

AABB 2006: TRALI becomes a key theme for the US blood supply industry

Emerging pathogens and new technologies were on the agenda at the annual AABB exhibition and meeting on October 21-24 2006, in Miami Beach, Florida. Donor screening for emerging threats to the blood supply from Chagas disease and malaria; bacterial contamination testing; the migration to individual donor testing versus the mini-pool NAT protocol; TRALI; and FDA requirements for the approval of new testing claims were among the key themes at the event, which drew some 6,800 attendees, write Kerri Weinert and Carrie Cresenzi of Boston Biomedical Consultants

Based on preliminary estimates from ARC, ABC, and the AABB, nationwide blood donations in the US increased modestly in 2006 over 2005, in the range of 2.5-4%. Increases in source plasma collections also rose, but percentage estimates were not available at the time of writing. Strategies to retain donors and to encourage more frequent donation continue to challenge all voluntary blood collection centres/hospitals, with collection of double red cells growing.

The leading cause of transfusion-related death reported to the FDA in the period 2003-05 was transfusion-related acute lung injury (TRALI), which was a hot topic at AABB 2006. The UK's haemovigilance programme, Serious Hazards of Transfusion (SHOT), found a strong association between leukocyte antibodies, which are found more frequently in women, in plasma and platelet components in TRALI cases. In 2002-2003, SHOT recommended the exclusion of female plasma and platelet donors; and, although it has not been possible to attain a 100% male plasma supply, there has been a significant reduction in reported TRALI cases. The ARC also reported data from its haemovigilance programme, and suggested that physicians be educated to avoid overuse/abuse of plasma, and that the US work towards an all-male plasma supply. Based on the UK and ARC surveillance data, the AABB working group on TRALI decided to focus its strategies for antibody-mediated TRALI and is recommending the following to reduce its incidence:

- minimise transfusion of high plasma-volume components from leukocyte-alloimmunised donors; and
- minimise inappropriate transfusion of blood components.

Based on current data, the incidence of TRALI can be significantly reduced by avoiding the transfusion of high plasma volume-based blood products – fresh frozen plasma and single-donor apheresis platelets. AABB has issued guidance to its membership to reduce the use of products containing high volumes of plasma from individuals at risk of alloimmunisation over the next two years.

Automation for NAT-based testing

No new instruments were shown at AABB 2006 for automation of NAT-based testing, with discussions focused mainly on individual donor testing (IDT), the inclusion of HBV NAT, and the use of automation. Presentations from NAT

customers in Australia and France discussed these aspects with comparisons of Chiron's Procleix Ultrio Assay on the Procleix TIGRIS instrument and Roche's TaqScreen Multiplex Assay on the cobas s 201 instrumentation.

In October 2006, Chiron's partner, Gen-Probe, received FDA approval of the Procleix Ultrio Assay for use on the semi-automated Procleix System (also known as the eSAS),

marking a significant business milestone. However, the Procleix Ultrio Assay was approved to screen donated blood, plasma, organs, and tissue for HIV-1 and HCV in individual blood donations or in pools of up to 16 blood samples, while approval for HBV at this time applies only to the detection of HBV (not donor screening). Therefore, the current FDA approval of the Procleix Ultrio Assay is

equivalent to the Procleix HIV-1/HCV assay, but the assay can be run with donation and donor management of the HBV portion under an IND.

The initial pivotal study for the Procleix Ultrio Assay was not designed to, and did not, demonstrate yield, defined as HBV-infected blood donations that are negative based on serology tests for HBsAg and anti-HBc, which prevented the granting of a screening claim for HBV. Based on discussions with the FDA, Gen-Probe and Chiron will initiate a post-marketing study to demonstrate HBV yield to gain a donor screening claim. The companies expect this study to begin in early 2007, as the commercial assay becomes available. Chiron and Gen-Probe are now in discussions with customers and hope to speak with the FDA regarding the nuances of the post-market study, such as whether or not it will use IDT or pools of eight or both. Gen-Probe must find a yield comparable to that found by Roche – two yield samples.

