Path-O-Gram
Pathology laboratory news for you!

Dr. Jude Abadie, Editor  January 2022  Volume 3 | No. 1

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I. Department highlights

Accomplishments

- Dr. Attilio Orazi, our Pathology Chair, is the only pathologist in El Paso selected for the Super-Doctors® list for both Pathology and Hematology specialties (https://www.superdoctors.com/texas/El-Paso/Pathology/browse). The selection process for Super Doctors is a rigorous, multi-step process designed to identify providers who have attained a high degree of peer recognition and professional achievement. Super Doctors is a selective, diverse listing of outstanding doctors, representing consumer-oriented medical specialties.

- Additionally, Dr. Orazi authored an update on myeloid neoplasms in The Pathologist (Myeloid Neoplasms...An introduction and brief historical perspective; DEC 2020; pp.12-26). This publication highlights myelodysplastic syndrome in the context of persistent cytopenia, as well as myeloid neoplasms with germline predisposition.

- Dr. Orazi’s 2021 Textbook: Diagnostic Bone Marrow Haematopathology (see cover here) has been published!

- Our pathology department is proud to announce that we will be offering a new clinical pathology elective rotation for our 4th year medical students (MS-4). This elective will include areas in clinical chemistry, hematology, toxicology, medical microbiology, transfusion medicine/blood bank, and molecular pathology.

- Dr. Aaron Geno first authored and communicated a manuscript entitled, “Gamma glutamyl
transferase activity has limited utility in assessment of alkaline phosphatase elevations”. This publication can be found here: J Applied Laboratory Medicine doi.org/10.1093/jalm/jfab085.


The 2019 mass shooting incident at an El Paso Walmart devastated our community. Our TTUHSC-UMC medical heroes demonstrated superior and immediate care for the victims and their families. A mass transfusion aspect of this tragic incident has been published:


Dr. Jesse Qiao and Mr. Bradford Ray led the 1st transfusion patient blood management regional symposium at UMC. The hybrid, (in person and remote) day-long presentation series was attended by professionals locally and internationally.
II. Anatomic Pathology

Lymph Node Tissue Triage
Dr. Osvaldo Padilla

Lymph node (LN) tissue (needle core biopsy or excision) is routinely sent to the pathology department for microscopic evaluation. Sometimes, questions arise on how to the tissue should be sent (“fresh” without or with fixative/formalin?). This guidance is intended to clarify proper submission processes.

Reasons LN tissue is sent to pathology:
- Lymphadenopathy of unknown etiology
- Assessment of potential association with a malignant tumor (metastatic or primary lymphoma)
- Evaluating a malignant neoplasm (e.g., melanoma, breast cancer, gastrointestinal carcinoma) that includes a sentinel LN for staging
- Post-lymphoma treatment to assess residual disease in the LN

Clinical indications for submitting LN without fixative:
- High pre-test probability of lymphoma
- Previous lymphoma diagnosis
  - Flow cytometry studies (FCS) can be used to analyze the phenotypic profile of each of hematopoietic cells (mostly lymphocytes), which can be helpful in diagnosing a lymphoma.
  - “Fresh” LN tissue may be needed for additional studies, such as cytogenetic studies, microbiological cultures, etc.

Clinical indications for submitting LN in formalin:
- High pre-test probability for metastatic carcinoma
- History of metastatic carcinoma
  - FCS are unhelpful in non-hematopoietic neoplasm, and rarely are cytogenetics or microbiological cultures needed.

Can sending tissue fresh/unfixed LN compromise histologic evaluation?
- YES.
- Tissue autolysis begins room temperature.

How can the risk of autolysis be minimized when submitting fresh LN tissue?
- Call the UMC histology department at 915-521-7791 to request a pickup of fresh tissue.
- Place the tissue in a gauze with normal saline to minimize desiccation.
- Place the specimen in a refrigerator for histology pick up. Refrigeration should prevent significant autolysis for about 24 hours.

