Critically Appraised Topic: Role of Chelation Therapy in Chronic Arsenic Toxicity by Irada Choudhuri

Case:

29-year-old woman living in Chamagram village of Bangladesh presents to the district clinic with new skin changes. Over the last two years, she has developed diffuse hypopigmented macules on the trunk and extremities, and hyperkeratotic papules on the palms and soles of her feet along. She moved to Chamagram three years ago with her husband for farming opportunity. She reports her husband has developed similar skin changes. Her neighbors, with whom they share a tubewell, also have similar lesions.

Background:

Arsenic is a metalloid element naturally distributed in the earth's crust and water. Classic acute-subacute arsenic toxicity develop gastrointestinal, cardiovascular, hematologic and neurologic abnormalities [1]. However, the majority of arsenic toxicity occurs from long term exposure due to contaminated water, soil, and food products [2]. Skin and peripheral neurologic symptoms tend to predominate, though multiorgan system pathology can also occur [3]. Acute toxicity is a life-threatening condition managed with chelation therapy [4]. Chronic arsenic toxicity is managed by identification and removal of the exposure. Contaminated ground water is a major source of arsenic exposure for Bangladeshis; it is estimated fifty million people are at risk [5]. Efforts to implement a sustainable, arsenic-free water supply in Bangladesh are ongoing but incomplete.

Randomized placebo-controlled trial of 2,3-dimercaptosuccinic acid in therapy of chronic arsenicosis due to drinking arsenic-contaminated subsoil water[6]

Patients: Twenty-one consecutive patients with chronic arsenicosis individually randomized into 2 groups
Intervention: 11 patients received 2,3-dimercaptosuccinic acid 1400 mg/d in the first week and 1050 mg/dduring the next 2 weeks with a repeat course 3 weeks later.
Comparison: The other 10 patients were given placebo capsules for the same schedule.
Outcome: clinical features were evaluated by an objective scoring system before and after treatment. Routine investigations including liver function tests, arsenic concentrations in urine, hair, and nails, and skin biopsy evaluations were also completed.
Results: Though there was improvement in the clinical score of 2,3-dimercaptosuccinic acid-treated patients, similar improvement was observed in the placebo-treated group. There were no statistical differences in the clinical scores between the 2 groups at the beginning and at the end of treatment. Similarly, no differences were found for the other investigated parameters.

Randomized placebo-controlled trial of 2,3-dimercapto-1-propanesulfonate (DMPS) in therapy of chronic arsenicosis due to drinking arsenic-contaminated water[7]

Subjects: Twenty-one consecutive patients with chronic arsenicosis were individually randomized into 2 groups. The consumption of arsenic-contaminated water was terminated by all 21 subjects.
Intervention: 11 patients received DMPS 100-mg capsules 4 times a day for 1 week and repeated in the 3rd, 5th, and 7th week
Comparison: The other 10 patients were given placebo capsules in the same schedule.
Results: Therapy with DMPS caused significant improvement in the clinical condition of chronic arsenicosis patients as evidenced by significant reduction of total clinical scores (< 0.0001). Exposure cessation alone with placebo treatment also reduced clinical scores ($p < 0.003$), but the posttreatment total clinical score of DMPS-treated patients was significantly lower than that of placebo-treated patients ($p < 0.01$). No difference was noted between groups in the hematological and biochemical parameters (which were normal) and skin histology before and after treatment. No DMPS-related adverse effects were noted.

Conclusion:
Single agent chelation therapy may be effective at reducing side effects due to chronic arsenic toxicity. More evidence is required to identify an agent of choice as well as detail which sequelae of arsenic toxicity may be mitigated. Not review includes combination chelation therapy or natural antioxidant chelation therapy.