Similar to the 2005 conference, Roche displayed its Cobas Amplicor and cobas s 201 systems in its booth. The cobas s 201 system consists of varying configurations of the Hamilton Star Pipettor, Cobas AmpliPrep instrument, and Cobas TaqMan 96. The TaqScreen Multiplex assay detects HIV-1 (M/O), HIV-2, HBV and HCV in pools of six and individual donations. It received CE Mark in March 2006. The US Biologic License Application (BLA) for the TaqScreen West Nile virus (WNV) assay was filed just after the 2006 conference at the end of October; the BLA for the TaqScreen Multiplex assay is expected to be filed by year-end 2006. The cobas s 201 is under evaluation at sites in the US, and was expected

171 companies exhibited at AABB 2006, which, for the first time, was open for four days instead of the usual three. Roaming the convention centre was "The Red Defender", who was highlighting a new series of public service announcements (PSAs) on behalf of the Bloodsaves campaign. This initiative, first launched in 2004, is supported by the Advertising Council, AABB, America's Blood Centers (ABC) and the American Red Cross (ARC). "The Red Defender" campaign began in August 2006 to encourage young adults (especially 17-24 year-olds) to make regular blood donations.

to be commercially-available by year-end 2007. The fully automated cobas s 401 (in development) will enter trials in Japan that are expected to conclude in spring 2007.

The debate continued at the AABB conference on the advantages and disadvantages of IDT versus mini-pool NAT. Depending upon what systems were compared, the following underlying issues remain key points of discussion:

- sensitivity or threshold;
- specificity;
- yield or desired/acceptable residual risk;
- affordability;
- test turnaround time; and
- degree of multiplexing.

With multiplexing of HIV, HCV, and HBV, the pool size is driven by HBV as larger pools reduce the sensitivity of the HBV test component.

Automation for IAS-based testing

Adding to the Prism HBcore assay, which received FDA approval at AABB 2005, Abbott promoted its Prism HBsAg test, FDA-approved in July 2006. As Abbott builds the menu of FDA-approved tests for the Prism, it has attracted two of the largest blood donor testing organisations to its platform. Prior to AABB 2006, Abbott announced the placement of 20 Prism instruments at the ARC in September 2006 and additional instruments at Blood Systems Laboratories approximately one week prior to the meeting.

Ortho-Clinical Diagnostics (OCD) conducted in-depth presentations describing its Paradigm system through an IMAX-type video display in a theatre housed in its booth. Paradigm preserves the current 96-well microtitre plate (MTP)-based assay. Depending on the instrument configuration of the Paradigm (multiple modules allow flexibility dependent on customer volume/labour requirements), IA-based testing is virtually hands free and fully automated. Track-linked pre-analytical preparation is a unique optional capability of the system. OCD anticipates that the Paradigm will be submitted for approval in the next couple of years in the US, with earlier release in the international markets.

Emerging agents

Chagas disease continued to be a major topic at the AABB conference, as both Abbott and OCD moved towards approval of their assays. Over approximately 20 years of observation, there have been seven cases of transfusion-transmitted Chagas disease in North America (including two in Canada) and five cases from organ transplantation in the US.

In addition to promoting its Chagas assay in published abstracts, OCD held a workshop profiling its Ortho *T cruzi* ELISA test (for use on the OCD Summit System), an MTP-based test format that utilises antigens from a whole cell lysate to coat the solid phase (MTP plates). The lysate allows for a complete antigen set to enhance sensitivity, while diluting the effect of potential cross-reactive antigens to maintain specificity. OCD had submitted its BLA to the FDA in February 2006, and it received FDA approval in December 2006. The FDA requested additional studies for prevalence data (demonstrating the assay's ability to detect positive yield cases), which are being conducted under IND. The FDA requested that OCD expand its studies to include areas where *T cruzi* antibody prevalence was previously documented.

