Critically Appraised Topics

For Practice in Low- and Middle-Income countries

October 22, 2021

Transfusion guidelines in low-resource settings for patients with severe anemia

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Background:

Low and middle income countries can have difficulty providing safe blood transfusions due to lack of donors and high frequency of transfusion-transmissible infections such as Hepatitis B, Hepatitis C, and HIV. Blood must be collected and used locally, which requires a large donor pool. The blood collection process must be organized, and the testing and processing of blood is associated with further financial costs and clinical and laboratory skills. An obvious major risk of transfusing unsafe blood is morbidity and mortality from infections, though there is an insidious risk of undermining trust in health care.

Demand for blood products in sub-Saharan Africa includes acutely anemic patients (malaria, peripartum hemorrhage) and patients with chronic anemia (sickle cell disease). Standardized national guidelines for blood transfusion protocols can be challenging to follow due to supply-demand mismatch and under-resourced settings. High-resource countries have shown that there is no significant difference in outcomes with a hemoglobin transfusion threshold of 7g/dL compared to 8-9g/dL, but a threshold of 7g/dL is quite challenging to achieve in under-resourced settings. Literature review demonstrates that research trials conducted in sub-Saharan African countries aim to pinpoint the transfusion threshold which is associated with significantly improved clinical outcomes.

Question:

In low-resource settings for children with severe anemia, what transfusion practices promote the best clinical outcome?

- *Problem/Patient: Patients with severe anemia in low-resource settings*
- *Intervention: Blood transfusions*
- *Comparison: Patients who do not receive proposed treatment per guideline*
- *Outcome: Difference in morbidity and mortality*

Evidence:

1) **Problems and Approaches for Blood Transfusion in the Developing Countries**
    a) Background: LMIC can have difficulty providing safe blood due to lack of donors and high frequency of transfusion-transmissible infections.
    b) Safety: direct morbidity and mortality from transfusion of infected blood as well as **undermining trust in health care**. Reduce unnecessary transfusions through appropriate clinical use of blood including use of IVF as alternative therapy when possible
    c) Supply
        i) Recruiting voluntary donors is expensive, requires regular education programs, **collection teams, vehicles, cold storage**
        ii) Understand local beliefs surrounding blood and donation (related to kinship or personal health)

iii) In Africa as a whole in 2002, WHO estimated that more than 60% of blood originated from family/replacement donors

d) Use of blood products
   i) Most transfusions in sub-Saharan African given for life-threatening emergencies
   ii) Clinical guidelines suggest transfusions for children indicated if Hgb <40 or 50g/L with symptoms of decompensation

	Indications for Transfusion		Volume and Speed of Transfusion
	Hb Level (g/L)	Clinical Symptoms	
WHO Pocket Book of Hospital Care for Children (2005)	40 or less OR 60 or less PLUS 1 or more	Not required Deep and labored breathing Cardiac failure Clinical dehydration or shock Impaired concentration Malaria parasitaemia >10%	20 mL/kg whole blood or 10 mL/kg packed cells over 3–4 h
Kenya Guidelines for Appropriate Use of Blood and Blood Products (2004)	<40 OR <50 PLUS	Not required Respiratory distress	20 mL/kg whole blood over 3–4 h
Ugandan National Guidelines (2010)	40 or less OR 60 or less PLUS 1 or more	Not required Hypoxia Cardiac decompensation Acidosis Impaired consciousness or cerebral malaria Septicaemia Meningitis Malaria parasitaemia >20%	20 mL/kg whole blood or 10 mL/kg packed cells over 3–4 h
Tanzania National Malaria Guidelines (2006)	40 or less OR 60 or less PLUS	Not required Cardiac failure	20 mL/kg whole blood or 10 mL/kg packed cells over 3–4 h

e) Common recipients of transfusions: children (malaria-related anemia), pregnant women (hemorrhagic emergencies), trauma patients
   i) **Chronic blood transfusion** has improved outcomes for patients with severe sickle cell disease in North America, but implementing these regimens in Africa has challenges: costs, unreliable/insufficient blood supply, cultural beliefs, transfusion reactions

f) System
   i) When an individual hospital provides transfusion service, huge burden on lab resources: overall cost 35% of total costs in a typical district hospital in southern Africa

2) Development and evaluation of a new paediatric blood transfusion protocol for Africa

a) Background: In some parts of sub-Saharan Africa, 20-47% of anemic children get transfused during their hospital stay. With each transfusion comes the risk of infection and depleting the supply for ill patients. Although protocols exist for pediatric transfusion, they are variably followed.

b) Methods:
   i) Took place at **Queen Elizabeth Central Hospital in Malawi**
   ii) Compared transfusion practices with existing guidelines vs new guidelines put forth for the study
      (1) Old guidelines: Hb <5 or Hb <6 in unwell children; 20mL/kg whole blood (10 pRBCs), give ½ if malnourished (to avoid volume overload)
      (2) New guidelines: **complicated (respiratory distress, neurological changes, circulatory changes), uncomplicated, severely malnourished (visible wasting or pitting edema bilateral feet)**

