services Medical Director/UAB/ Professir of Pathology 619 19th Street South/P230G/Birmingham/AL 35233 mmarques@uabmc.edu

128. Larry Martin, MD

University of Mississippi Medical Center 2500 N. State St. Jackson, MS 39216 Imartin3@umc.edu

129. Elisabeth Maurer, PhD

Clin. Associate Prof., University of British Columbia; Chief Technology Officer, LightIntegra

Technology Inc. 330-2285 Clark Drive, Vancouver, BC, V5N 3G9 emaurer@lightintegra.com

130. Jeffrey McCullough, MD

Emeritus Prof university of Minnesota 7400 Shannon dr Edina MN 55439 mccul002@umn.edu

131. Michael T. Meyer, MD, MS

Chief, Pediatric Critical Care/Medical College of Wisconsin/Associate Professor 9000 West Wisconsin Avenue, M.S. #681 Milwaukee, WI 53226 mtmeyer@mcw.edu Timothy Miller MB ChB FRCA Associate Professor of Anesthesiology Chief, Division of General, Vascular and Transplant Anesthesia Director, Perioperative Medicine Fellowship Duke University School of Medicine timothy.miller2@duke.edu

132. Ethan A Miles, MD

LTC, US Army

Associate Proffessor, Uniformed Services University of the Health Sciences ethanamiles@yahoo.com

133. Ernest E Moore, MD

University of Colorado Denver/Surgery/Professor Journal of Trauma, 655 Broadway, Denver 80203 ernest.moore@dhha.org

134. David S. Morris, MD

5161 S. Cottonwood St. Murray UT 84107 davidstephenmorris@gmail.com

135. Johan Storm Munch, MD

LtCol OPSTØ/Hæren, N-9325 Bardufoss, NORWAY johmunch@bbnett.no

136. Alan Murdock, MD

Chief of Emergency Surgery, Allegheny General Hospital, Pittsburgh PA 320 E North Ave, 5th Fl South Tower, Suite 594 Alan.murdock@ahn.org

137. Jennifer A Muszynski, MD, MPH

Assistant Professor of Pediatrics, Division of Critical Care Medicine, Nationwide Children's Hospital and The Ohio State University College of Medicine 700 Children's Drive, Columbus Ohio 43205 jennifer.muszynski@nationwidechildrens.org

138. Lena M. Napolitano, MD, FACS, FCCP, MCCM

Massey Foundation Professor of Surgery Division Chief, Acute Care Surgery Director, Trauma and Surgical Critical Care Acute Care Surgery [Trauma, Burn, Critical Care, Emergency Surgery] Department of Surgery University of Michigan Health System lenan@umich.edu

139. Matthew D. Neal, MD

Assistant Professor of Surgery and Critical Care Medicine Attending Surgeon, Division of Trauma and Acute Care Surgery University of Pittsburgh Medical Center F1271.2 PUH 200 Lothrop Street Pittsburgh, PA 15213 nealm2@upmc.edu

140. Marianne Nellis, MD, MS

Assistant Professor 525 East 68th St, M512, NY, NY 10065 man9026@med.cornell.edu

141. Andrea Neisser-Svae, PhD

Octapharma, Head of Business Unit ICEM Oberlaaerstrasse 235, A-1100 Vienna, Austria andrea.neisser-svae@octapharma.com

142. Paul M Ness, MD

Director, Transfusion Medicine; Professor of Pathology and Medicine; Johns Hopkins Medical Institutions Zayed 3081; Johns Hopkins Hospital: Baltimore MD 21287 pness@jhmi.edu

143. Adrian Newland, CBE MA FRCP FRCPath

Professor of Haematology The Royal London Hospital Barts Health NHS Trust Pathology and Pharmacy Building 80, Newark Street London, E1 2ES a.c.newland@gmul.ac.uk

144. Philip Norris, MD

Senior Investigator

270 Masonic Ave., San Francisco, CA 94118 pnorris@bloodsystems.org

145. COL (R) Adam Olszewski, MD

Deputy Director Of Military Blood Center 00-671 Warsaw, Koszykowa 78 zdyrmed@wckik.pl Poland

146. E. Mary ONeill, MD Interim Chief Medical Officer 180 Rustcraft Rd, Dedham, Mass 02026 Mary.oneill@redcross.org

147. Yaacov Orlin, MD

Director of the Dept. of Transfusion Medicine Maayane Hayeshua Medical Center Bnei Brak, Israel jerorlin@gmail.com