A Radioimmune Precipitation Assay (RIPA) has been established and validated at OCD as a reference assay, and is being transferred to a reference laboratory for testing of ELISA reactive donors. RIPA is a labour-intensive confirmatory method with low throughput due to many controls and special requirements needed for processing using Iodine¹²⁵; however, it is considered the gold standard test. Ortho *T cruzi* ELISA test system launched in Europe in July 2006.

Abbott read two abstracts on its recombinant antigen Chagas assay for the PRISM and immunoblot confirmatory assay. Performance data on the Abbott Chagas test from a total of 402 *T cruzi* antibody positive specimens from endemic areas (across multiple reagent preparations) resulted in a detection sensitivity of 100% (402/402). Overall, from a total of 1,848 normal blood donors evaluated, the repeat reactive rate was 0.11% for a specificity of 99.89%. The prototype immunoblot assay using recombinant antigens correlated well with RIPA test results.

With approximately 150,000 donors deferred each year in the US due to travel outside of the US to locations with malarial exposure, there continues to be an appeal to manufacturers to develop a screening test for malaria. Abbott provided AABB attendees with a "Who Will Be Next" educational package to inform the blood testing community on the challenges posed by malaria deferrals.

From the 1980s to 1990s, data indicated that transfusion-transmitted malaria resulted overwhelmingly from residents of malarious areas rather than from travellers who live in non-endemic regions. From 1998 to the present, there have been <5 cases of malaria in the US. However, deferrals have resulted in lost donations not only during the deferral period, but also for future donations, as some possible donors do not respond to call backs or self-select themselves out of the donor pool. In addition, recruiting programmes to help maintain the blood supply as a result of these deferrals cost time and money. As a result, with an average of one new case of infection per year in the US, malaria has become more of a blood availability issue rather than a safety issue.

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When parasitaemia is low, a small test sample of blood taken from an infected unit may not be informative; consequently, it has been challenging to achieve the sensitivity required for a direct antigen or NAT test. Methods to concentrate malaria parasites from a large volume of blood for subsequent detection by a sensitive NAT may help to resolve the issue; however, such technologies are under development and are neither available nor feasible in the donor screening setting. An antibody test could identify donors who had experienced an acute infection or who carry low-grade parasitaemia without clinical symptoms, and could therefore help reduce the deferral period and re-enter donors. Abbott is evaluating options for Prism test development.

Blood grouping and typing (BGT)

Following an active year of new BGT automation introductions, 2006 witnessed no new platforms at the meeting. An update to the Olympus/Biotest distribution agreement in the US for the automated BGT system, the Tango, was announced just before the conference. Under the agreement, Biotest will now directly market the system to hospital-based customers, while Olympus will focus on its traditional customer base in free-standing donor centres. Biotest announced that it has submitted additional test menu items to the FDA for the Tango instrument. The company also has submitted to the FDA a full line of traditional blood bank reagents; anticipated release for both product lines is the third quarter of 2007.

Olympus announced that the submission for the new line of dedicated PK reagents and the PK7300, the next model in the PK instrument series, have been submitted to the FDA

with an anticipated release in the second quarter.

A new technology was presented by Immucor, the Atlanta-based company that shares US market leadership with OCD. Immucor presented data on the performance of its quality control reagents for ABO/Rh, which are still under development. The reagents are based on the licensed KODE technology, which enables the development of designer synthetic glycolipids, which can be synthesised and inserted into red cell membranes. Using KODE technology, red cells were able to be created, which precisely and reproducibly expressed desired A, B, H, acquired-B and Lewis A antigen. The Immucor QC reagents will be submitted to the FDA with the Echo submission for US clearance.

OCD's activities at the conference, in addition to showcasing the Ortho ProVue for US customers and the Ortho AutoVue Innova for international customers, centred on the benefits of process improvements in the transfusion service through the application of LEAN quality tools.