(a) Followed WHO guidelines, but changed wording to more simple, concrete terms

c) Results:
   i) Old guidelines: 29 patients; 11 complicated, 10 transfused, 1 died waiting for transfusion; 11 uncomplicated, all transfused; 7 severely malnourished
      (1) Enough blood for transfusion in 19/28 cases
   ii) New guidelines: 215 children; 180 complicated, 25 uncomplicated, 10 malnourished
      (1) 17 not transfused (12 uncomplicated, 5 malnourished)- potential **29% decrease in transfusions**
      (2) Good adherence w/ plain language and easy bedside analysis
d) Conclusions:
   i) Adapting WHO guidelines into more clinically-relevant, understandable terms can **increase compliance**
   ii) Potential to avoid unnecessary transfusions (saving blood and avoiding risks that accompany transfusions) with new guidelines

3) Phase II Trial of Standard versus Increased Transfusion Volume in Ugandan Children with Acute Severe Anemia

a) Background
   i) Severe anemia (Hb <6) **leading cause of pediatric admissions** in Africa, significant in-hospital mortality. Etiology is often infectious.
   ii) Guidelines encouraged 20mL/kg for transfusion, commonly associated w/ need for repeat transfusions/poor outcome leading to poor adherence to guidelines, high in-hospital mortality (9-10%).
   iii) Only 2.3 units blood donated per 1,000 in sub-Saharan Africa (vs 8.1 and 36.7 in medium and high-income countries), **usually whole blood vs pRBCs**. 63% of early deaths in emergency situations occur while awaiting blood.
b) Methods: Safety and efficacy of 30mL/kg vs 20mL/kg for 24hr anemia correction and 28 day survival in 155 Ugandan children
   i) Two clinical centers in Eastern Uganda, randomized children >60days and <12yrs old
   ii) 20% had sickle cell, 59% positive malaria slide or RDT; 50% respiratory distress, 30% lactic acidosis
c) Results:
   i) 24hr results: 90% in 30mL group corrected, 74% 20mL group corrected, greater reductions in lactate in 30mL group
   ii) 28 days: 6 children (7%) 20mL group died, 1 in 30mL group, no difference in end Hb
d) Conclusion:
   i) **Higher-volume transfusion had no increased harm** and resulted in faster hematologic recovery with less need for repeat transfusions, theoretically limiting risk of multiple donors

4) Transfusion thresholds and other strategies for allogeneic red blood cell transfusion

a) Background:
   i) Uncertainty regarding optimal Hgb threshold for use of RBC transfusion in anemic patients. Blood is scarce resource and transfusions may be less safe in some countries due to lack of pathogen testing. Objective: compare **30-day mortality** and other outcomes in participants randomized to **restrictive (7g/dL) vs liberal (8-9g/dL)** RBC transfusion thresholds for all conditions

b) Methods
    i) Selected randomized trials where intervention groups were assigned on the basis of a clear transfusion trigger, then pooled risk ratios of clinical outcomes across trials.
c) Results
    i) 31 trials, 12,587 participants. About half used 7g/dL threshold, others used 8-9g/dL. Restrictive transfusion strategies reduced risk of receiving RBC transfusion by 43% (RR 0.57, 95% CI 0.49-0.65). Restrictive strategies didn't alter risk of 30d mortality compared to liberal strategies (RR 0.97, 95% CI 0.81-1.16) or any other outcomes assessed (cardiac events, MI, stroke, thromboembolism). Liberal transfusion didn't affect risk of infection (PNA, wound, bacteremia)
d) Conclusions
    i) No evidence that restrictive transfusion strategy impacts 30-day mortality or morbidity compared with liberal transfusion strategy. Insufficient data in some subgroups (ACS, MI, neurological injury/TBI, acute neurological disorders, stroke, thrombocytopenia, cancer, bone marrow failure).

5) Anemia and Blood Transfusion in African Children Presenting to Hospital with Severe Febrile Illness

a) Background:
    i) Severe anemia in children is a leading cause for admission, and accounts for high-proportion of malaria-related deaths
    ii) WHO guidelines promote **rational use of transfusion to preserve scarce resource**, but adherence is variable
b) Methods: Large RCT, 2009-2011 at 6 centers in 3 East African Countries (Kenya, Tanzania, Uganda)
    i) Eligible children: 60 days - 12 years, presented with severe febrile illness with impaired consciousness and/or respiratory distress, plus one sign of impaired peripheral perfusion
    ii) Followed WHO guidelines of transfusion, administered over 4h
    iii) Randomized children to immediate bolus of saline or human albumin
c) Results:
    i) 76% children anemic, 33% severe (Hb <5)
    ii) 45% transfused, 23% required re-transfusion; 94% severely anemic children transfused, 29% receiving >2 transfusions; 70% moderate anemia (Hb 5-7) transfused, 12% mild anemia
        (1) Predictors of re-transfusion: admission Hb, coma, pallor, severe tachycardia
        (2) Of the **severely-anemic children who were not transfused within the first 8 hours, 52% died (100% within 5 hours)**; for the 70% who died total, found likely to be myocardial dysfunction
    iii) 91% of all deaths within 24 hours
    iv) Increased mortality with fluid boluses, no matter initial Hb
d) Conclusions:
    i) High rate of re-transfusion suggest that **current guidelines may undertreat significant proportion of children**
    ii) Adherence to WHO guidelines overall poor
    iii) Increased mortality with fluid boluses at all levels of admission Hb