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Critically Appraised Topic: Abdominal ultrasound as a reasonable alternative to CT imaging for the diagnosis of acute appendicitis by Radu Mitran

Case: A 36-year old male in Malawi presents to the local emergency department. He complains of diffuse abdominal pain, most prominent in the central and right lower quadrant, one episode of vomiting, and a mild fever. He is tender to palpation on exam, particularly in the RLQ, though has no rebound tenderness, guarding, or rigidity. Psoas and obturator signs are negative. The patient is hemodynamically stable and has a mild fever. You are concerned about acute appendicitis but would like more imaging. Unfortunately, the CT scanner is broken, and the nearest CT is 4 hours away.

Question: Is abdominal POCUS a reasonable alternative to CT scanning for the diagnosis of in a patient with moderate suspicion for acute appendicitis?

Background: Appendicitis is one of the most common surgical emergencies worldwide. The global incidence of appendicitis has grown 64% in the last 30 years, though the number of disability-adjusted life years (DALYs) declined by 32% during this period. Acute appendicitis in LMICs is associated with a longer presentation to care following symptom onset, higher degree of complications (rupture, abscess), and postoperative complications. Currently, the mortality rate for acute appendicitis in Africa is estimated between 1-4%. Diagnostic imaging is often required when acute appendicitis is suspected. The gold standard is contrasted CT imaging, however in many low-resource scenarios CT imaging is cost-prohibitive or impossible to obtain. Point-of-care ultrasound (POCUS) has rapidly grown in popularity in LMICs.

A comparison of the Accuracy of Ultrasound and Computed Tomography in common diagnoses causing acute abdominal pain (2011)

Patients: 1021 patients who presented to the ED of six European hospitals with acute abdominal pain lasting for more than 2 hours but less than 5 days. After clinical assessment in the ED, patients who consented to the study underwent both ultrasound and CT within a few hours of presentation to the ED.

Intervention: Ultrasound and CT imaging for acute abdominal pain

Comparison: Head-to-head comparison between ultrasound and CT. A final diagnosis was assigned after 6 months by an independent expert panel.

Outcome: The most common diagnosis was appendicitis (28% of all patients). The sensitivity of CT imaging was 94% in detecting appendicitis versus 76% in ultrasound. Positive predictive values of both US and CT scanning were similar.

Diagnostic Accuracy of Emergency Physician-Performed Ultrasound for Acute Appendicitis in a Remote Location (2016)

Patients: 104 patients referred to an ED at French military hospital in the capital of Djibouti with suspicion for acute appendicitis.

Intervention: All patients received abdominal ultrasound. The main diagnostic criteria for acute appendicitis was a noncompressible appendix with a diameter greater than 6mm.

Comparison: N/A

Outcome: The sensitivity of ultrasound for acute appendicitis was 88%, specificity was 96%, and the positive predictive value was 96%. Abdominal ultrasound was able to identify the appendix in 100/104 patients. 25 patients had an ultrasound indicative of acute appendicitis, on surgical intervention 22 of these patients were diagnosed with acute appendicitis.

An international evaluation of ultrasound vs. computed tomography in the diagnosis of appendicitis (2011)

Patients: Retrospective chart analysis at two tertiary care teaching hospitals in the US and Israel. Patients met inclusion criteria if they had a working diagnosis of appendicitis in the ED, had at least one imaging study performed, and were managed operatively for appendicitis. The US was assigned as the "CT" cohort and Israel as the "US" cohort. 79 patients in the US met criteria for the CT cohort, and 197 patients in Israel met criteria for the US cohort.

Intervention: No direct intervention given this was a retrospective chart review.

Comparison: Ultrasound and CT cohorts were compared.

Outcome: The sensitivity of ultrasound was 69% with a positive predictive value of 95%. CT scanning had a 100% sensitivity and PPV in this study. Additionally, 0 patients had a negative appendectomy after positive CT imaging, while 7 patients with positive ultrasound imaging had a negative appendectomy.

Conclusions: Although ultrasound is not as sensitive at CT imaging for the diagnosis of acute appendicitis, it appears to be a reasonable alternative in resource-limited settings, especially when considering the delays of care associated with CT imaging and the risk for clinical progression.

