Pathogen inactivation tops agenda with TRALI & emerging pathogens at AABB 2008

Like its predecessor in 2007, the 2008 AABB conference featured updates on TRALI, emerging pathogens and bacterial contamination testing. But in 2008, there was also increased coverage of pathogen inactivation, now that the PASSPORT study has been halted and the probability of it being reinstated is low. Elsewhere, in support of the worldwide "green" initiative, the conference featured several environment-friendly changes. The 2008 conference was different for one other major reason: it was held outside the US – in Montreal, Canada – for the first time in its history. In this special conference review for *Clinica*, Boston Biomedical Consultants reports on the themes that emerged at the 2008 AABB annual meeting and exhibitions event, held on October 4-7

The AABB 2008 conference attracted nearly 7,000 people, a slight decline from 2007, and approximately 200 exhibitors, *write Carrie Cresenzi and Leigh Stokey of US company Boston Biomedical Consultants.*

It would appear that in 2008, blood donation activity did not change materially over 2007, again increasing only slightly in the US (by some 1-2%), influenced by several stimulating and opposing factors.

The chronic lack of consistent and current national data on blood use continues to challenge the industry, according to Jim MacPherson, CEO of America's Blood Centers (ABC). The American Red Cross (ARC) has seen a slight increase in whole blood donations over its fiscal 2007 year, which is attributed to the expanding youth market (high school and college student donations). The frequency of platelet donors has also increased.

Automation for NAT-based testing

A significant focus at AABB was automation for NAT-based testing and associated multiplex testing. Both Chiron and Roche focused on expanded menus for their current automation platforms.

Chiron displayed its Procleix Tigris instrument and promoted its recently fully FDA- approved Procleix Ultrio assay (HIV1, HCV, and HBV). Chiron's partner, Gen-Probe, achieved a significant milestone in early August 2008 when the FDA approved its supplemental Biologics License Application (BLA) for the Procleix Ultrio assay; the assay had previously received FDA approval for use on the semi-automated Procleix eSAS to screen donated blood, plasma, organs, and tissue for HIV1 and HCV in individual blood donations or in pools of up to 16 blood samples, while approval for HBV at this time applied only to the detection of HBV (not donor screening).

The assay now has full approval in the US and can be used to screen blood, plasma, organs, and tissue for HIV1, HCV, and HBV in both individual blood donations or in pools of up to 16 blood samples using both the semi-automated Procleix eSAS system and the fully-automated Procleix Tigris system.

In order to obtain the data for the full approval, Gen-Probe conducted a post-marketing study starting in early 2007 to detect two HBV yield cases (serology negative, NAT positive). Through abstracts, results of the Procleix ultrio assay post-marketing study were released by the ARC, ABC, and Association of Independent Blood Centers (AIBC). Gen-Probe continues to investigate the development of a dengue virus test, as well as tests for parvovirus and HAV that are early in development.

Roche highlighted its modular real-time PCR automation in the cobas s 201 system, which is currently available in the US with a West Nile virus (WNV) assay. Roche's multiplex assay for HIV1 (groups M & O), HIV2, HCV, and HBV is in the final stages of FDA review. Roche expects this to be the most comprehensive multiplex assay available in the US once approved.

The company also emphasised its long-term commitment to partnering with the blood screening industry to develop next-generation assays and systems, which was evidenced by its extensive visibility in corporate sponsorships at the event.

In its booth, Roche showcased its fully-automated cobas s 201 real-time PCR system, emphasising its HBV NAT performance through posters and investigator presentations. The test was launched in Europe in 2006 on the fully-automated cobas s 201 system and has been used since June 2008 to test the entire Japanese blood supply on the fully-integrated and automated cobas s 401 system.

The company continues development of its next-generation multiplex assay, which is being designed to eliminate the need for separate resolution testing. In addition, it continues development of a separate duplex test for HAV and parvovirus B19. Roche is also actively exploring development of tests for emerging pathogens. Looking to the future, Roche is actively developing its next-generation platform to support fully-integrated and automated real-time PCR testing for high and medium throughput applications.