6) Chronic blood transfusion for primary and secondary stroke prevention in Nigerian children with sickle cell disease: A 5-year appraisal

a) Background
    i) Sickle cell disease is a leading genetic disorder worldwide, #1 genetic disorder in Nigeria (2-3% newborns have disease, 25% of population are carriers)

ii) Stroke is seen in 10% of children with SCD
iii) **Chronic blood transfusion (CBT)** is recommended treatment for primary and secondary stroke prevention. Recommend for all children with abnormal cerebral blood flow on transcranial Doppler.
iv) Problems: high cost of repeated transfusions, unavailability of blood, risk of infections, transfusion reactions, iron overload, iron chelation cost (CBT + iron chelation USD 50,000/patient/year)

b) Methods
i) All new cases of SCD with indication for CBT seen over 5 years (Jan '08 to Dec '12) at Paediatric Hematology and Paediatric Neurology clinics of University College Hospital in Ibadan, Nigeria (tertiary center, 810 bed hospital, 180 beds for peds). Weekly TCD clinic, free routine screenings.
ii) Children eligible if SCD confirmed by hgb electrophoresis and had either abnormal TCDs x2, 1 week apart (category A = primary prevention) or history of stroke event determined by clinical signs (category B = secondary prevention).
iii) Children placed on chronic transfusion program = partial exchange blood transfusion given monthly with Hgb A blood. Families requested to provide blood donors after screening negative for HBV/HCV/HIV/syphilis
iv) Children monitored with monthly CBC, Hgb S level, LFT, Fe/ferritin/TIBC. Aim to keep HgbS <30% and maintain Hgb >10g/dL
v) If caregiver declined CBT, were offered oral hydroxyurea (starting 10 mg/kg/day with increase to 25 mg/kg/day)

c) Results
i) 50 children with need for CBT, indication stroke in 30 and abnormal TCD velocities in 20. All had homozygous sickle cell anemia. Duration of follow up ranged from 8 to 60 months, mean 27.3 months.
ii) **Caregivers of 5 (10%) of children with indication for CBT consented to treatment**. 4 had previously had stroke, one child's caregiver originally declined, then child developed stroke 38 months after first TCD exam, and caregiver consented to CBT after this event
iii) Higher social class of parents associated with acceptance of CBT (p = 0.008)
iv) CBT outcomes: 1 child died during sixth session of blood transfusion from severe blood-transfusion-related reaction
v) Declining CBT: 90% declined. **93.3% cited unaffordable cost of care**, 88.9% cited need to get blood donor every month before child could receive transfusion, 84.4% transfusion would need to go on several years, 77.8% fear of dangers assoc with multiple blood transfusions
vi) Cost of CBT (without iron chelation) = USD 2,314-5,338 annually. Didn't estimate cost of child's repeated absenteeism from school

d) Discussion
i) 1-2 of every 10 new cases of homozygous SS disease seen at this center in Nigeria requires CBT for primary or secondary stroke prevention
ii) Major barriers to CBT uptake: cost, provision of donor blood transfusion
iii) 70% of Nigerians live on less than a dollar/day, medical expenses are largely out-of-pocket, 10% have health insurance

Discussion and Limitations:

Current WHO guidelines strive to conserve the limited resource of blood and minimize exposure to potential transfusion reactions. For children, current WHO guidelines advise transfusion for all patients with Hb <4 and for children with Hb 4-6 with accompanying signs of cardiovascular, respiratory, or neurologic compromise. However, multiple studies that we reviewed demonstrated that these guidelines are often followed inconsistently. One study demonstrated improved adherence to the guidelines and a potential for significant avoidance of unnecessary transfusions by adapting the language into a more clinically-relevant and tangible form (2). However, this was a small study, and it is unclear how much of the increased adherence may have come from the presence of oversight and education by the study administrators.

Additionally, several studies have suggested that the amount of blood recommended by the WHO guidelines may be insufficient to resuscitate many severely anemic children. This may lead to possible mistrust in the guidelines and non-adherence. Current guidelines are 20mL/kg whole blood (10mL/kg pRBCs). The FEAST study showed a 29% re-transfusion rate in their severely-anemic cohort (5). Another study we examined demonstrated a faster correction of anemia and lactic acidosis with no increased morbidity or mortality, using 30mL/kg vs 20mL/kg (3). Given that the majority of deaths from severe anemia occur within 24h of admission, there is likely a significant benefit to more rapid correction of anemia. Additionally, reducing re-transfusion also reduces the need for multiple donors and therefore the risk of infection. Given that this study was rather small, further studies are likely needed to fully evaluate the safety of the increased 30mL/kg transfusion guideline.

Ultimately, our research has demonstrated that there may be benefits to increased transfusion volume in children. Our research demonstrated increased mortality associated with pre-transfusion fluid boluses, regardless of baseline hemoglobin. Additionally, for there to be more consistent adherence to guidelines, they should be written in more concrete, simple language that busy clinicians may easily interpret. Finally, there are many patient-specific barriers to blood transfusion that may limit access, such as cost and provision of donor blood. As of yet, there is no research published on specific transfusion guidelines for chronic anemia.

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Critically Appraised Topic

Ultrasound vs. CT for suspected diverticulitis

UPMC GH Seminar 2021

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Background

Diverticular disease (in particular, diverticulosis and diverticulitis) has historically occurred at dramatically different rates between the Global North and the Global South [1]. It is thought that one of the key risk factors is a diet rich in refined sugars and poor in natural fibers, which was initially prevalent in just the Western world. Recently, however, processed foods have started to become more common in low and middle-income countries – most notably India and Sub-Saharan Africa [2,3].

In the US, the American Society of Colon and Rectal Surgeons identify CT as the most appropriate first-line imaging modality [4]. However, this may not be feasible in rural/under-resourced settings: in this CAT we explore the utility of ultrasound as a first-line imaging modality for the diagnosis of acute diverticulitis.