Contact Dr. Osvaldo Padilla (Osvaldo.padilla@ttuhsc.edu or 915-215-4956) or the histology laboratory with related questions.

III A. Clinical Pathology: Microbiology

COVID-19: Challenges & Triumphs
Dr. Aaron Geno & Mr. Roland Perea

The COVID-19 pandemic affected everyone and every lab, dramatically changing scopes of practice. Our UMC lab was no exception.

Our UMC lab serves the clinical hospital and functions as a reference lab to several institutions throughout the community. UMC does not have sister hospitals, nor is it associated with a large multihospital system for support. Our satellite labs offer limited testing and provides no on-site COVID-19 testing.

The initial wave of the pandemic reached El Paso late. New York and New Jersey had ridden out the first wave by May and had successfully approached a more manageable daily case-count by the time Texas joined Florida and California in leading the 2nd wave through the summer. However, early supply diversions to the Northeast left the lab in the same situation as many labs around the country, struggling to begin testing.

UMC leaned heavily on reference testing early in the pandemic, which gave a result, but at the cost of precious time—the average turnaround time was 87 hours, about 3½ days. This was time that was ill-afforded to be lost, either in confirming the disease in an outpatient, who might continue to expose those around them, or in tying up valuable inpatient resources for a patient who were not infected by the novel coronavirus.

Supply ordering was generally uneventful prior to the pandemic. However, once the WHO classified COVID-19 as a pandemic, everything changed. Our first major challenge was to procure testing—initially close to impossible. Every major vendor who had a SARS-CoV-2 molecular test was placed on government allocation,
leaving labs scrambling. For example, the lead-time for a new Roche molecular analyzer (which uses polymerase chain reaction [PCR] to detect COVID-19) was 7 to 9 months from the time the order was placed and purchased. Sometimes, reagents were unavailable, again due to allocations.

UMC was able to procure analyzers and reagents for our patients due to combined efforts from TTUHSC El Paso and UMC clinical leaders and administrators.

Our first test onsite for SARS-CoV-2 was a rapid nucleic acid test for the Abbott ID Now analyzer. Unfortunately, we were allocated a paltry amount of reagents against an overwhelming volume of patients. Collaborating again, TTUHSC El Paso and UMC created the first internal algorithms guiding when to order and who to test.

Emergency Use Authorization (EUA) became a term/acronym familiar to all laboratorians, clinical personnel, and the public. For our lab, EUA meant we had a green light to use an analyzer and/or test, but we still had to fulfill our regulatory obligation to perform robust validations and implementation protocols against a growing demand. A process that in normal times could take months to be completed, could now be done in days.

Once we were able to implement COVID-19 testing, staff were trained, and ensured testing was available 24/7, or until reagents were exhausted. Challenges included staffing extra phlebotomists to transport samples from the hospital to the lab across the street. CDC guidelines discouraged pneumatic tube systems for use with specimens to be tested for COVID-19.

As our positivity rate rocketed, COVID-19 testing increased, and all other routine laboratory tests increased as well. The increased demand coincided with reduced staff due to caring for ill loved ones if not sick themselves. Our staff maintained all safety rules (social distancing, masks, etc.) to reduce the likelihood of an outbreak through the lab, which would have been catastrophic for our mission and patients.

Our staff rose to the challenges, working long-hours, and overtime to maintain continuous, apparently seamless operations to everyone on the “outside”.

Increased responsibilities, such as morgue duty, quickly became a daunting task for our lab staff. Grim images and stories had emerged from New York City in the earliest heights of the pandemic. People died of COVID-19 at such rates that hospital morgues were unable to keep up with the capacity; refrigerated trucks were required to contain the overflow.

Through its Regional Lab Director, the UMC lab was in conversation with directors in New York as early as March 2020, and was surprised when morgue preparation was the number one takeaway from the experience.