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Critically Appraised Topic: Can non laboratory based cardiovascular risk scores accurately assess CVD risk compared to lab based scores by Sarah Falta

Study overview:

Gaziano TA, Abrahams-Gessel S, Alam S, Alam D, Ali M, Bloomfield G, Carrillo-Larco RM, Dorairaj P, Gutierrez L, Irazola V, Levitt NS, Miranda JJ, Bernabe-Ortiz A, Pandya A, Rubinstein A, Steyn K, Xavier D,

Yan LL. Comparison of Nonblood-Based and Blood-Based Total CV Risk Scores in Global Populations. Glob Heart. 2016 Mar;11(1):37-46.e2. doi: 10.1016/j.gheart.2015.12.003. PMID: 27102021.

- Standard calculators of CV risk use sex, age, tobacco use, SBP, and blood cholesterol levels generate risk prediction however blood lipid screening is costly and not always available in LMIC
- This study used cross-sectional data from 7 regions including sociodemographic/anthropometric, BP, self reported medical history/smoking status and lipid levels from adults aged 35-74 in 7 regions: southern cone (Argentina, Chile, Uruguay), Bangalore (rural India), New Delhi (urban India), Karachi (Pakistan), Kenya, Peru and South Africa. These countries all had demographic, medical history and laboratory data and were used in the primary analysis. Secondary analysis included regions that did not have laboratory lipid data and included China and Bangladesh
- For primary analysis CV risk scores were calculated using Harvard NHANES risk and 4 accepted lab based risk scores including Framingham 2008, Pooled Cohort Equation (ASCVD), SCORE, and SCORE-Low and decree of concordance was calculated for men and women in all 7 regions.
- For secondary analysis Harvard NHANES risk was calculated for regions without available lab data and used to predict percentage of population and age-adjusted population at high risk of CV disease over 10 years
- Overall concordance with Harvard NHANES and the 4 laboratory risk scores were high with the lowest degree of concordance >88% and average in the low 90s and secondary analysis showed many countries had a high percent of their population at high risk for CV disease over next 10 years (range from 8% in Pakistan to 51% in China)
- Limitations include cross-sectional nature of study without availability of subsequent death and CV disease data to validate studies, large and diverse population student, and bias for including individuals who had available data registered with country's health system

PICO question

Population: Adults between 35-74 without prior history of MI, CAD, PAD or CVA living in LMIC
Intervention: Use of a non laboratory-based CV risk score (Harvard NHANES) to predict 10 year CV disease risk to guide treatment and preventative management
Comparison: CV risk based on non lab-based CV risk score's concordance risk based on 4 accepted predictors of 10 year cardiovascular risk using blood lipid measurements (Framingham 2008, Poole Cohort Equation (ASCVD), SCORE and SCORE-Low)
Outcome: There was a high concordance for non lab-based risk scores and 4 lab based risk scores for both men and women with an aggregate of >0.91 for women and >0.92 for men. Indicating that these scores could be effectively used to predict CV risk and initiate preventive treatment in low resource settings where laboratory assessment is not available

Additional studies looking at use of ASCVD risk predictor in persons with HIV

Msoka T, Rogath J, Van Guilder G, Kapanda G, Smulders Y, Tutu van Furth M, Bartlett J, van Agtmael M. Comparison of Predicted Cardiovascular Risk Profiles by Different CVD Risk-Scoring Algorithms between HIV-1-Infected and Uninfected Adults: A Cross-Sectional Study in Tanzania. HIV AIDS (Auckl). 2021 Jun 3;13:605-615. doi: 10.2147/HIV.S304982. PMID: 34113177; PMCID: PMC8184149.