Given that HBV NAT is not mandated by the FDA, it is not clear how its availability will affect pricing for centres that implement HBV NAT in addition to their routine HIV and HCV NAT screening. Of note, in addition to adding the HBV NAT test, multiplex tests offered by Chiron and Roche provide customers with enhanced automation compared to older generation systems from each company.

Automation for IAS-based testing

New product activity in the immunoassay-related testing category from Abbott was focused on the promotion of its Prism nEXT instrument upgrade (which was recently released outside the US). Secondarily, the Prism Director (a retest server in p14 ▶

development) and the Architect i2000SR, which is used for blood donor screening in the international markets, were featured.

The Prism nEXT software builds on the features/benefits of the current Architect series software (Windows XP-based). With the necessary CPU upgrade of the system (in field upgraded or available on new instruments), moving from the current DOS-based software, the speed, computing and data storage capacity, data retrieval, and a host of other features will increase end-user productivity. Based on Abbott's 510(k) submission at the end of 2008, the product should be available by H1:09.

On the assay side, the company also promoted its Abbott Prism HIV O Plus test, which has been submitted to the FDA; licensing of the test should take place in 2009, with availability, presumably, in the same year. The Abbott Prism Chagas test and the Chagas Confirmatory immunoblot assay continue to progress in the clinical testing phase and are expected to launch in 2010 (technical updates were featured in a series of multiple abstracts).

OCD displayed the new Ortho Verseia Pipetter, intended for use in pipetting licensed ELISAs supplied by OCD for donor screening. Key features include multiassay pipetting per sample batch, total aspiration and dispense monitoring, maintenance/verification lock-out, and e-connectivity. It will be launched initially with two assays (TCruzi and HCV); OCD will seek FDA approval for other assays after its initial launch.

Emerging analytes

Similar to AABB 2007, babesiosis was discussed at this year's conference. To recap, Babesia, the agent that causes babesiosis, is transmitted by ixodes ticks, infects red blood cells, and causes a flu/malaria-like illness that usually resolves. There is a lifetime deferral for history of babesiosis, and currently no test is available. This year, there continued to be a "call to action" to manufacturers for a test, as the risk factor questions lack sensitivity and specificity. Because window period infections can occur, a NAT test may be applicable; however, because chronic carriers may also exist, an antibody test may also be relevant.

Ideally, the industry would like to eliminate the permanent deferral and develop re-entry algorithms to help support maintaining the donor pool. Because selective testing is thought to be more appropriate than universal testing, key discussions are ongoing among the blood community, blood bankers, test manufacturers, and the FDA, with the ultimate goal of designing a test at a reasonable price for selective testing.

For blood centres, another important issue is automating data movement to be sure that donors who need to be tested receive testing before labelling and distribution of products.

Although malaria was not as heavily discussed, chikungunya virus, which is an arboviral transmitted by mosquitoes of the genus Aedes, was highlighted. The virus has been reported in many parts of Africa, South-East Asia, the Western Pacific and India.

In 2006, there was a massive outbreak of chikungunya fever in a number of islands in the Indian Ocean. Diagnostic tests currently include virus isolation, PCR, and serology (IgG and IgM); there is no screening test for this virus. Pathogen inactivation by Intercept on all collected platelets in La Reunion in the Indian Ocean was implemented to help with this epidemic.

However, some arguments make blood transmission highly plausible, among them high viral load during acute phase of the infections. There were no reported proven cases of transfusion transmission of chikungunya.

Seven-day platelets

Similar to 2007, bacterial contamination testing continued to be emphasised at this year's conference with a focus on seven-day platelets and point-of-issue testing (see below). Of great importance this year was the discussion of the impact of the discontinuation of the Post Approval Surveillance Study of Platelet Outcomes, Release Testing (PASSPORT). In January 2008, Caridian BCT (formerly Gambro BCT) and Fenwal (formerly Baxter) announced their decision to suspend the PASSPORT study for sevenday platelet storage. The companies voluntarily suspended the study based on an interim data analysis of the PASSPORT study, along with a review of other published studies, which estimated that up to 50% of bacterially-contaminated platelets may escape detection by culture at 24 hours. The study was halted long before it reached its target of testing 50,000 outdated units (surveillance cultures). Seven-day apheresis platelets were phased out over a 90-day period, instead of the originally proposed four-week timeline.