New technologies – DNA-based BGT

DNA-based BGT methods for Rh, ABO determination, and most importantly, extended genotyping, were discussed at AABB 2006, with many abstracts published on "home-brew" or user-developed methods. Current serological BGT methods may be used to assess sensitisation to multiple antigens for sickle cell disease and thalassaemia patients who tend to receive multiple transfusions, as well as for typing and confirmation of blood group antigens for donor RBCs. The discussion at AABB 2006 focused on initial applications with Rh status (or some minor erythrocyte antigens) versus ABO determination as it was thought that it was not technically and legally feasible to replace serology ABO at this time because of the idea that type O blood could be transfused to someone with an unknown BGT status. DNA-based BGT methods are thought to have the following advantages:

- no dependence on a limited or variable availability of some antisera reagents for traditional BGT techniques;
- no need for RBCs (focus on nucleated cells without collection of a traditional blood sample, perhaps using a buccal swab);
- no confounding by weak antigens;
- in-depth analysis, including zygosity determination; and
- ability to multiplex test.

High-throughput platforms will permit affordable genotyping; however, cost considerations include adding on PCR or PCR replacing serological techniques. Mass-scale genotyping of all blood donors and patients could decrease alloimmunisation events and improve transfusion outcomes for vulnerable patients (eg, multi-transfused individuals); however, IT or registry solutions (not yet in place) will be required to handle the significant data input from the blood bank.

BloodGen is a European consortium conducting a large-scale trial of blood grouping and genotyping. It was founded in September 2000 with funding received in 2002 followed by the start of the trials in 2003. The goal is to validate a genotyping platform versus standard serology. BloodGen's commercial partner, Progenika, supplies its glass array which utilises three different multiplex PCR reactions to analyse >100 SNPs. The company is currently in clinical trials for CE Marking. In addition to Progenika, Bioarray Solutions offers a colour-coded bead array assembled on a planar surface that utilises a multiplex PCR reaction and requires five hours for processing. RHD and RHCE typing systems are in development.

Bacterial testing

Within the area of bacterial contamination testing, seven-day platelets and rapid point-of-issue (POI) tests were emphasised at AABB 2006. The motivation for seven-day platelets is to

increase product availability as well as to reduce outdates. The impetus for rapid tests is to close the gap on culture false negative units in the inventory by testing near the time of transfusion and to test whole blood derived (also known as random donor) units, which may be tested with insensitive surrogate measures, such as pH and glucose strips.

To recap for seven-day platelets, in March 2005, Gambro received FDA approval for a shelf-life extension of apheresis (also known as single donor) platelets collected with its Trima and Cobe Spectra collection systems for routine storage and patient transfusion up to seven days when tested with bioMérieux's BacT/ALERT Microbial Detection System as a Release Test. In November 2005, Baxter received 510(k) clearance for seven-day storage of leukoreduced, apheresis platelets collected on the Amicus Separator and stored in the company's PL 2410 collection container; the release test must also be used with these products.

As part of these seven-day claims, the FDA required these companies to perform a post-market study called Post Approval Surveillance Study of Platelet Outcomes, Release Tested (PASSPORT). Uniquely, this study is not sponsored or supported by the test manufacturer itself; instead, in order to expedite the data collection, Baxter and Gambro teamed up for this study in May 2006.

PASSPORT involves testing expired products from 50,000 platelet collections to assess the performance of the bioMérieux BacT/ALERT system as a release test. Please note that the BacT/ALERT system was only FDA cleared as a quality control (QC) test by the FDA upon bioMérieux's submission data; it is only referred to as a release test in the Gambro/Baxter PASSPORT protocol, as bioMérieux has not received FDA approval for its system as a release test. The BacT/ALERT release test is the only FDA-cleared bacterial detection method that permits seven-day storage of single donor platelet products under the approved PASSPORT study protocol. Although bioMérieux's QC test package insert indicates that use of two bottles is "strongly recommended", the FDA requires both aerobic and anaerobic bottles to be used for the release of seven-day platelets as part of the PASSPORT protocol.