Prior to the pandemic, the lab’s role in the morgue was to monitor temperatures, assist with autopsies, and respond to mortuary requests. This drastically changed during the height of COVID-19 in El Paso, requiring the lab to be present at every single body intake, ensuring that proper wrapping and labeling of the body had taken place. Furthermore, we mitigated space restrictions.

A hospital morgue with a maximum capacity of six, suddenly had to handle storage of over 100 bodies per day at the height of the pandemic in El Paso. Refrigerated trailers were placed at the Medical Examiners’ Office and provided relief for the space, but accumulation was so rapid at times that the morgue would need to be emptied by 5 PM daily to make room for additional bodies arriving the next morning.

The paperwork was voluminous and logistically cumbersome. The hospital was responsible for the body of every decedent until released to Legacy Mortuary Services or a funeral home.

Our lab staff accepted the challenge of the four-hour shifts of “morgue duty,” for work that was physically difficult and emotionally challenging.

**They are all true heroes!**

Night-shift lab staff rotated bodies from refrigerated storage in the morgue to accommodate high turn-over. Managers were sometimes called in the middle of the night for urgent space and transportation requirements.

This pandemic demonstrated how resource-vulnerable we were. Hospital labs associated with large healthcare systems were able to receive reagents and/or analyzers sooner than labs at a single institution. We could not procure analyzers and/or tests as fast as others who had access to more resources and sister hospitals.

UMC laboratory rose past the challenges due to the strong, dedicated, and self-less service of our staff. In
the end, our staff was resilient and demonstrated an unswerving sense of duty to support our physicians and care for our patients.

Again, they are all heroes of our community, we will be forever grateful for their service, and we are proud to have them as part of our lab team!

III. Clinical Pathology: Transfusion Medicine/Coagulation

Is whole blood the transfusion product of choice?
Dr. Jesse Qiao

History of Transfusion Medicine

- 1492: The earliest documented transfusion
  o Patient died immediately, likely due to ABO hemolysis
- 1901: Discovery of the ABO blood groups
- Transfusion therapy using whole blood became more widespread.
- 1970s: Apheresis (separation of whole blood into components), yielded to fractionated products consisting of packed red blood cells (pRBC), platelet concentrates (PLT), and plasma (FFP).
- 1980s: United States has adopted the widespread and exclusive use of component therapy in civilian transfusions.

While apheresis platelets are manufactured instead of platelet concentrates (1 apheresis platelet = 6 pooled platelet concentrates), other components have remained in practice.

Mass transfusions with components in the civilian population presents a special challenge, as the transfusion of pRBCs to FFPs to PLTs struggled to meet the 1:1:1 ratio during early resuscitation. Early administration of plasma leads to improved survival and outcomes. However, thawing of plasma takes at least 20 minutes, often leading to issuing delays. Whole blood transfusions have been consistently used in military and combat trauma. In the last decade, there is emerging research supporting the use of whole blood in civilian trauma.

Presently, whole blood is used in approximately one-third of all major trauma centers across the United States.

- Whole blood has been demonstrated to be safe, even when transfused at large volumes.
- During hemorrhage resuscitation, whole blood is superior to component therapy for a number of reasons: less preparation time, less total anticoagulant transfused, less total donor exposure, better hemostatic ability, and at least equivalent (if not superior) laboratory indices (see Table 1).
- Despite platelets stored at 4°C, their hemostatic potential remains intact for up to 15 days, possibly due to interactions with red blood cells and coagulation proteins in vitro.

Because whole blood contains superior hemostatic potential, early resuscitation using whole blood may achieve hemostasis earlier, potentially decreasing or eliminating the need for subsequent component transfusions. This not only leads to improved utilization and cost, but also decreased donor exposure and potentially mitigates the risks for circulatory overload.

Table 1: Comparison of Resuscitation using Whole Blood versus Reconstituted Blood at 1:1:1 ratio using pRBCs, FFPs, and PLTs.