148. Anand Padmanabhan, MD PhD QIA

Medical Director, BloodCenter of Wisconsin Associate Professor, Medical College of Wisconsin Associate Investigator, Blood Research Institute 8733 Watertown Plank Road Milwaukee, WI 53226-3548 anand.padmanabhan@bcw.edu

149. Pierre Pasquier, MD

HIA PERCY 101 avenue Henri Barbusse 92141 CLAMART France pasquier9606@me.com

150. Heather Pidcoke, MD PhD

Director, Global Clinical Safety&PRT Scientific Affairs/TerumoBCT 10810 West Collins Avenue, Lakewood, CO 80215 heather.pidcoke@terumobct.com

151. Dr.med. Urs Pietsch / DESA / EDIC

Kantonsspital St.Gallen, Switzerland Institute of Anaesthesiology & Intensive Care Medicine, Air Zermatt, Switzerland, Consultant ICU Air Zermatt, Heliport Raron, Switzerland pietsch@gmx.de

152. Timothy A Pritts, MD, PhD

Professor of Surgery, University of Cincinnati 231 Albert Sabin Way, ML 0558, Cincinnati, Ohio 45268 prittsta@ucmail.uc.edu

153. Naomi Rahimi-Levene, MD

Director of the Blood Bank, Assaf Harofeh Medical Center, Zerifin, Israel Member of the Transfusion Medicine Advisory Board to the Ministry of Health in Israel Head of the Israeli Transfusion Medicine Study Group nrlevene@asaf.health.gov.il

154. Joseph Rappold, MD, FACS

CAPT MC USN (Ret); Chief, Acute Care Surgery Trauma Medical Director, Department of Surgery Tufts University School of Medicine Maine Medical Center jrappold@mmc.org

155. Jørn E Rasmussen

Head of ED Specialist in Internal medicine and Cardiologi. Drammen Hospital Trust, Vestre Viken HF | www.vestreviken.no Major, MD in Norwegian Armjed Forces. Call: 7675 Mobilnr: +47 91720615 rasj@vestreviken.no

156. Jay S. Raval, MD

Assistant Professor Department of Pathology and Laboratory Medicine Director of Therapeutic Apheresis and Blood Donor Center Associate Director of HPC Laboratories jay_raval@med.unc.edu

157. COL Michael Reade, MBBS MPH DPhil DMedSc FANZCA FCICM

Level 9 Health Sciences Bldg, Royal Brisbane & Women's Hospital 4029 Australia m.reade@ug.edu.au

158. LT COL Rich Reed, FRCA RAMC

16 Medical Regiment, Defence Medical Services, UK Anaesthetic Department, Derriford Hospital, Plymouth, PL6 8DH, UK richard.reed1@nhs.net

159. Oliver Reisten, PhD

Medical Director of Rescue Service Solothurn Hospitals, Consultant in Anaesthesia and Emergency Medicine Allmendstrasse 61, CH-4612 Wange bei Olten, Switzerland oliver.reisten@air-zermatt.ch

160. Kenneth E. Remy, MD, MHSc Washington University in St. Louis 1 Children's Place St. Louis, MO 63005 kremy@wustl.edu

161. Peter Rhee, MD, MPH, FACS, FCCM

Senior Vice President Chief of Acute Care Surgery and Trauma Medical Director Grady Memorial Hospital 80 Jesse Hill Jr. Drive SE, Atlanta, Georgia 30303 prhee@GMH.EDU

162. John D. Roback, MD, PhD

Professor of Pathology and Laboratory Medicine Medical Director, Emory Medical Laboratories Vice-Chair, Clinical Pathology and Laboratory Medicine Director, Center for Transfusion and Cellular Therapies Emory University School of Medicine EUH D-655, 1364 Clifton Rd NE Atlanta, GA 30322 jroback@emory.edu

163. Nareg Roubinain, MD

Clinical investigator Blood systems research institute Nareg.Roubinian@ucsf.edu

164. Rob Russell, MD, MPH

Assistant Professor of Pediatric Surgery Children's of Alabama University of Alabama at Birmingham 1600 7th Ave. S., Lowder Building Suite 300 Birmingham, AL 35233 Robert.Russell@childrensal.org

165. Anne Sailliol

physician, specialist in hemobiology and transfusion expert. Clamart. France anne.sailliol@wanadoo.fr

