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TITLE: Hemovigilance: A Quality Tool for Blood Transfusion

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Hello, my name is Matthew Karafin. I am an Associate Medical Director for the BloodCenter of Wisconsin, part of Versiti. Welcome to this Pearl of Laboratory Medicine on "Hemovigilance: A quality tool for blood transfusion."

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The word **hemovigilance** is derived from the combination of the greek word haema, or "blood", and the latin word vigilans, or "watchful". Hemovigilance began in earnest in Japan in 1993 and France in 1994 as a reaction to the events that transpired in the 1980s and early 1990s, when HIV was first defined as a viral agent that could be transmitted by blood transfusion. While several definitions now exist for the modern term hemovigilance, the one to be used for the sake of discussion today is the one now used by the international hemovigilance network. In this definition, hemovigilance is "*a set of surveillance procedures covering the whole transfusion chain, intended to collect and assess information on unexpected or undesirable effects resulting from the therapeutic use of labile blood products, and to prevent their occurrence or recurrence*."

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The basic unit of hemovigilance is the blood transfusion chain. As shown in the figure, an adequate hemovigilance system must be able to account for and monitor all processes that lead

to patient blood transfusion. The interlinked and dependent steps in this chain include: the process of blood collection, including donor monitoring and safety, blood component preparation (or the creation of the common blood components from whole blood, such as red blood cells, platelets, and plasma), blood testing for quality and infectious diseases, blood issuing from the donor center to the hospital and from the hospital transfusion service to the patient, blood transport from the donor service to the hospital and from the hospital transfusion service to the patient, blood administration and monitoring, and hospital physician decision making.

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Hemovigilance is an important part of a quality management system in healthcare. It exists at three levels: 1) the blood collector and hospital, 2) regional or national levels, and 3) international levels. At all 3 levels, the system is structured to observe, record, report, and analyze anything that goes wrong in the blood transfusion chain as noted in the previous slide. Perhaps more importantly, the system is only effective when it can use the lessons learned to take action to avoid future problems.

Recognition of the importance of sharing lessons learned led to, in 2008, the development of the International Surveillance of Transfusion Associated Reaction and Events Database (ISTARE). As of 2016, 23 countries have hemovigilance systems that report data into ISTARE.

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In all hemovigilance systems, there is a reliance on the donor centers or hospital systems to accurately record data into a central database repository. Consequently, systems such as these are all challenged to overcome a number of hurdles to be informative and successful. While we will be unable to describe in this brief lecture all of the solutions to these issues, it is important to realize that hemovigilance systems are often limited by 1) significant delays in the submission and reporting of system data, 2) limited captured detail regarding reported adverse events, 3) an inability of the system to be flexible enough to capture new or evolving problems, 4) data entry errors, 5) limited institutional participation, and 6) limited resources (financial or staffing), such that the system cannot feasibly capture and report what is expected or promised.

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Despite these challenges, it is now well-accepted that national hemovigilance programs can and do impact patient safety. One of the best examples of this comes from the UK's Serious Hazards of Transfusion (SHOT) program.

Specifically, a serial review of reported cases of transfusion-related acute lung injury (TRALI) from 1996 to 2003 demonstrated that the risk was greatest after receiving plasma-rich blood components. They specifically found that there was a 7-8 fold increased risk for TRALI when receiving plasma or platelets, which is often stored in essentially 100% plasma, compared to red cells. Moreover, female donors were more often implicated in these cases.

Because of these observations, Blood Services in the UK introduced risk-reducing strategies, such as the move to all-male donors for fresh frozen plasma in 2003, and the preferential recruitment of male apheresis platelet donors. Newly recruited female platelet donors were also screened for antibodies to human leukocyte antigens, or HLA, and human neutrophil antigens, or HNA, and retested after pregnancies. With the introduction of these strategies, the number of reported TRALI cases were shown to decrease from a peak of 36 suspected cases, and seven deaths, in 2003 to 11 suspected cases, and no deaths, in 2012.

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As I alluded to earlier, many countries around the world now have organized transfusion hemovigilance systems. As you can see on this slide, countries in Europe, Asia, Africa, and North America now have hemovigilance systems that produce written reports and have public websites such that data can be viewed and shared by others.

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For the remainder of this lecture, I will now turn our focus to the United States. Hemovigilance in the United States is truly a highly complex patchwork of separate mandatory and voluntary reporting processes.

At the national level, only fatal transfusion reactions, donation-related deaths, and product deviations discovered after distribution, are required to be reported to the US Food and Drug Administration. This requirement is mandated as part of the Code of Federal Regulations. For

those who are unfamiliar with the term, biological product deviations in transfusion medicine relate to manufactured blood products that are in violation of a rule, standard, or specification. These events are reported publically as annual reports, and can be found on the FDA's website. A representative table from the 2017 annual report is shown on this slide. This table shows the reported number and proportion of deaths from transfusion by etiology from 2013 to 2017. Hopefully, you can see from this table that in 2017, the most commonly reported cause of transfusion-related mortality in the US was from transfusion-associated cardiac overload, or TACO.