The primary hypothesis of the study is that seven-day single donor platelets, when tested using the release test will not present a greater risk of a detectable bacterially contaminated platelet unit than five-day single donor platelets untested for bacterial contamination. Blood centres wanting to store their single donor platelets collected using either Amicus, Cobe Spectra or Trima systems for up to seven days are required by the FDA to participate in the PASSPORT study and must test using both aerobic and anaerobic culture bottles. Of note, New York Blood Center was the first to release seven-day platelets in September 2005, and Blood Systems Laboratories began doing so in September 2006. It is estimated that the PASSPORT study will require three years to complete.

5-day vs 7-day stored platelets

The debate over the quality of five-day versus seven-day stored platelets continued at AABB 2006. In January 2006, bioMérieux received clearance for testing of whole blood-derived platelets on the BacT/ALERT. As a result, its package insert changed from an original 4mL volume to a range of 4-10mL in order to obtain adequate samples from each of five or six random platelets; it also more readily accommodates the use of two bottles. Near the same time, but in a separate submission, Pall received clearance for its Acrodose bag without the eBDS attached, so customers could utilise the pooling bag to test with the BacT/ALERT. Pall's approval of its Acrodose-PL system (pooling/bag device) for use with the

BacT/ALERT provides another option for platelet storage and testing and helps address the issue of availability. It was the first whole blood derived system for pre-storage pooling and testing of leukoreduced whole blood derived platelets, resulting in a transfusion-ready product for hospitals; at the time of initial launch at the 2005 AABB (approval just before the conference), testing was performed on the eBDS, which measures oxygen consumption and therefore limits detection of anaerobes. The Acrodose platelet represents a new product for platelet transfusions that provides many of the benefits of apheresis platelets, but at a lower cost. As a result of the approvals from bioMérieux and Pall, currently, five whole blood-derived platelet units can be pooled using the Acrodose-PL System and then tested on the BacT/ALERT or eBDS.

Boston Biomedical Consultants Inc is based in Waltham, Massachusetts. Kerri Weinert and Carrie Cresenzi can be reached at kweinert@bostonbiomed.com and ccresenzi@bostonbiomed.com

Rapid POI tests

In addition to seven-day platelets, rapid POI tests were also highlighted at AABB 2006, supported by promotional efforts from Abbott and Verax. In October 2006, both companies announced an exclusive distribution agreement wherein Abbott received worldwide rights to market and distribute the Verax Platelet PGD Test. This is still in clinical trials, which are expected to finish by end-2006, at which point Verax will file for a QC claim. University Hospitals Case Medical Center, Cleveland Clinic, and Dartmouth Hitchcock Medical Center participated in the clinical trials that will generate data for the 510(k) application for the QC claim.

The application of rapid POI tests would be to test platelets just prior to issuing platelet products on the day they are

transfused in order to avoid false negatives associated with culture testing; however, questions over sensitivity and practicality were raised, as some rapid POI tests require the addition of reagents and centrifugation prior to sample application on a strip or cartridge, which could be considered too much "hands-on" time.

At the March 2006 Blood Products Advisory Committee (BPAC) meeting, several rapid test companies were present, including BCR Diagnostics, GenPrime, Immunetics, and Verax, to discuss the regulatory path for POI products. The committee proposed a three-tiered regulatory pathway for

clearance of rapid bacterial detection tests, consisting of:

- QC indication;
- adjunct to a release test indication; and
- release test indication.

The QC indication would require the establishment of defined analytical sensitivity by spiking studies and the establishment of substantial equivalence through a kinetic comparison to a marketed culture-based device. The adjunct to a release test would require a clearance for a QC indication and a commitment to a post-market field trial with a timed sampling study. The release test indication would require clearance for a QC indication, a standard operating procedure (assures substantial equivalence to a bacterial detection device marketed as a release test), extensive data set of QC performance (hundreds of thousands of samples), and a commitment to a post-market study on 50,000 units that will be retested as outdate. Each of these studies and pathways is modelled after the FDA proposed pathways for release labels for culture-based tests.



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