166. Thomas M. Scalea, MD

Physician in Chief, R Adams Cowley Shock Trauma Center Francis X Kelly Distinguished Professor of Trauma, Director Program in Trauma University of Maryland School of Medicine System Chief for Critical care University of Maryland Medical System tscalea@umm.edu

167. MAJ Jo Schmid, BScN, RN, CNCC(C)
527 Gardner Cres, Petawawa, ON, K8H 0C4
Canada
jschmid817@hotmail.com

168. Martin A. Schreiber, MD FACS Professor of Surgery

3181 SW Sam Jackson Park Road, Mail Code L611, Portland, OR 97239 schreibm@ohsu.edu

169. C. William Schwab MD, FACS, FRCS (Glas)

Emeritus Professor of Surgery Perlman School of Medicine University of Pennsylvania Senior Consultant Penn Medicine Philadelphia,PA, USA Charles.Schwab@uphs.upenn.edu

170. Beth H Shaz, MD

New York Blood Center, CMSO 310 E 67th St, NY, NY 10065 bshaz@nybc.org

171. Forest Sheppard, MD

Associate Professor of Surgery Acute and Critical Care Surgery Department of Surgery Washington University forest.r.sheppard@wustl.edu

172. Eilat Shinar, MD

Director, Magen David Adom in Israel Tel HaShomer, Israel eilats@mda.org.il

173. Cees Th. Smit Sibinga, MD, PhD, FRCP Edinburgh, FRCPath (London)

emProfessor of International Development of Quality Management in Transfusion Medicine, University of Groningen, Groningen, NI. Director IQM Consulting for International Development of Quality Management in Transfusion Medicine, Zuidhorn, NL c.sibinga@planet.nl

174. Jeffrey Siegler, MD

EMS Physician, Instructor of Emergency Medicine

Washington University School of Medicine Sieglerj@wustl.edu

175. Christopher C Silliman, MD, PhD

Professor of Pediatrics and Surgery School of Medicine University of Colorado Denver Senior Independent Investigator Research Department Bonfils Blood Center Attending Physician Center for Cancer and Blood Disorders Children's Hospital of Colorado Christopher.Silliman@ucdenver.edu

176. Sven Chr Skaiaa

Consultant Anesthesiologist University of Oslo, Air Amb dep. Stupulvegen 5, 3560 Hemsedal, Norway scskaiaa@gmail.com

177. Surgeon Rear Admiral Jan Sommerfelt-Pettersen

Surgeon Genereal Norwegian Defence Joint Medical Service Joint Medical Service, N-2058 Sessvollmoen, Norway jan@sommerfelt-pettersen.no

178. Jason L. Sperry, MD, MPH

Professor of Surgery and Critical Care Medicine Presbyterian Hospital, Suite F1268, 200 Lothrop Street, Pittsburgh PA 15213 sperryjl@upmc.edu

179. Philip C. Spinella, MD, FCCM

Professor of Pediatrics, Division of Critical Care Medicine Director, Critical Care Translational Research Program Washington University in St. Louis USA

180. Ulrik Sprogøe, MD, PhD

Deputy Medical Director Department of Clinical Immunology (part of South Danish Transfusion Service) Odense University Hospital DK-5000 Odense C Denmark ulrik.sprogoe@rsyd.dk

181. Simon J Stanworth, DPhil MD

Consultant Haematologist NHS Blood and Transplant/ Oxford University Hospitals NHS Foundation Trust Level 2, John Radcliffe Hospital Honorary Senior Clinical Lecturer, University of Oxford simon.stanworth@nhsbt.nhs.uk

182. Marie Steiner, MD, MS

Professor, Pediatrics MMC 484, University of Minnesota, Minneapolis, MN 55455 stein083@umn.edu

183. Zsolt Stockinger, MD, FACS

CAPT, MC, USN Director, Joint Trauma System/Defence Center of Excellence for Trauma Associate Professor of Surgery, Uniformed Services University of Health Sciences 3698 Chamber Pass, STE B JBSA Fort Sam Houston, TX 78234-7767 210-539-9174 DSN 389 zsolt.t.stockinger.mil@mail.mil

184. Geir Strandenes, MD, SMO NORNAVSOC

Senior Medical Officer, Norwegian Naval Special Operation Commando Researcher, Department of Immunology and Transfusion Medicine Haukeland University Hospital Norway geir@docfish.no