Clinical Question

In a resource-limited setting, in patients with suspected acute diverticulitis, what is the comparative diagnostic accuracy of ultrasound as compared to CT?

Evidence & Search Terms

In order to gather evidence relevant to this clinical question, we searched for prospective studies and systematic reviews of prospective studies with the search terms “ultrasound, CT, computed tomography, diverticulitis, diverticular disease”.

The most comprehensive reviews were cited by the European Federation of Societies for Ultrasound in Medicine and Biology:

- Lameris et al 2008 [5]
    - N = 12 prospective diagnostic accuracy studies
    - Sensitivity: US – 92%; CT – 94%
    - Specificity: US – 90%; CT – 99%
- Andeweg et al 2014 [6]
    - N = 8 prospective, diagnostic studies
    - Sensitivity: US – 90%; CT – 95%
    - Specificity: US – 90%; CT – 96%

Caveats

These studies included numerous methodological caveats. Neither meta-analysis included many head-to-head comparisons of U/S to CT (they were primarily composed of papers that were looking specifically at one imaging modality), so there is the potential for bias between populations selected for U/S and CT. Study settings were also heterogenous, combining studies of patients admitted to hospital floors with all-comers to ED with suspected diverticulitis. The “gold standard” verification of diagnoses is highly variable between studies – ranging from histopathology in surgery to “expert panel” review of CT. Lastly, it is difficult to

generalize the PPVs to under-resourced settings – all prospective studies included in both meta-analyses were from Europe and the USA, areas with much prevalence of diverticular disease than most LMICs.

Takeaways/Applicability

EFSUMB recommends using US as first-line imaging technique for diagnosis of acute diverticulitis with the benefits of better availability, low cost, no radiation, lack of contrast, and acceptability with uncomplicated diverticulitis. They further recommend a “2nd look” with US if there is no clinical improvement within 72 hours with consideration for CT as a “step up” method in more complicated cases. These include deeper inflammation, distal sigmoid colon involvement, significant obesity, planning for surgical/interventional drainage, plans for immediate surgery, or increased suspicion for alternative diseases.

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Critically Appraised Topic: Utility of chest radiography compared to point-of-care lung ultrasound in diagnosing acute decompensated heart failure

Ato Howard

BACKGROUND

Chest radiography (CXR) is commonly used in the diagnosis of acute decompensated heart failure (ADHF) and is generally considered to be quick and inexpensive in the U.S., however it may be misleading in emergency department (ED) patients with ADHF, leading to misdiagnosis and mistreatment [1].

In resource-limited settings where cost, distance from a center with chest radiography and ease/speed of use in reaching a diagnosis are typical limitations, it is reasonable to consider the utility of other imaging modalities for accurate diagnosis. A small study of 99 patients from a teaching hospital ED in Rwanda showed that for patients with dyspnea, the most frequent discharge diagnosis was ADHF. In addition, this same study showed that when point-of-care ultrasonography (POCUS) was incorporated, the diagnostic accuracy of ADHF was **increased from 53.8% to 100% pre- and post-ultrasound** with an increase in clinician confidence and diagnostic accuracy [2].

Also, one review discussed how bedside point-of-care lung ultrasonography (LUS) was a great adjunct to echocardiography with superiority to auscultation and CXR, hence urging for more adoption into routine cardiology practice [3]. This brief review seeks to shed more light on the available data/evidence to guide imaging modality preference for accurate diagnosis of ADHF.

SEARCH TERMS: diagnosis; decompensated heart failure; chest radiography; CXR; underserved; low-income; access; available; availability; POCUS; point of care ultrasound

Problem/**p**atient: patients with ADHF | **I**ntervention: CXR | **C**omparison: LUS | **O**utcome: accurate diagnosis of ADHF

EVIDENCE

I. Prevalence of negative chest radiography results in the emergency department patient with decompensated heart failure [1].
   - Comparative study including 85376 patients from the Acute Decompensated Heart Failure National Registry (ADHERE): registry of patients with a primary hospital discharge diagnosis of heart failure.
   - 15937 patients **(18.7%)** had **no sign of congestion of ED CXR**.
   - There were more patients with **negative CXR** who had non-ADHF admitting diagnosis (23.3%) compared to patients who had **positive CXR** with non-ADHF admitting diagnosis (13.0%).
   - It was more likely to have a non-ADHF diagnosis WITH a negative CXR, however almost 20% of patients admitted from ED who in fact had ADHF also had negative CXR.

II. Diagnostic Accuracy of Point-of-Care Lung Ultrasonography and Chest Radiography in Adults With Symptoms Suggestive of Acute Decompensated Heart Failure: A Systematic Review and Meta-analysis [4].
   - Meta-analysis of 1827 patients across 6 studies that investigated the diagnostic accuracy of patients who presented to any clinical setting with dyspnea.
   - Patients underwent both LUS and CXR on initial assessment with compared to reference standard for ADHF which included BNP and ECHO findings.
   - Pooled estimates: **LUS sensitivity 0.88**, specificity 0.90; **CXR sensitivity 0.73**, specificity 0.90
   - The superiority of LUS sensitivity compared to CXR for ADHF diagnosis was statistically significant $p < 0.001$.