Testing centres that remained on five-day platelets usually did not have high "outdate" rates and/or argue that a younger platelet is safer and more viable. In an effort to resume the PASSPORT study, the study sponsors recommended the following:

- perform aerobic and anaerobic culture with an 8 mL inoculation in each bottle;
- standardise skin preparation;
- mandate the use of diversion pouches;
- track the age of the platelet product at transfusion for a subset of products;
- institute active surveillance of septic transfusion reactions as a measure of clinical outcome; and
- exclude surveillance cultures in favour of clinical outcome as the more appropriate study endpoint.

Performance of a second test at day five of storage had been raised, but was determined not to be feasible because the products may already be at the hospital transfusion service. Major differences between the industry and FDA proposals for reinstitution of seven-day platelets were discussed at the September 2008 Blood Products Advisory Committee (BPAC) meeting and are listed below:

- the FDA recommends day five bacterial testing and bacterial testing at outdate while industry does not;
- primary outcome for the FDA is septic transfusion reaction rate on day seven, and bacterial contamination rate on day seven, while for industry, it is the septic transfusion reaction rate on days six to seven;
- the criterion for success for the FDA is that the day seven rate is no higher than the day five rate, while for industry, it is that the days six to seven rate is not higher than the day five rate;
- tracking of septic transfusion reactions is active for the FDA and generally passive for industry (active on subset);
- tracking age of transfused products is recommended on all by the FDA and a subset by industry; and
- industry recommends labelling, while the FDA does not.

AABB and other stakeholders concluded that suspension of seven-day platelet availability may avoid two to six septic transfusion reactions per year, while resulting in an increased number of TRALI cases. With apheresis platelets that are predominantly used for transfusion, availability is an issue because of the shortened shelf life of platelets from seven to five days.

Therefore, to meet clinical demand, blood centres must adjust collection schedules, make more frequent deliveries to hospitals, and discard more (apheresis) platelets. Although whole blood-derived platelets would help in providing another source of platelets, they are currently not widely used, with some industry representatives citing the need for infrastructure changes for processing and use as limiting factors.

While the move towards primary reliance of male plasma has taken place, the HLA testing of platelets has been more of the testing focus. The number of available donors would be reduced, and extra testing would cost more money. Thus, blood centres are faced with reduced donor pool, more expensive testing and

logistics, and increased discarding of (apheresis) platelets.

As a result, blood centres have had to compromise on the timing of TRALI mitigation steps (see also TRALI below). The organisation believes that a comprehensive assessment that considered the major morbidity and mortality risks of platelet transfusion conducted prior to the decision to discontinue seven-day platelet availability (PASSPORT) would have allowed for a more informed debate on whether the risks of continuing exceeded the risk of discontinuation.

From a company standpoint at AABB, bioMérieux continued to promote its BacT/Alert system, the leading system for bacterial contamination testing for platelets. Since there were no requirements set for sensitivity in the past, there were many discussions about the optimal bacterial testing protocol (timing of sampling, sample volume, aerobic/anaerobic testing). Based on studies presented at AABB, it is likely that blood bank professionals will now start to increase sample volume based on the company's package insert range of 4 mL to 10 mL per bottle to further increase platelet safety.

Similar to last year, Pall promoted its Leukotrap System with RC2D Filter and the Acrodose PLus System. The Acrodose PLus System allows for the pooling of up to six individual platelet units, and then a sample is taken with the Pall eBDS prior to moving from the pooled bag through a leukocyte filtration device to the final five-day storage bag; any blood collection system can be used. With the discontinuation of the PASSPORT study and the full implementation of TRALI management measures relating to platelet components in November 2008, Pall promoted its Acrodose PLus System as a solution for limited availability of platelets. Pall is also working on a rapid bacterial contamination product that will be targeted towards high-volume processing; the partner with which Pall is collaborating has not yet been announced.

Rapid point-of-issue (POI) tests

POI testing of whole blood-derived platelets may be helpful in increasing platelet availability in light of the discontinuation of the PASSPORT study and the implementation of TRALI management measures in November 2008. However, there is a disagreement over the sensitivity required for this type of testing as the Verax product is currently FDA-cleared as an adjunct test, not a release test.