185. Ronald G. Strauss, MD

Professor Emeritus Departments of Pathology & Pediatrics University of Iowa College of Medicine Associate Medical Director, Associate Medical Director, LifeSource/ITxM rstrauss@itxm.org

186. Paul Stricker, MD

Associate Professor of Anesthesiology and Critical Care, The Children's Hospital of Philadelphia and the Perelman School of Medicine at the University of Pennsylvania 3401 Civic Center Blvd, Philadelphia, PA 19104 strickerp@email.chop.edu

187. James R. Stubbs, MD

Consultant, Department of Laboratory Medicine and Pathology Chair, Division of Transfusion Medicine Mayo Clinic 200 First Street SW Rochester, Minnesota, 55905 stubbs.james@mayo.edu

188. Marius Svanevik, MD

Vestfold Hospital Trust (Consultant Gastrointestinal Surgery) Norwegian Army NorSOST, SMO (OF-3) drsvanevik@hotmail.com

189. Joseph Sweeney, MD

Director, Transfusion Medicine Professor, Brown University The Miriam Hospital 164 Summit Ave Providence RI 02806 JSweeney@Lifespan.org

190. Matthew Sztajnkrycer, MD, PhD

Associate Professor of Emergency Medicine Mayo Clinic, Rochester, MN Sztajnkrycer.Matthew@mayo.edu

191. Lt Cdr Øystein Tandberg, MD

Dept of orthopedics, Haukeland University Hospital, Bergen – Norway OT HUS, Jonas Lies vei 65, Bergen NO oystein.tandberg@gmail.com

192. Patrick Thompson

Paramedic United Kingdom divemedicpatrick@yahoo.co.uk

193. Isaiah R. Turnbull, MD, PhD

Assistant Professor of Surgery Department of Surgery Barnes-Jewish Hospital Washington University Medical Center Campus Box 8109 Saint Louis, Missouri 63110-8109 iturnbull@wustl.edu

194. Darrell J. Triulzi, MD

Medical Director Institute For Transfusion Medicine 3636 Blvd of the Allies Pittsburgh PA 15213 Director, Division of Transfusion Medicine Department of Pathology University of Pittsburgh dtriulzi@itxm.org

195. Gunnar Vangberg, MD, Maj

Norwegian Armed Forces Joint Medical Forces St. Olavs University Hospital, Trondheim, Norway Gunnarvangberg@hotmail.com

196. Adam M. Vogel, MD, FACS, FAAP

Associate Professor, Surgery and Pediatrics Baylor College of Medicine and Texas Children's Hospital 6701 Fannin Street, Suite 1210 Houston, TX 77030 adamv@bcm.edu

197. Ville Voipio, MD, SSAI-ECC HEMS-physician Kipinämikontie 20, Oulu 90420, Finland voipio@mac.com

198. LT COL Jerome Vinluan

Deputy for Policy US Armed services blood procurement office

199. Terje Wadahl

Nurse Anesthesist Head Nurse Norwegian Army/E8 terje@wadahl.org

200. Kevin Ward, MD

Department of Emergency Medicine University of Michigan Michigan Center for Integrative Research in Critical Care (MCIRCC) USA

201. Daniel R Walker, MD, MS, FCAP

Col, USAF, MC, FS Medical Director, Apheresis and Cellular Therapy, San Antonio Military Medical Center Medical Director, Armed Services Blood Bank Center - San Antonio Assistant Professor of Pathology, Uniformed Services University of the Health Sciences clotmeister@outlook.com

202. Jonathan Wallis, BA. Oxon, MB. BS. Lond, FRCP (UK), FRCPath.

Consultant Haematologist Head of Blood Transfusion Newcastle upon Tyne Hospitals UK (Regional Major trauma centre) Chair of the National Blood Transfusion Committee, England President of the British Blood Transfusion Society Jonathan.Wallis@nuth.nhs.uk

203. Elizabeth Waltman, MBA

Chief Operating Officer, South Texas Blood and Tissue Center

Executive Director, Blood and Tissue Center Foundation 6211 IH-10 West, San Antonio, TX 78201 elizabeth.waltman@southtexasblood.org

204. Agneta Wikman, MD, PhD

Associate professor Karolinska University Hospital and Karolinska Institutet Transfusion Medicine L2:01, Karolinska 17176 Stockholm Sweden Agneta.wikman@sll.se