<table>
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<tr>
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<th>6 units Whole Blood Transfusion</th>
<th>Transfusing 6 Equivalent Reconstituted Components</th>
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<tr>
<td>Total donor exposure</td>
<td>6</td>
<td>13</td>
</tr>
<tr>
<td>Availability from blood bank (if present in inventory)</td>
<td>Immediately</td>
<td>At least 20 minute wait for plasma, if no pre-thawed components ready</td>
</tr>
<tr>
<td>Total volume transfused</td>
<td>3,000</td>
<td>3,680</td>
</tr>
<tr>
<td>Excess anticoagulant transfused</td>
<td>380</td>
<td>1,055 (~670 mL extra)</td>
</tr>
<tr>
<td>Hematocrit of unit</td>
<td>51% (normal)</td>
<td>29% (“anemic blood”)</td>
</tr>
<tr>
<td>Platelet Count of unit</td>
<td>150,000/µL</td>
<td>85,000 / µL</td>
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Coagulation factor activity of unit | Not yet well studied | Estimated at least 80% | 65-70%
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What type of whole blood is available? What is the definition of “low titer”?

- Only individuals who are group O are eligible to donate.
- The predominant whole blood donors are D (Rh) positive, and distinction of units based on Rh type is currently not done.

In addition to being group O, donors must test “low-titer” for Anti-A and Anti-B. The definition of “low-titer” may vary depending on the institution, but they are typically no more than 1:200 to 1:256.

Should there be concern for hemolysis caused by Anti-A and Anti-B in low-titer, group O, whole blood?

Remember: Quantity and dosage matters with regards to hemolysis in general

- ABO hemolysis is severe and clinically significant when there is a forward-type incompatibility (e.g. transfusion of RBCs with incompatible antigen). Reverse-type (back-type) incompatibilities are typically less severe.
- Because all units are tested for low-titer strength, hemolysis (if any) is subclinical and negligible.
- The projected risk of severe hemolysis due to low titer whole blood is 1:120,000, while the theoretical risk for an ABO induced clerical error is 1:80,0005
- Group O, low-titer whole blood is a safe, universal product for use in all individuals; elimination of ABO-related clerical errors.

Potential applications of whole blood outside of adult trauma and mass hemorrhage

**Pediatrics**

- While whole blood is not used for pediatric patients under 40-kg at UMC
- At other institutions across the country (e.g., University of Pittsburgh and University of Texas Health Science Center San Antonio), whole blood is dosed according to weight in pediatric trauma.

There has been no reported adverse effects to date regarding the use of whole blood in the pediatric population.

**Obstetrics**

There may be benefits for the use of whole blood in the setting of postpartum hemorrhage and obstetrical mass hemorrhages.6 However, transfusing excessive plasma contained in whole blood units, when transfusions are not necessary, may lead to adverse effects related to circulatory overload. Further research is needed in the use of whole blood in obstetrics.

- Because the majority of obstetrical patients have a type and screen drawn and tested prior to delivery/C-section, Rh alloimmunization is typically not an issue for all females who test D (Rh) positive prior to delivery.

**Post-Surgical Bleeding, Medicine Patients, and Medicine Subspecialties**

- A unit of whole blood, instead of “1 and 1” pRBC and FFP, may be considered for symptomatic anemia or post-surgical bleeding with concurrent coagulopathy.
- Hemodynamically stable patients often have specific transfusion needs in which component therapy is adequate (e.g., heme/onc patients with thrombocytopenia and petechiae only need platelets).
- Transfusions to correct a laboratory value alone in the absence of clinical context or symptoms is not recommended.

**Logistical limitations of whole blood**

- Compared to pRBCs with a 42-day shelf life, whole blood has a shelf life of 21 days
- Cold-stored platelet functions decrease after 15-21 days.
- Transfusing whole blood may not always be required and depends on the clinical setting, as well as other lab results such as viscoelastic testing (e.g., ROTEM).