Verax promoted its Platelet PGD test, which received FDA approval for use with leukoreduced apheresis platelets in September 2007 and CE Mark in September 2008. Although the Verax product was also promoted in the Abbott booth as part of the companies' distribution agreement, it was emphasised less compared to 2007. Verax has clinical trials ongoing to gather data for a release claim as well as to use the product for whole blood-derived platelets, which is where the demand has really been for this type of POI test. Also promoted in the Verax booth was a Mixed Titer Bacteria Panel from ZeptoMetrix, which was developed for use in the clinical trials for the Platelet PGD test.

New this year, Gen-Prime showcased the Dynex DS2 Two Plate Automated ELISA Processing System that will allow for high volume processing of its Bacterial Contamination test. The instrument currently can process 180 samples in approximately three hours. For the automated system, the user would collect a 1 mL sample from a platelet bag, add a reagent to the platelets and spin for three minutes. Following decantation of plasma/reagent liquid, the pellet is manually re-suspended and loaded onto the microtiter plate for analysis.

Similar to last year, Gen-Prime promoted its single test device, the BacSTAT. The total time from collection to results is approximately 20 minutes. Although Gen-Prime's BacSTAT detects the amount of light generated from the oxidation of luciferase to luciferin, which is directly proportional to the level of ATP and has been shown to be a sensitive indicator of viable micro-organisms for detection, the company's automated ELISA-based test uses a recombinant human form of a pattern recognition protein (PRP), which has high affinity binding for sites on peptidoglycan, for detection. The single-use test is anticipated to enter clinical trials by year-end 2008, and the automated instrument is expected to enter clinical trials in 2009.

Similar to last year, Immunetics promoted its BacTx, which is slated to begin clinical trials by year-end 2008. New this year, the company promoted its BacTx 1.3 and 1.4 versions via a video display. The BacTx 1.3, which is a "high throughput" version, can process 100 tests within 60-90 minutes. The BacTx 1.4 is a Near Patient Testing (NPT) version that is in the early stages of development.

Filter technology and special chemistry is expected to eliminate most if not all of the manual steps required by other rapid tests, thus allowing the test to be performed in the blood centre or at the transfusion site with minimal manual labour by technicians, who will not need special training (ie, generalists). Immunetics is working with undisclosed companies to develop these different platforms, but the company has not entered into any partnerships yet. Immunetics is also working on a user interface that provides a number of data management features (print and save), calibration on command, QC runs, HL7 interface, chain of custody (barcode) configuration, audible alarm toggle, password protection, and a tutorial.

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Pathogen reduction/inactivation

There was increased coverage on Pathogen Reduction at AABB 2008 compared to the prior year, including more sessions regarding the topic since the PASSPORT study was halted in April 2008, with the low likelihood of it being reinstated (see Seven Day Platelet Section for more background on the PASSPORT study).

CaridianBCT and Cerus are developing technologies for pathogen reduction. Cerus filed a premarket approval application for INTERCEPT blood system for plasma in 2005 and received approval in Germany and France in January 2007. After AABB 2008, CaridianBCT announced that it received CE Mark approval for its Mirasol pathogen reduction technology system enabling the storing of treated apheresis-collected platelets in Platelet Additive Solution (PAS). The approval provides the flexibility to store platelets in 100% plasma or an approved PAS solution.

The cost associated with pathogen inactivation is high and is one of the downsides to adopting the processes. Suggestions to offset cost include eliminating some current assays, pre-empting future testing, eliminating bacterial testing, eliminating irradiation, allowing for continued mini-pool testing, and reducing donor exclusions based on geography (malaria). As such, there still remain several barriers that will inhibit the industry successfully implementing the pathogen reduction technology.

Additionally, there are concerns regarding the safety of some of the pathogen inactivation agents and the risks associated with introducing these compounds to the blood supply. Although studies for several of the agents have proven this to be untrue, the perception still persists that there are safety issues with p16 ▶

introducing a foreign compound to the blood supply. There is no single pathogen inactivation process for all blood products, which ultimately could produce work flow problems within laboratories. Currently, solvent-detergent and methylene blue have been approved in select country markets for the use with plasma and derivatives, while riboflavin has been approved in select markets for use with platelets.