- For patients on ART, cardio/cerebrovascular disease are important causes of mortality of HIV-infected patients however limitations exist in accurately identifying risk in this population as studies using standard CV predictors have yielded inconsistent data and there is some debate to the underlying cause for increased CV risk in HIV-infected patients ranging from increased inflammation, direct viral cytotoxic effects and ART associated dyslipidemia and metabolic syndrome
- Study through the Kilimanjaro Christian Medical Center Infectious Disease Clinic. Included adults >40 years with known HIV status and excluded pregnant women and people with lower extremities amputations
- 104 HIV + individuals (40 treatment naïve and 64 on ART) and 50 uninfected individuals participated. Major differences between groups include greater proportion of women in HIV infected group (34% compared to 67.5 and 73.4% respectively), and younger population in HIV uninfected, and higher blood lipid levels and BPl in HIV infected individuals.
- Study found higher average ASCVD and Framingham risk scores for HIV infected individuals both on ART and treatment naïve
- Major limitations including confounding with substantial demographic difference between HIV + and – groups (HIV negative group also largely recruited from volunteers from hospital staff and family members), cross-sectional nature of study as well as small sample size

Achhra AC, Lyass A, Borowsky L, Bogorodskaya M, Plutzky J, Massaro JM, D'Agostino RB Sr, Triant VA. Assessing Cardiovascular Risk in People Living with HIV: Current Tools and Limitations. Curr HIV/AIDS Rep. 2021 Aug;18(4):271-279. doi: 10.1007/s11904-021-00567-w. Epub 2021 Jul 11. PMID: 34247329; PMCID: PMC8733948.

- People living with HIV (PLWH) are approx. 1.5-2 higher riskfo CVD and tend to experience at a younger age
- Framingham heart study (mean age 49, <10% black, used age, SBP, BP Rx, smoking, total cholesterol, HLD, diabetes; ASCVD (age 40-70, 21% black, age, SBP, smoking, cholesterol, HLD, diabetes); SCORE (race not reported, >smoking for men, used age, sex, SBP, smoking and total cholesterol); data collection on adverse ART drugs (average age 39, race not reported, age, sex, SBP, smoking, total cholesterol, diabetes, smoking history, family hx, CD4, years using ART)
- Application of generalized models to PLWH have shown underestimation of risk, particularly for low-moderate risk individuals and in female or black individuals
- PLWH tend to be younger with higher % non-white, higher smoking rates, higher comorbidity burden. Inflammation and immune dysfunction likely play role as well as ART. No predictive models have been studies/generated using cohort studies form LMIC
- Alternative risk factors include coronary artery calcium, hsCRP, ABI and advanced lipid testing with HIV specific biomarkers include CRP, IL-6, D-dimer

- AHA recommends multiplying risk for PLWH by 1.5-2 times especially in individuals with delayed ART initiation/prologued viremia, low CD4 count or HCV
- Currently REPRIEVE is investigating if PLWH with low/intermediate CVD risk by predictive models merit aggressive prevention therapies and is enrolling patients in Asia and sub-Saharan Africa

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Critically Appraised Topic: Treating TTP without PLEX by David Lazris

Clinical Question: What is the prognosis of treating TTP with plasma infusion and steroids vs PLEX and steroids?
Clinical bottom line: In many LMIC, PLEX is not a viable option for treatment. Plasma, while also often not available, is more common in LMIC. How does plasma infusion affect survival and recurrence rates when compared to PLEX? While steroid treatment alone is the most available, there is no evidence found for steroids alone vs plasma infusions or PLEX.
Citations:

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Background/ rationale for study: In high income countries, steroids along with plasmapheresis has become standard treatment for TTP, decreasing morality from ~85-90% without treatment to 10-20% (though mortality pretreatment data is from a 1966 study with many limitations). PLEX is not always an option for many LMIC health care settings with limited resources and limited technicians. Steroids are often available and plasma is more available than PLEX in many LMIC. This CAT looks to examine the survival and recurrence differences between these two treatment modalities. While there are no incidence and prevalence studies involving TTP in Sub Saharan Africa, there is at least one case report of TTP.
The evidence: A RCTs from Canada in 1991 randomly assigned 102 patients with TTP to get plasma infusion or plasmapheresis, with both arms getting aspirin and dipyridamole. Primary outcomes were mortality and platelet count response after the initial treatment cycle and mortality and recurrence after 6 months. The plasmapheresis arm was superior at the end of initial treatment cycle (day 9), showing increase in platelet count in 47.1% vs 25.5% and decrease in morality 3.9% vs 15.7%. It was also superior 6 months later showing a sustained response rate of 78.4% vs 49.0% and decreased mortality of 21.5% vs 37.3%.
A retrospective study from 1994 analyzed 20 patients. Patients receiving plasma infusions or PLEX were all on corticosteroids and antiplatelet drugs. They found no difference in response rate and mortality between those who used plasma infusions and plasmapheresis. Only the abstract was available for this study.
A second retrospective trial from Paris in 2003 studied 19 patients using high dose plasma infusion (HDPI) (25–30 mL/kg per day) until remission and 18 using PLEX. Steroids and aspirin were given to both groups. Patients were switched from plasma infusion to PLEX if remission could not be reached or for side effects. There was no significant difference between recovery times of platelets and LDH for both groups. 8 patients had to be switched from HDPI to PLEX, with the most common reason being for fluid overload. Only one was switched due to failure to reach remission and their illness was not responsive to PLEX or other interventions. 4/19 (21.1%) died in the HDPI arm vs 16.7% in the PLEX arm. The main PLEX side effect was infection (2 people). 3 patients in each group relapsed.

Analysis and conclusions: Based on 2 retrospective cohort studies, there is Level 2b evidence that there is minimal mortality and response difference between plasma infusion and PLEX. There is a difference in side effects, mainly the increase of fluid overload with the use of plasma infusions. However, it is important to note that the only RCT, level 1b evidence, did show a significant difference in response and mortality both after initial treatment and 6 months later, though this study had the large limitation of not using steroids which is now standard of care. There is no evidence of the effect of steroids on TTP treatment vs only antiplatelets as used in the RCT. If I had a patient in a LMIC with TTP, I would give PLEX first but if unavailable, I would consider giving plasma infusion, despite side effects, as it decreases morality by a substantial amount from the 10-15% survival rate of not giving treatment. Unfortunately, there is no data to show what benefit steroids alone would give vs no treatment.

Critically Appraised Topic: A sweet solution to a growing problem - use of honey in treatment of burns by Lilli Schussler

Clinical Q: What is the evidence basis for the use of undiluted honey in the treatment of mild to moderate burns?

Background: The abundance of unhealed wounds, ulcers, and burns has a significant impact on public health. Adequate resources to treat burns—including burn-experienced personnel and supplies—are often lacking in LMICs and especially mass casualty situations. Topical antimicrobial agents, dressings, and medications (analgesics, sedation) are often poorly available. It is important to both have a strong evidence basis for resource triage and to consider low-cost options. Honey is a promising avenue as it has antimicrobial and anti-inflammatory properties and a therapeutic effect on the healing process and, unlike with antibiotics, studies have shown no development of bacterial resistance.

Study 1 – Clinical trial
A comparative study to evaluate the effect of honey dressing and silver sulfadiazene dressing on wound healing in burn patients. Indian J Plastic Surg. Baghel et al 2009.

Population: 78 patients, age 10-50 years, with 1st and 2nd degree burns of <50% of TBSA (total body surface area), over a period of 2 years (2006-8).

Variable: Undiluted pure honey (n=37) vs SSD cream (n=41).

Endpoints: Status of the wound was assessed every 3rd and 7th day and on day study completion. Patients were followed up every fortnight till epithelialization. Bacteriological examination of the wound was done every 7th day.

Results: Mean age in HG vs SSD was 34.5 versus 28.5 years, respectively. Average duration of healing in was 18.2 and 32.7 days in HG vs SSD. In HG, 100% of pts who reported within 1 hour of injury became sterile with honey dressing <7 days vs none with SSD. All wounds became sterile in <21 days in HG vs 36.5% in SSD.

Conclusion: Honey dressing improves wound healing, makes the wound sterile in less time, is better able to prevent hypertrophic scarring and post-burn contractures, and decreases the need for debridement irrespective of time of admission, when compared to SSD dressing.