III. Lung ultrasound integrated with clinical assessment for the diagnosis of acute decompensated heart failure in the emergency department: a randomized controlled trial [5].
- Randomized controlled trial of 518 patients comparing diagnostic accuracy and clinical usefulness of LUS and CXR/NT-proBNP in addition to clinical evaluation.
- Addition of LUS to clinical evaluation **increased diagnostic accuracy of identifying ADHF** with statistical significance ($p < 0.01$) whereas use of CXR/NT-proBNP did not significantly increase diagnostic accuracy of ADHF ($p > 0.05$).
- Again, diagnostic accuracy of LUS-integrated approach was **higher than** that of the CXR/NT-proBNP-integrated approach with **AUC 0.95 vs. 0.87, $p < 0.01$**.

IV. Emergency department ultrasound for the detection of B-lines in the early diagnosis of acute decompensated heart failure: a systematic review and meta-analysis [6].
- Meta-analysis of 1861 patients across 7 studies that investigated sensitivity of B-lines from early LUS in patients presenting with dyspnea for ADHF.
- For diagnosis of ADHF, bedside LUS identification of B-lines had a **pooled sensitivity of 82.5% & pooled specificity of 83.6%**.

DISCUSSION

Based on above studies, for the diagnosis of ADHF the sensitivity of LUS was ~82.5%-88% compared to sensitivity of CXR at ~73%-81.3% [1, 4, 6]. With other smaller evidence/lower quality evidence also discussing feasibility of POCUS and reflecting similar superiority of LUS compared to CXR, it appears very reasonable to suggest the incorporation of LUS into diagnostic algorithms when ADHF is being considered [2, 3, 5-7].

Considering incorporation of POCUS/LUS in diagnostic algorithm of ADHF in low-income countries or low-resource settings, areas for further study could be the immediate-term and long-term cost effectiveness of this incorporation, as well as other outcomes including impact on mortality and length of hospital stay [7]. Nonetheless, incorporating POCUS/LUS could decrease the burden of dependence on CXR for diagnoses of ADHF and allow for more use of CXR in diagnosing other etiologies of dyspnea in low-resource or low-income settings.

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Clinically Appraised Topic (CAT): TXA and Upper GI Bleeds

Valerie Gobao

Clinical question: In adults with acute upper GI bleed, does administration of TXA with standard therapies decrease mortality or need for transfusion in comparison to standard therapy alone?

Clinical Bottom Line: TXA administration does not reduce mortality or blood transfusion secondary to acute GI bleeding when compared to standard therapy alone.

Citation: HALT-IT Trial Collaborators. Effects of a high-dose 24-h infusion of tranexamic acid on death and thromboembolic events in patients with acute gastrointestinal bleeding (HALT-IT): an international randomised, double-blind, placebo-controlled trial. Lancet. 2020 Jun 20;395(10241):1927-1936. doi: 10.1016/S0140-6736(20)30848-5. PMID: 32563378; PMCID: PMC7306161.

Karadaş A, Doğan NÖ, Pinar SG, Yeşil O, Pekdemir M, Yilmaz S, Yaka E. A randomized controlled trial of the effects of local tranexamic acid on mortality, rebleeding, and recurrent endoscopy need in patients with upper gastrointestinal hemorrhage. Eur J Gastroenterol Hepatol. 2020 Jan;32(1):26-31. doi: 10.1097/MEG.0000000000001555. PMID: 31567714.

Background/rationale for study: Acute upper GI bleeding is a common cause of morbidity and mortality around the world. In many countries, blood product transfusions are either difficult to access and/or poorly regulated (leading to reactions and infectious complications). TXA is a cost-effective, antifibrinolytic agent commonly used in trauma, obstetric trauma, and orthopedic surgery to reduce bleeding. A meta-analysis in 2014 of seven trials (1624 patients) suggested that administration of TXA reduced mortality when used to treat acute upper GI bleeding. The purpose of this study was to rigorously evaluate the effect of TXA on mortality due to GI bleeding with a randomized, double-blind, placebo-controlled trial.

Evidence:

HALT IT Trial: 12,009 patients with from 164 hospitals across 15 countries were included in the trial. The primary outcome was death secondary to bleeding within 5 days of randomization. Secondary outcomes included death secondary to bleeding at 24 hours and 28 days post randomization, blood product transfusion, and thromboembolic events. Patients randomized to TXA were given drug as follows: loading dose 1g/100ml NS pushed over 10 mins, maintenance dose 3g/1L NS given at 125mg/hr over 24 hours. There were 1112 deaths. There was no difference in mortality between TXA and placebo groups at any time point after randomization: within 24 hours (RR 1.04, 95% CI 0.81-1.33), within 5 days (RR 0.99, 95% CI 0.82–1.18), and within 28 days (RR 0.97, 95% CI 0.82-1.15). There was no difference in rates of any kind of blood product transfusion between TXA and placebo groups (RR 0.99, 95% CI 0.97-1.02). The risk of venous events (DVT/PE) was increased in the TXA group (RR 1.85, 95% CI 1.15 - 2.98). Interestingly, they reported no difference in mortality between TXA and placebo when results were stratified by income (high income countries and LMIC), although the statistics were not included in the paper or supplement.

Karadas et al (2020): 157 patients, single center, double-blind placebo-controlled trial. Patients were randomized to received 2000mg TXA through NG tube vs. placebo. Primary outcome was a composite of recurrent endoscopy need, rebleeding, surgery need, recurrent admission to the ED, and mortality after one month. There was no difference between TXA and placebo in the composite outcome (32.1%, 29.1%, p =0.69). There were also no differences in mortality (10.3%, 12.17%, p=0.637) or thromboembolic events (3.8%, 1.8%, p=0.367).