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Unfortunately, the reporting of other adverse events from transfusion, such as non-fatal donor and patient reactions, and errors that do not lead to product deviations, are not required in the US. As a result, clinically useful findings such as those produced by the SHOT system in the UK, cannot be currently obtained via a single formal hemovigilance system in the US.

That said, voluntary national reporting systems, however, are available for those who wish to participate.

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In 2010, the Centers for Disease Control and Prevention (CDC) began managing the National Healthcare Safety Network (NHSN) Hemovigilance Module, a free, voluntary, passive surveillance system. This database serves as the only national surveillance platform for recipient hemovigilance that is available for use by all US health care facilities performing transfusions, and captures standardized data on reaction type, including transfusion-transmitted infections, procedure errors, and near-miss events. Data entered into the system may be voluntarily shared by facilities with external partners for patient safety improvement initiatives and to fulfill reporting mandates. Enrollment has steadily increased from 82 facilities in 2010 to 277 facilities in 2016 of the estimated 4600 facilities in the United States, with mandatory reporting required for all 69 facilities in the state of Massachusetts.

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In order to compare adverse events between sites, all aspects of the data elements reported by each site into the database should be as similar and uniform as possible. To account for these interpretive differences, the NHSN created specific terms and definitions that were vetted by subject matter experts to be used by all sites. As an example, for transfusion reactions, 12 different specific diagnostic entities were defined with specific case definition criteria. Additionally, respondents are required to determine reaction severity, or how medically critical the reaction symptoms were, and imputability, or how likely the transfusion was actually the cause of the symptoms.

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As the number of NHSN participating sites continues to increase, the clinical utility of the database continues to improve. In 2015, Harvey et al. identified the frequency and severity of reported adverse events from only 77 participating sites over 2 years, and found that the proportion and frequency of reported adverse events in the US to be comparable to that reported in other countries with larger hemovigilance networks. In 2019, Haass et al. used the data from 195 sites over 6 years to evaluate characteristics of transfusion-transmitted infections in the US. With this much larger sample size, they were able to highlight rare events, such as babesiosis and bacterial infections from older age, day 4 and 5 platelets, that represent current challenges to the safety of the blood supply.

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NHSN is not the only option for hemovigilance monitoring in the US. The AABB Patient Safety Organization (PSO) sponsored a Center for patient safety up until this year, and provided participating hospitals a similar mechanism to NHSN by which adverse transfusion events could be reported and monitored. Additionally, a separate AABB donor hemovigilance program allows blood collection centers to report and monitor donation-related adverse events using the Donor Hemovigilance Analysis and Reporting Tool (DonorHART). As of 2014, 9 US blood centers and 3 hospital blood banks participated in this reporting effort. Lastly, monitoring of emerging infectious diseases, noninfectious complications of transfusion and donation-related reactions have been performed by investigator-led collaborative research initiatives, and include independent efforts by the American Red Cross, Blood Systems Research Institute, and the National Institutes of health, to name a few.

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It is difficult to see what the future holds for national hemovigilance in the United States, but it is quite clear the value it holds for the Transfusion Medicine community. While it does not seem likely that reporting of non-fatal adverse events will become a nationally required activity in the near future, state governments may play a key role in improving participation in critical hemovigilance activities. For instance, in partnership with the Massachusetts Department of Public Health, all licensed blood banks in the state of Massachusetts, as of June 2014, were required to report events into the NHSN. Given the published success of this partnership, Massachusetts represents one example whereby adverse event monitoring could be systematically improved and regulated. Other than that, the future success of national hemovigilance monitoring remains up to us: through dissemination of knowledge, such as through this pearl, it is my hope that all hospitals will see value in this effort, and will volunteer to participate in these important monitoring activities.

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In conclusion, hemovigilance plays a critical quality function at both local and national levels. National hemovigilance efforts, in particular, can be incredibly helpful to public health, as has been seen by the efforts of the SHOT network in the UK to reduce the risk of TRALI. Unfortunately, US national hemovigilance efforts has lagged behind other countries, and even today, consists of a patchwork of disparate national reporting processes. A key challenge for these networks moving forward is increasing the number of voluntary participant's and improving awareness regarding the critical importance of these systems. That said, the data captured in these systems are growing each year, and are beginning to produce important data that can inform future domestic transfusion initiatives to improve blood safety.

Slide 16: References

Slide 17: Disclosures

Slide 18: Thank You from www.TraineeCouncil.org

Thank you for joining me on this Pearl of Laboratory Medicine on “Hemovigilance: A Quality Tool for Blood Transfusion.”