205. Rob Woods, MD MMEd FRCPC

Emergency Physician & Trauma Team Leader - Saskatoon Health Region STARS Transport Physician Assistant Professor & Residency Program Director - Department of Emergency Medicine, College of Medicine, University of Saskatchewan rob.woods@usask.ca

206. LT COL Thomas Woolley, FRCA RAMC

Defence Senior Lecturer in Trauma Anaesthesia UK tomwoolley@me.com

207. Arino Yaguchi

Tokyo Women's Medical University 8-1 Kawadacho, Shinjuku, Tokyo, 1620054, Japan ayaguchi@twmu.ac.jp

208. Vered Yahalom, MD

Transfusion & Apheresis Services Director Rabin Medical Center, Petah Tikva, Israel veredya2@clalit.org.il

209. Mark Yazer, MD

Professor of Pathology, University of Pittsburgh Medical Director, RBC serology reference laboratory, Centralized Transfusion Service Associate Medical Director, Centralized Transfusion Service Adjunct Professor of Clinical Immunology, University of Southern Denmark 3636 Blvd of the Allies Pittsburgh PA 15213 myazer@itxm.org

210. LTC Avraham Yitzhak, MD, MHA

General Surgeon Head of Trauma and Combat Branch Israeli Defense Forces Medical Corps headquarters Tel Hashomer, Ramat Gan Israelayitzhak@gmail.com

211. Pampee P. Young, MD, PhD

Associate Professor Medical Director, Transfusion Medicine Department of Pathology, Microbiology, immunology 1161 21st Ave South, MCN C2217 Vanderbilt University Medical Center Nashville, TN 37232 pampee.young@Vanderbilt.Edu

212. Nicole Dodge Zantek, MD, PhD

University of Minnesota, Associate Professor University of Minnesota, 420 Delaware Street SE, MNC 609, Minneapolis, MN 55455 Zant0005@umn.edu

213. Martin D. Zielinski, MD, FACS

Professor of Surgery Medical Director of Trauma Research Division of Trauma, Critical Care, and General Surgery Department of Surgery Mayo Clinic 200 First Street SW Rochester, MN 55902 Zielinski.Martin@mayo.edu

214. Alyssa Ziman, M.D.

Professor, Pathology and Laboratory Medicine Division Chief, Clinical Laboratory Medicine Medical Director, Clinical Laboratories, Ronald Reagan UCLA Medical Center Medical Director, Transfusion Medicine UCLA Health System AZiman@mednet.ucla.edu

Proposal to modify Standard 5.15.1 to permit the use of low titer, group O whole blood in massively bleeding patients regardless of their ABO group

The AABB/THOR working party (WP) is suggesting that the AABB Standards Committee modify standard 5.15.1 to permit the use of low titer, group O whole blood (WB) in all massively bleeding patients regardless of their ABO group.

There is extensive literature and experience indicating that it is desirable and safe to use cold stored, low antibody titer WB early in the management of traumatic hemorrhagic shock.¹ Reports from the Korean war detailed the efficacy and safety of transfusing low titer Group O whole blood; in 1952 over 600,000 units of low titer (defined as <256) group O whole blood were transfused to combat casualties. Patients typically received 10-30 units of low titer, group O WB, and only 4 patients were noted to have post-transfusion hemaglobinuria, which might or might not have been related to the receipt of the WB.¹ During an approximately 18 month period during the Vietnam war, 230,323 WB units were transfused,² and only one hemolytic reaction to a group O unit was reported. In fact, this lone, non-fatal reaction only occurred because a labeled high titer group O unit was accidentally transfused to a group A recipient.³

The recent wars in Iraq and Afghanistan have highlighted the high mortality associated with traumatic hemorrhagic shock and provided the opportunity to reevaluate the potential benefits of WB resuscitation in this context. One analysis from Iraq indicated the use of WB was independently associated with improved 30 day survival compared to the use of blood components for US casualties with life-threatening hemorrhage.⁴