Analysis and Conclusions: Based on these trials, TXA does not reduce risk of mortality or blood product transfusion in adults with acute GI bleeding and may increase the risk of thromboembolic events (level 1b evidence from HALT-IT trial). Notably, the HALT-IT trial looked at all acute GI bleeds, although most of the sample was upper GI bleeds (89%). Another important limitation to is that the HALT-IT trial was not designed to evaluate the use of TXA vs. placebo in different types

of GI bleeds. Approximately half of the patients in this trial likely had variceal bleeding due to liver disease, which may impact the fibrinolytic pathway and thus, the efficacy of TXA. Furthermore, the TXA infusion protocol was longer with drug given at higher doses than when used in other clinical settings. While Karadas et al (2020) only looked at acute upper GI bleeds (majority due to PUD), the study was quite small and only looked at a single center, making the findings less robust.

Further research is certainly needed to investigate the use of TXA with different GI bleeding pathologies, delivery methods, and doses. However, based on this evidence, I would not use TXA as an adjunct to standard therapies if I suspected an acute upper GI bleed in my patients, as it may do them more harm.

Global Health Critically Appraised Topic (CAT):

ELISA vs Kato-Katz for detection of *Schistosoma japonica*

Amanda Tompkins and Lee Varelas

Background:

Schistosomiasis, caused by *Schistosoma japonicum,* is endemic in China and the Philippines. It remains a major public health concern in both countries, although significant reductions in prevalence and morbidity have been achieved in recent decades. In fact, through successful screening and treatment programs, *S. japonicum* is no longer endemic in many areas of China and the Philippines. Elimination has been achieved in other areas of the world, and is also considered to be a realistic goal in Asia. As morbidity diminishes, more sensitive diagnostic techniques are needed to detect infections in people living in areas with active transmission. However, WHO continues to recommend the Kato-Katz (KK) method as the gold standard diagnostic technique given its affordability and availability in low resource settings. Given the accurate detection of *S. japonicum* infections plays a crucial role in control, particularly with decreasing prevalence, the use of an affordable and highly accurate field diagnostic tool is essential if elimination is to be achieved. Therefore, an evaluation of alternative, affordable diagnostic techniques such as ELISA is warranted.

PICO Question:

How does ELISA compare to Kato-Katz method at detecting *S. japonicum* in low resource settings?

Evidence:

Cai et al: In an area in Philippines determined to be moderately endemic for *Schistosoma japnicum,* prevalence among 412 individuals was determined by KK, ELISA and PCR. ELISA (five different antigen targets) and PCR (both fecal and serum) both determined prevalence at a rate approx 2.5x higher than as estimated by KK method. KK remains the test with highest specificity (95.6%, CI 90.6 - 98.4), but sensitivity may be unacceptably low for detection (36.8%, CI 31.1-42.8). ELISA testing had a sensitivity of up to 79.4% (95%, CI 74.2%-82%). Researchers felt the testing for SjSAP4 + Sj23-LHD antigen specifically was a viable diagnostic option.

Deng et al: Meta-analysis reviewed 23 articles investigating the diagnosis of schistosomiasis in China. The ratio of serological (ELISA or IHA) to egg-positive (KK) prevalence was calculated. *S. japonicum* seroprevalence detected by immunological methods (ELISA or IHA) was 4-5x higher than estimated by coprological prevalence (KK method). Pooled ratio for ELISA to KK specifically was 4.65 (95%CI: 3.50-6.17), suggesting KK may significantly underestimate prevalence. The degree of underestimation was more pronounced in low endemic areas.

Discussion:

The WHO cites Kato-Katz method as being the gold standard for *Schistosoma japnicum* detection and diagnosis. However, while KK remains the most specific test available in detecting high egg burden within stool, it leads to gross underestimation of prevalence when compared to PCR and ELISA testing methods. This underperformance seems to be most dramatic in areas with low disease burden. As prevalence decreases in endemic areas, more sensitive diagnostic detection techniques are needed to detect and address infection.

While PCR testing remains cost-prohibitive due to the need for specialized equipment and training, ELISA may be a viable alternative and a vastly better screening test to utilize as prevalence of this infection decreases Accordingly, ELISA appears to be a sensitive, cost-effective diagnostic alternative to KK to detect schistosomiasis given the changing epidemiological landscape in China and the Philippines.