Community blood supply is more limited than components, as the donors not only must be group O, but they must also be tested for Anti-A and Anti-B titers.
Conclusions

- The use of whole blood, ROTEM, and tranexamic acid (TXA) provides current state of the art trauma resuscitation at UMC.
- Whole Blood has clear and distinct advantages and better hemostatic potential during initial resuscitation of acute mass hemorrhage of any etiology.
- Recent studies performed report at least similar outcomes between whole blood and component resuscitation (moderate improvement with whole blood).
- Ongoing large-scale clinical studies continue to demonstrate the efficacy and outcomes of whole blood.
- Use of whole blood in other settings is not well explored, but given its efficacy and improved hemostatic potential, may be used in other specialties with judicious clinical decisions.

References


Direct questions to Dr. Jesse Qiao. Medical Director, Blood Bank and Transfusion Services at University Medical Center El Paso; Laboratory Medical Director, Hospitals of Providence at Transmountain jesse.qiao@ttuhs.edu

III D. Clinical Pathology:

High-Sensitivity Cardiac Troponin (cTn)

The next chapter....

Dr. Jude Abadie

Our laboratory will be transitioning from the current, contemporary cTnI assay to a high-sensitivity cardiac troponin (hs-cTn) assay in 12-18 months.

Managing acute coronary syndrome (ACS) remains a major challenge in laboratory medicine, and ACS can be discussed in the context of:

- Non-ST elevation myocardial infarction (NSTEMI)
- ST-elevation myocardial infarction (STEMI)
- Unstable angina with or without EKG changes

With respect to AMIs in the United States:

- There are > 600,000 new and > 200,000 recurrent AMI annually
- Only 1/5th of those have continual chest pain.
- There are > 6 million ER visits due to chest pain
- Up to 5% of AMIs are “missed”.
- Fewer than half of patients present in the ED < 2 hours of symptom onset.
- Mortality rates are highest for those over 45 years old and higher for females.

Diagnostic challenges include:

- Differentiating cause of chest pain
- Managing patients with slightly elevated cTn

Myocardium consists of three troponin proteins. This protein complex (cTnI, cTnT, and cTnC) regulates calcium mediated myocardial actin and myosin contraction. Only cTnI and cTnT are specific to heart muscle. Therefore, cTnC is not used to assess AMIs. Analytical assays can measure cTnI or cTnT in the circulation of patient who are having an AMI. cTn detection and interpretation depends on time of presentation and the extend of myocardial injury.

Defining characteristics of an AMI

- A rise and/or fall (delta cTn) of cardiac troponin above the 99th %-tile
- One of those cTn levels should be above the 99th %-tile of the assay, as determined from a reference/normal population
- EKG evidence of myocardial ischemia
- Other defining criteria are related to differentiating myocardial injury (chronic cTn elevation— mycarditis vs. infarction (ischemia + delta cTn)

Definition of hs-cTn is an analytical characteristic that includes a coefficient of variation (CV) ≤ 10% at the 99th%-tile at

Characteristics of hs-cTn assays vs. contemporary cTn assays:

- Higher analytical sensitivity allows for targeted diagnostic approaches to rule-in or -out AMI.
- Decreased number of serial sampling to make a diagnosis through measurable increases and decreases in cTn levels (Accelerated Diagnostic Protocols).
- A sole hs-cTn result be defined to meet specific clinical needs in some cases.
- Reporting sex-specific upper reference limits (i.e., 99th %tile) to address cardiac physiologic differences between males and females:
  - higher myocardial mass in males
  - discordant cardiovascular health and risks between males and females.

One striking difference between the high-sensitivity and contemporary cTn assays is the reporting units, as espoused by the International Federation of Clinical Chemistry (IFCC)

- The contemporary cTn assay is reported in ng/mL, and results are reported as a decimal.
- The hs-cTn assay is reported in ng/L, and results are reported in whole numbers.
- A contemporary cTn assay result of 0.014 ng/mL would be reported in our lab as 0.01 ng/mL.
- A hs-cTn assay with the same result would be reported as 14 ng/L.