Reducing death from hemorrhage is essential since the mortality for patients with traumatic hemorrhagic shock is high (approximately 20%) and there are approximately 30,000 preventable civilian deaths due to traumatic hemorrhage per year in the US alone.⁵ The rationale for the use of group O WB

early in the resuscitation of massively bleeding patients is multifactorial and has been recently reviewed.^{5,6} Group O whole blood provides a balanced resuscitation that simultaneously addresses oxygen debt and coagulopathy, both of which are associated with high mortality in this population.^{4,7,8} The use of a blood based transfusion strategy that approximates whole blood with 1:1:1 unit ratios has been shown to reduce death from hemorrhage in adult trauma patients.^{4,8} Whole blood is a more concentrated product containing a smaller quantity of anticoagulant and preservative solutions compared to an equivalent amount of reconstituted WB from blood components.⁴ The cold stored platelets in WB improve hemostasis more effectively compared to platelet units stored at room temperature (RT). ^{9,10} Improved hemostasis with platelets stored at 4C has been extensively reviewed and is based on a significant amount of in vitro data and 2 RCTs.⁹⁻¹² One RCT in children demonstrated reduced blood loss and improved platelet aggregation in the cold stored whole blood arm compared to those in the conventional components arm who were transfused with RT stored platelets in a 1:1:1 ratio.¹³ Another trial of adults on aspirin showed improved correction in the bleeding time when a cold stored platelet unit was transfused compared to a conventional RT unit.¹⁴ Furthermore, the use of WB will greatly simplify the logistics of the resuscitation by transfusing the contents of one bag instead of up to three bags that all have to be separately procured and transported from the blood bank under different temperature conditions. This latter advantage is especially important in the pre-hospital setting where space in the helicopter or ambulance is at a premium, and often intravenous (IV) access in the patient is limited. The ability to quickly provide a transfusion to traumatically injured patients has been shown to improve outcomes in both military and civilian trials,^{15,16} and it is known that mortality is increased by 5% for every minute that initiating a transfusion was delayed in these patients.¹⁶ Since it is not feasible to transport RBCs, plasma and platelet units in the prehospital setting, the most effective method of resuscitating a patient with traumatic hemorrhagic shock in the prehospital setting is with WB. Effective resuscitation in the prehospital phase of treatment is essential because of the 30,000

preventable deaths per year in the US due to traumatic hemorrhage, approximately 25,000 of these deaths occur in the prehospital phase of resuscitation.^{5,17}

A major limitation to implementing low titer group O WB at civilian medical centers is the AABB standard regarding its use. The AABB's Standards for Blood Banks and Transfusion Services require that WB units be ABO-identical with the recipient (standard 5.15.1 in the 31st edition of the standards). There is a theoretical concern that a minor incompatible plasma transfusion could lead to hemolysis of the recipient's RBCs. However, a subsequent standard permits the transfusion of minor incompatible plasma so long as the transfusion service has a policy guiding this practice (standard 5.15.4 in the 31st edition of the standards). According to the latter standard, a minor incompatible transfusion of group O platelets or plasma could be administered to a group A recipient, as long as the transfusion service has a policy that permits this practice. Therefore, there is a circularity in the AABB standards: a transfusion service is permitted to transfuse the minor incompatible plasma in platelets and plasma units, but not from WB. Standard 5.15.4 does not provide guidance on the number of units or the total quantity of minor incompatible plasma that can be transfused, any specific donor-recipient ABO pairings that are forbidden, what to do with group O minor incompatible units in particular, whether an antibody titer must be performed on the minor incompatible product before it is transfused, or under which clinical circumstances minor incompatible plasma may be transfused – all of this is left to the discretion of the individual transfusion service's medical director. It therefore remains unclear why the regulation of WB transfusion was specifically excluded from Standard 5.15.4.

The safety of transfusing minor incompatible plasma, mainly through platelet transfusions, is well documented. In 2015, there were nearly 2 million apheresis and whole blood platelet units transfused in the US,¹⁸ and in the United Kingdom there were over 300,000 doses issued to hospitals in 2016.¹⁹ Many of these transfusions would surely have featured a minor incompatibility between donor and

recipient.²⁰ Yet the number of times that recipients experienced a hemolytic episode from the minor incompatible plasma in the platelet dose remains very small, on the order of a few case reports (reviewed in references 21 and 22). Furthermore, in a study of 16 hematology/oncology patients who received at least one ABO-identical and a minor mismatched platelet transfusion within a 24 hour period,²³ Mair and Benson found that there was no significant difference in the mean change in hemoglobin concentration following the ABO-identical vs. the minor mismatched platelet transfusions. This indicates that hemolysis did not occur following the transfusion of the minor mismatched platelet unit in spite of the fact that most of the minor incompatible platelets were group O; these units potentially have higher titers of anti-A and/or anti-B compared to platelets from the other blood groups and are considered to be the highest risk product in terms of causing hemolysis following a minor incompatible transfusion. None of these minor incompatible platelet transfusions were shown to contain low titers of anti-A and/or –B, and yet significant hemolysis did not occur. Furthermore, traumatically injured patients are often transfused with large quantities of platelet units. In fact, in the recent PROPPR trial the median number of whole blood platelet units transfused in the high ratio group was 12 (effectively a double dose of platelets in adults) within the first 24 hours.⁸ A double dose of platelets contains approximately 600 ml of potentially minor-incompatible plasma. Thus, it is commonplace to provide traumatically injured patients with large quantities of potentially incompatible plasma.