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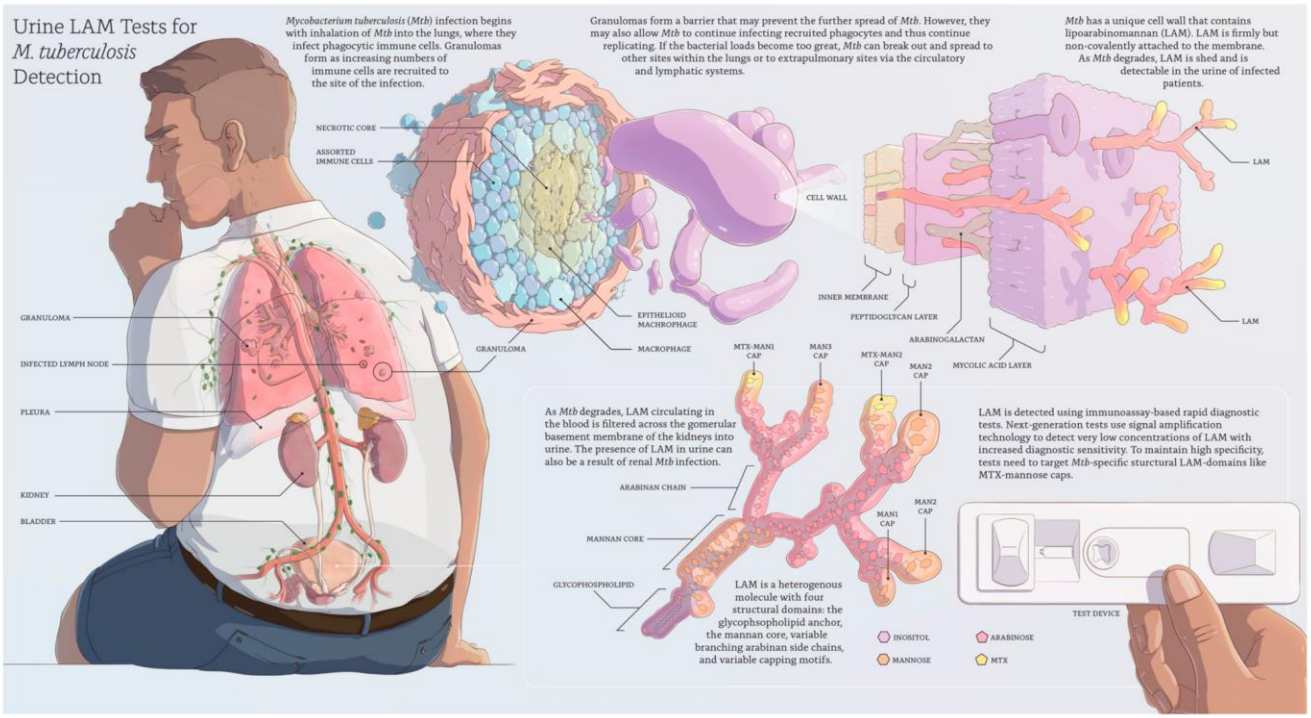
Use of Urine LAM Testing for Rapid Dx of Active Tuberculosis in PLWH

Emily Min and Emily Evans

Background:

In resource-limited regions where *Mycobacterium tuberculosis* (MTB) infection prevalence and incidence are high, rapid diagnosis and treatment are key to reduce transmission, morbidity and mortality. This is true in all patients but especially notable for persons living with HIV (PLWH), who have increased risk for TB infection as well as increased risk of mortality, as TB comprises one of the leading causes of deaths in PLWH worldwide. While the gold standard for diagnosis is positive culture from sputum/bronchoalveolar lavage/pleural fluid or MTB isolation in tissue, this diagnostic method may take weeks to result and not all laboratories have the necessary resources to process samples. In the meantime, rapid diagnostic methods have been developed to expedite this process. These include isolation of acid-fast bacilli on sputum smear and Gene Xpert (nucleic acid amplification) and Xpert Ultra.

However, these methods are not without their issues. Sputum smear may be difficult to obtain from critically ill patients or children - sensitivity varies widely and can be especially reduced in PLWH. GeneXpert has improved sensitivity and can identify rifampicin resistance but carries higher cost and also requires sputum. More inexpensive and easily obtainable diagnostic methods have been evaluated, including the use of urinary lipoarabinomannan (LAM) antigen testing. LAM is a component of the MTB cell wall, which is filtered from the bloodstream into urine as mycobacteria degrade during active TB infection. Notable benefits of urine LAM testing include the relative accessibility of an adequate urine sample compared to sputum, reduced cost, low tech requirements, and availability of results in a short period of time. Evaluating accuracy of urine LAM testing will be helpful in guiding clinical decision-making in resource-limited settings.



AlereLAM

LAM tests Initially produced in 1997→ 2003 Chemogen developed lab based assay which was commercialized by Iverness as Clearwater test. in 2010 Iverness changed the name to AlereLAM as a POC LAM test was developed. This test uses polyclonal antibodies and ELISA to detect MTBc specific LAM domains. Priced ~$3/test.

FujiLAM

Uses a pair of monoclonal antibodies in combination with a silver amplification step to identify the MTX-LAM epitope specific to MTBc. Has a LoD 30x lower than that of AlereLAM, however, cost data has yet to be released.

Question:

How accurately does urine LAM (either AlereLAM or FujiLAM) detect active tuberculosis compared to other rapid detection methods (smear, GeneXpert, Xpert Ultra)?

Problem/Patient:

Hospitalized people living with HIV

Intervention:

Application of novel tuberculous diagnostic technology including either AlereLAM or FujiLAM products.

Comparison:

Composite group of sputum Xpert, Xpert ultra (limited), sputum AFB smear +/- culture

Outcome:

Sensitivity, specificity, PPV, NPV

Search terms:

LAM, pulmonary tuberculosis, HIV

Evidence:

1. Cochrane Database, systematic review: 2019
    a. Evaluated 15 studies (8 in symptomatic adults ie “diagnostic”, 7 in “unselected” adults ie “screening”), PLWH 15+, in LMIC
        i. Specifically evaluated AlereLAM
        ii. Reference standard: +MTB culture or NAAT
    b. n=6814, 26% with reference standard-confirmed active TB

i. Diagnostic studies: n=3449, 37% with active TB confirmed
    1. Median CD4 count: 81-210

c.