Psolarens is the only agent approved for plasma, derivatives, and platelets in select country markets. However, the ability to pre-emptively protect the blood supply from emerging diseases is an advantage and would ultimately result in greater protection of the blood supply as there will no longer be a delay from when an emerging disease is recognised as a threat and the need to prevent transmitting that disease through transfusion. While none of the developed pathogen inactivation technologies has been approved by the FDA, several are currently in use ex-US.

BGT automation/molecular BGT

With no new products unveiled or in development in the field of BGT automation, AABB 2008 focused on the upgrades to current automation technology and the conversion to new technology, such as molecular BGT. Biotest promoted the Tango Optimo and its recently approved expanded test menu as well as its recently approved manual reagents (July 2008). The company sponsored workshops on both in order to further promote customer awareness.

Within the US, Biotest took over complete distribution of the Tango Optimo in August 2008, prior to which Olympus handled distribution duties for the instrument in the hospital setting, while Biotest distributed the instrument in the blood bank setting.

Immucor promoted its Galileo Echo and its continued rollout of the system, which received approval in June 2007. In March 2008, Immucor announced the acquisition of BioArray Solutions (BioArray), with the transaction closing in August 2008 for a purchase price of approximately $177m. The Immucor booth featured signs that directed customer attendees to the adjacent BioArray booth. Adoption of molecular BGT is slowly increasing as more laboratories see the advantages compared to traditional BGT technology.

On the Friday prior to the start of the meeting, BioArray held a companion day session where the company released information on a multicentre study evaluating the incorporation of molecular testing technologies in hospital transfusion services.

Micronics attended the AABB 2008 for the first time and displayed a novel technology, the ABORh Card, which allows for simultaneous ABO and Rh testing in less than 30 seconds using a fingerstick. The card is approximately the size of a business card and will be released for donor typing. The company received a research grant at the beginning of October 2008 to continue studies involving the card with the hopes of moving into clinical testing and further product development.

TRALI

HLA and HNA product companies continued to exhibit at AABB this year given the developments within TRALI management. Full implementation of the measures relating to plasma components and whole blood occurred in November 2007 and measures relating to platelet components by November 2008; these measures did not mandate HLA and HNA testing, which is currently one option to help with TRALI management.

If HLA and HNA testing is implemented at testing sites, it seems that it would not be used for deferral of donors, but rather for data gathering and management of use of blood products as antibody levels can be episodic. Also, there appears to be a lack of consensus as to what HNA groups should be tested for, and there is no consensus among countries, or even within a country among regions or testing sites, which is impeding test adoption.

Currently, it is not clear what one does with test results such as deferring all donors that test positive or those that test positive but with no implication. Also, the general concept is that donors with antibodies can be deferred to donate only plasma poor

components as TRALI is seen less often with them; however, this has yet to be officially established (in addition, fractionators do not want to accept plasma with known HLA antibodies).

For platelet donor testing, testing sites may consider testing donors for white cell antibodies; these sites could test all apheresis donors, only donors previously exposed to blood, or only female donors. In addition, they could defer donors implicated in TRALI reactions or develop a system to prevent distribution of plasma rich components from donors with HLA antibodies (maintain donor in donor pool if not implicated in reaction but tests positive for antibodies). In the meantime, it is recommended to reduce collections from donors with likely previous blood exposure and reduce use of plasma rich components (plasma and apheresis platelets).

In May 2007, the ARC implemented a program to produce predominantly male plasma and quickly began running at between 95% to 99%.

On August 6 2008, the FDA approved GTI Diagnostics' (GTI) DonorScreen-HLA test on the QuickStep Automated ELISA Processor (which is manufactured for Biotest by Stratec and is OEM supplied to GTI) to test donor plasma and serum for HLA antibodies. The company displayed the instrumentation in its booth at AABB 2008. The DonorScreenHLA test, which combines the QuikScreen and BScreen ELISA kits with slight modifications, provides class I and class II HLA assays for use on the instrument. The QuickStep has the following features:

- processes plasma or sera samples;
- can screen 176 donor samples (up to four microtiter plates) for both class I and class II HLA antibodies in a single run;
- most kit reagents are ready-to-use and can be directly placed on the instrument;
- donor samples stored for up to 96 hours at room temperature in primary collection tubes can be processed; and
- accepts eight barcodes at a time.