The safety of the use of group A plasma in trauma (STAT) study demonstrated that group B and AB trauma recipients who received an average of 4 units of group A plasma during their resuscitation did not have increased early- or in-hospital mortality, or longer hospital lengths of stay compared to group A trauma patients who also received group A plasma.²⁴ There were also no reported acute hemolytic reactions reported amongst these B and AB recipients. Importantly, the vast majority of the participating hospitals in this study (76%) did not titer the anti-B in the plasma and were thus not

intentionally providing low titer units to their trauma patients, and yet there were no demonstrably worse outcomes amongst the B and AB recipients who received minor incompatible plasma transfusions compared to those who received fully compatible transfusions.

The safety of using cold stored, low titer (<50 anti-A and –B by manual saline tube immediate spin without enhancements) WB in traumatically injured civilian patients has been demonstrated.^{25,26} In a study of 27 non-group O and 17 group O recipients, there was no laboratory or clinical evidence of hemolysis in the former group compared to the latter group of recipients, with the exception of a higher median level of total bilirubin amongst the non-group O recipients on the day of receipt of WB.²⁵ This higher median total bilirubin level was still within the normal range, and the difference in this parameter between the group O and non-group O recipients was no longer apparent on the following day. These observations have been extended to include additional recipients, and recipients of greater numbers of WB units (3 and 4 units), and there continues to be no biochemical or clinical evidence of hemolysis amongst the non-group O wB has also been successfully implemented at the Children's Hospital of Pittsburgh. Traumatically injured children older than 3 years and weighing more than 15 kg can receive up to 30 ml/kg of uncrossmatched group O WB. The non-O pediatric recipients did not demonstrate clinical or laboratory evidence of hemolysis compared to the group O pediatric recipients (data to be presented as an oral abstract at the 2017 AABB annual meeting).

It is interesting to note that the 5 civilian trauma centers or emergency medical systems in the US and Norway that are using group O WB have all adopted an anti-A and anti-B titer threshold of between <50 and <200 to define "low titer".²⁷ This could be a reasonable range for blood centers and transfusion services to consider when creating their local definition of a low titer. Thus, as the evidence from the civilian adult and pediatric experience with WB indicates, these low titer group O WB units have an

enhanced safety margin compared to untitered minor incompatible plasma that is transfused with non ABO compatible platelet units. Furthermore, the fact that only low titer WB units are being issued to civilian trauma patients in the US adds yet another layer of safety and reassurance about the safety of using low titer WB in trauma patients regardless of whether their ABO group is known at the time of the transfusion or not.

The safety of transfusing minor incompatible plasma is well established and indeed this practice is permitted in the AABB standards (5.15.4) for all plasma-containing products except WB. However, the transfusion of WB to a recipient of unknown ABO group is prohibited by standard 5.15.1 thereby delaying the administration of this product to some massively bleeding patients. This prohibition is retarding the implementation of civilian pre- and early in-hospital WB transfusion programs. The AABB/THOR working party has generated a petition that has been signed by 214 experts in the fields of transfusion medicine and resuscitation medicine from 24 countries, demonstrating that there is significant domestic and international interest in using low titer group O WB in traumatically injured patients or in others with life-threatening hemorrhage.

With the growing body of evidence indicating that low titer group O WB is serologically safe for non-O recipients in adults and children, and the increasing support and demand for this product in the US, Standard 5.15.1 should be modified to permit the use of low titer, group O WB in massively bleeding patients regardless of their ABO group. Requiring each individual medical center to submit a variance is an inefficient approach to permitting the use of low titer group O WB. Each transfusion service would also follow Standard 5.15.4 and devise a policy that specifies the definition of low titer, the quantity of group O WB that can be transfused per patient, the nature of massively bleeding patients who would qualify to receive it, and any clinical surveillance of the recipients of this product that may be necessary.

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