	Pooled sensitivity	Pooled specificity
Across all "diagnostic studies"	42%	91%
CD4 count >200	16%	94%
CD4 count <=200	45%	89%
CD4 count >100	17%	95%
CD4 count <=100	54%	88%

d. Evaluation of mortality outcomes:
    i. 2 studies evaluated effect of urine LAM use and deaths attributed to TB
        1. RCTs, multinational, inpatient, all-cause mortality at 8 weeks
    ii. Peter 2016:
        1. RRR 0.83 (urine LAM vs no urine LAM)
        2. Symptomatic patients only
    iii. Gupta-Wright 2018:
        1. Adjusted risk reduction -2.8% (p=0.07) overall (evaluated all PLWH regardless of sx)
        2. Noted statistically significant reductions in pts with CD4 <100, severe anemia, CLINICALLY SUSPECTED TB

e. Overall:
    i. Improved sensitivity of urine LAM in patients with CD4 <=100
        1. "No role as replacement or triage test"
    ii. In patients with advanced HIV/AIDS, health outcomes may be improved due to feasibility and due to atypical presentations of TB

2. Lancet Diagnostic accuracy study comparing FujiLAM to AlereLAM
    a. Used biobanked urine samples from University of CapeTown during 3 prospective studies done at 2 hospitals
        i. Patients had to be > 18 y/o and living with HIV and were not already on antitubercular therapy
        ii. From previous study protocols, had full workup to identify tuberculosis or alternative diagnosis
            1. Cohort 1 PLWH at any CD4 and had TB symptoms and were able to produce sputum (excluded extrapulmonary manifestations)
            2. Cohort 2 PLWH at any CD4 regardless of ability to produce sputum or tuberculosis symptoms
            3. Cohort 3 PLWH CD4 < 350 where tuberculosis was the most likely diagnosis

b. Urine was tested with FujiLAM and AlereLAM; patients were classified as Definite, possible, and not TB (no tx, improvement in sx 3 months) by clinical case definition; possible TB cases were considered negative for micro reference standard but positive for composite reference standard.
    i. Excluded patients that were "unclassifiable" (LTFU, death before Dx), no LAM test available, or LAM testing failed
c. Enrolled 968 patients
    i. Prevalence of microbiologically confirmed TB was 62%; median CD4 was 86.
    ii. Definite micro was from non-sputum samples for 20% of micro proven TB
    iii. 45% had hx of previous Tb tx
d. Using the microbiological reference standard, sensitivity of FujiLAM was 70.4% vs 42.3% for AlereLAM. Specificity was 90.8% and 95%, respectively.
e. Against a composite reference standard, sensitivity was 65% for FujiLAM and 38.2% for AlereLAM and specificity of 96 and 98, respectively.
    i. Specificity was lower for FujiLAM at lower CD4 counts.
    ii. PPV was 90.6-99.4% for FujiLAM and 93.8%-100% for AlereLAM.
    iii. NPV ranged from 24.8-71.8% for FujiLAM and 13.7-62.5% for AlereLAM
f. Among the 121 unclassifiable patients, 18 had a positive LAM and 9 died within 3 months; 6/9 were never started on ATT

3. Status update assessing relative performance of AlereLAM and FujiLAM since market debut (2020)
    a. Benefits
        i. Cost-effective (no additional equipment requirements)
        ii. <1 hour time to result (compared to 100 min for Gene Xpert)
        iii. Ability to translate into lower-resource settings without electricity, labs
    b.

	Sensitivity in PLWH (regardless of CD4)	Sensitivity in persons who are HIV-negative	Specificity
FujiLAM	70.7%	In process	95.7%
AlereLAM	42%	18%	96-98%
Gene Xpert	77% (reg), 90% (Ultra)	90% (reg), 91% (Ultra)	98% (reg), 96% (Ultra)

    c. TB patients diagnosed on day 1 of presentation:
        i. While contemplating the myriad reasons why a patient may have "delayed presentation", in the context of these POC tests:
            1. FujiLAM: 64.5%
            2. AlereLAM: 43.3%
            3. Gene Xpert: 26.2%
    d. WHO guidelines for POC diagnosis of TB (2019): AlereLAM only

i. Inpatient: use to ASSIST in diagnosis of symptomatic PLWH, advanced HIV disease, CD4 count <200 (regardless if symptomatic)
ii. Outpatient (less robust recs): assist in diagnosis of symptomatic PLWH, seriously ill, CD4 count <100
iii. Do NOT use urine LAM if asymptomatic and CD4 count either unknown or >=200

Limitations and Discussion:

While these novel, point of care, rapid assays of easily accessible specimen (urine), sensitivity remains lacking compared to Xpert and Xpert ultra. Utility of this tool remains highest in patients who are the most immunosuppressed (PLWH and CD4 <100 cells/uL) but is less sensitive in patients without HIV or with well controlled HIV. As we move forward with advances in and access to ART, the landscape of tuberculous diagnostics will have to advance in parallel. There is still limited data regarding accuracy when evaluating organ specific involvement. Lastly, there is limited information regarding cost comparison, especially with the second generation LAM assays such as the FujiLAM. The low tech and lack of skilled provider, however, does make these attractive options when compared to AFB smear and Xpert/Xpert Ultra. Additionally, while there is some evidence that AlereLAM improved mortality among hospitalized PLWH, we do not know that improved diagnosis/sensitivity will lead to linear improvement in mortality given high rates of empiric antituberculous therapy regardless of definitive diagnosis.

Reading primary literature has not been our strength over the past 1.5 years.

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