GTI also promoted a new PAK LX test, which is a Luminex-based assay designed to detect anti-platelet antibodies; it was also promoted in the Tepnel booth as Tepnel distributes it ex US. and GTI distributes the product in the US. Similar to last year, One Lambda promoted its LABXpress instrument, a Luminex-based instrument OEM supplied by Stratec for HLA and HNA testing.

Currently, there is no FDA licensed test available for neutrophil antibodies. Additional automated testing platforms are being evaluated for donor testing as manual testing is expensive and time-consuming.

US Biovigilance Network: a public/private Collaborative (USBVN)

Reporting on an update of the inception of the US Biovigilance Network, Dr Matthew Kuehnert, Dr James AuBuchon, and Dr Barbee Whitaker, of the Centers for Disease Control and Prevention (CDC), the Puget Sound Blood Center and AABB respectively, stated that the new date for the kick-off of the pilot study was moved to early 2009; initially the pilot trials were slated for spring 2008 and the nationwide opening of surveillance system in autumn 2008.

Given the complexity of implementing this reporting and benchmarking system across the US, the initial timelines were indeed aggressive. However, this year the audience was given an idea of how data entry screens would appear and examples of the types of output one can get from the system to improve their practice.

Organisers reinforced the numerous benefits to patients and institutions once such a vigilance network is fully operational in the US and expanded upon what the payback would be for the institution's effort (beyond the obvious universal desire for improved patient safety):

- a national system can be used as a surveillance/sentinel function;
- benchmarking at an institution (comparison across nationwide benchmarks and/or same-capacity institutions) will be made possible via data charting and analysis tools a major goal of the project;
- opportunity to learn from reactions and deviations of other hospitals (may identify weak links within hospital and/or aberrant national trends (reactions or errors))j; and
- currently, the user cannot compare from one hospital to another (hospital to hospital definitions of adverse events vary, and so do requirements for reporting to transfusion services).

Of note, the organisers predict that in its first full year of operation, across the institutions that have agreed to participate (following the successful nine-institution pilot study) in the aggregate, the data reporting will be the single largest "biovigilance-based" data repository in the world. (The US Biovigilance Network has commitments from facilities to take part in the network/collaborative that represents approximately 20% of the transfusion activity in the US.

A complete listing of institutions that have agreed to contribute data to the network has been posted on the AABB Web site and is updated as more institutions commit to the program and agree to have their names used; however, the identities of the pilot study institutions have not been disclosed.) Hospital personnel that attended the AABB sessions, as expected, were trying to understand how their current information systems could be integrated with this biovigilance data collection/reporting system in order to minimise any redundant data entry.

As described previously (last year's AABB review in *Clinica*), the CDC and AABB formed this public-private partnership to develop a haemovigilance surveillance system based on the CDC's existing surveillance systems. As such, the backbone of the biovigilance data collection program is the CDC-developed National Healthcare Safety Network (NHSN), a component of which has been used for data collection on nosocomial infections for years (the other capabilities and functions of the NHSN are beyond the scope of this article).

To date, partial funding for the network has taken place, with the most recent September 2008 estimate of $1.3m from private sources. The remaining $2m in funding to cover training and implementation has not been secured as of October 2008, although the AABB has committed to training. The organisers of the US Biovigilance "Collaborative" have remained true to their original phase I mission (Transfusion Service Recipient Hemovigilance), which is to affect the improvement of patient outcomes and safety, initially, for the patient undergoing transfusion of blood, blood components and derivatives (blood donor haemovigilance designed to promote donor health is slated for 2009 as well; other biological therapies will be phased in under the programme for cells, tissues and organs) and to presumably reduced costs over time. See *Clinica* No 1293 (February 2008) for and www.aabb.org/biovigilance for more information.

Next year's update of the pilot studies and initial hospital implementation should be of great interest to hospitals that have already committed to joining the collaborative and no doubt will be watched closely by the international organisations that have maintained (and benefited from) such activity for years to see if any new US-based initiatives could translate into better patient care in their institutions.

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