Before we implement the new hs-cTn assay, reference interval studies will need to be established for our population, as well as clinical decision cut-points. This will require about 250 reference males and 250 reference females to establish the 99th %tile and other samples to determine the utility of cut-points from patients presenting to the emergency room with chest pain.

It is essential that the validation of our new hs-cTn be established through collaborative efforts among pathology, cardiology, and emergency medicine.

Key points to remember:
- Hs-cTn are defined in the context of analytical (not clinical) sensitivity.
- A % CV < 10% at the 99th % tile
- Results reported in whole numbers
- Sex-specific decision points
- In the context of the clinical presentation, an AMI can be ruled-out with fewer serial cTn tests within 3 hours.
- More than one cTn result, used with delta cTn values, can support an AMI diagnosis.
- Delta cTn values can differentiate between myocardial injury and myocardial infarction.

- Acute changes in high-sensitivity troponin are essential for interpretation and diagnosis of either myocardial infarction or myocardial injury.
- The hs-cTn assay is a test performed on laboratory instrumentation and cannot be performed on a point-of-care device.
- It’s essential that validation of our new hs-cTn is established through collaborative efforts among pathology, cardiology, & emergency medicine.

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**Lab Update Brief (LUB)**

**Dr. Jude Abadie**

**Osmolality testing resumes in-house:** The UMC laboratory acquired and validated our new osmometer so that we are performing osmolality testing back in-house as of 15 October 2021. The previous instrument experienced mechanical problems that could not be addressed by the vendor. Therefore, we were sending osmolality testing to a local lab during the time while waiting to acquire the new instrumentation. Subsequently, we performed and reviewed all validation studies so that we were able to resume in-house testing.

**Biotin message when reviewing patient results:**
The lengthy biotin warning accompanying some patient results have been shortened to the following:

- "Biotin can interfere with **TEST NAME** testing and may lead to inaccurate results that do not correlate clinically. Instruct patients to stop biotin 2 days prior to phlebotomy to mitigate testing interference."

- This shorter message is intended to make result reviews more efficient.

**Removing Creatine Kinase MB isoenzyme (CK-MB) from our testing menu:**

- As the result of discussions among Pathology, Internal Medicine, and EM, the UMC pathology laboratory will be removing CK-MB as an in-house testing option on 17 JAN 2022. This has been reviewed with our medical staff, and the reasons for removal are explained here.

- The American Association of Clinical Chemistry guidelines state that routine measurement of CKMB is no longer indicated when evaluating patients with a possible acute coronary syndrome (ACS) or reinfarction.

- CK-MB testing provides no added value to patient care and only adds to testing cost, and has no
longer has clinical value in order-sets when troponin testing is available. Cardiac troponin (cTnT or cTnI) are superior markers of myocardial injury, infarction, and re-infarction diagnosis.

Address questions to Dr. Jude Abadie: judie.abadie@ttuhsc.edu

Removing Cyclic Citrullinated Antibodies (CCP AB IGG/IGA) from our testing menu:
- Effective December 1, the orderable for Cyclic Citrullinated Antibodies (CCP AB IGG/IGA) will be removed from the UMC laboratory order-set.
- The preferred orderable test is “Cyclic Citrullinated Peptide Ab”, which will be renamed to “Cyclic Citrullinated Peptide (CCP) Antibody.”
- This change is being made to reduce ordering confusion and support correct ordering.
- There is no established clinical benefit to the inclusion of CCP IgA in CCP antibody testing, and CCP IgA is not reported separately in this testing.
- CCP AB IGG/IGA is sent outside of our preferred contracted laboratory, incurring additional expense and requiring the reporting of laboratory results as a scanned document rather than included with the patient’s other laboratory results.

Testosterone testing guidance: Keep in mind that the most accurate and clinically actionable testosterone results should be performed on samples drawn from patients who are fasting and prior to 10 a.m. or prior 3-hrs after waking for shift workers. Fasting or time-of-draw is not restricted for patients who are on testosterone replacement therapy (Testosterone Therapy for Hypogonadism Guideline Resources | Endocrine Society).