Study 2 – Clinical trial
A prospective randomised clinical and histological study of superficial burn wound healing with honey and silver sulfadiazine. Burns. Subrahymanyam 1998.

Population: Two groups of 25 randomly allocated patients with fresh partial thickness burns, treated within 6 hours of the burn from 1995-1996.

Variable: Undiluted pure honey (n=25) versus SSD-impregnated gauze (25).

Endpoints: Evidence of infection, excessive exudate or leakage, and time to heal.

Results: HG- 84% showed satisfactory epithelialization by day 7, and in 100% of patients by day 21. SSD- epithelialization occurred by day 7 in 72% and by day 21 in 84%. By day 7 histological evidence of reparative activity was seen in 80% in HG vs 52% in SSD and notably persistent inflammatory changes at this date. Reparative activity reached 100% by day 21 in HG and 84% in SSD.

Conclusion: In honey dressed wounds, early subsidence of acute inflammatory changes, better control of infection and quicker wound healing was observed while in the SSD treated wounds sustained inflammatory reaction was noted even on epithelialization.

Study 3 – Systematic review
The effects of honey compared to silver sulfadiazine for the treatment of burns: A systematic review of randomized controlled trials. Burns. Aziz et al 2017

Studies: RCTs of honey versus SSD. The quality of the selected trials was assessed using the Cochrane Risk of Bias Assessment Tool.

Endpoints: wound healing time and the number of infected wounds rendered sterile.

Results: Nine RCTs met inclusion criteria. Based on moderate quality evidence there was a statistically significant difference between the two groups, favoring honey in healing time (MD -5.76 days, 95% CI -8.14 to -3.39) and the proportions of infected wounds rendered sterile (RR 2.59; 95% CI 1.58-2.88).

Conclusion: The number of infected wounds rendered sterile is higher in the honey group. The proportion of patients with complete pain relief is similar using honey or silver. Honey promotes better wound healing for burns than silver. The available evidence suggests that honey dressings promote better wound healing than silver sulfadiazine for burns. However, there is a lack of high quality evidence to justify routine use of honey in clinical practice.

Critically Appraised Topic: Adjunctive Dexamethasone Use in Bacterial Meningitis in LMIC by Katherine Boyd

Case:
A 14-year old male is brought to the hospital by his parents for a headache, dizziness, nausea, and feeling very weak. On examination, he is found to have a temperature to 103.5F and tachycardia to 115. He has notable stiffness in his neck. LP is in the process of being performed. In addition to antibiotics to treat a presumed bacterial pneumonia, are you considering adjunctive steroids?

Questions:

1. Are there mortality and morbidity benefits to using adjunctive steroids in all types of bacterial meningitis?
2. Are the studies showing the benefit of adjunctive steroids in bacterial meningitis applicable to LMIC?

Background:
Bacterial meningitis occurs in between 2.6 and 6 adults per 100,000 per year in high-income countries, and might be up to 10 times more prevalent in some areas of LMIC. The urgent diagnosis and treatment of this life-threatening condition is challenging, and severe disability or death can ensue even with appropriate antibiotic treatment. It is known that adding adjunctive therapy with dexamethasone to treatments for bacterial meningitis improves patient outcome, as evidenced by many studies conducted in HIC and with benefit being seen especially in cases of strep pneumonia. However, there is not the same strength of evidence for adjunctive steroids in bacterial meningitis in LMIC, with a well-known study conducted in Malawi published 2012 suggesting no benefit.

Populations:

- Vietnamese adults with confirmed tuberculous meningitis
- Children and adults with bacterial meningitis across both HIC and LMIC in RCTs

Interventions:

- Randomized, double-blind, placebo-controlled trial of adjunctive dexamethasone were followed-up at five years, to determine the effect of dexamethasone on long-term survival and neurological disability
- Review of 18 RCTs on corticosteroids as adjuvant therapy in acute bacterial meningitis. Patients of any age and in any clinical condition, treated with antibacterial agents and randomized to corticosteroid therapy (or placebo) of any type, could be included. At least case fatality rate or hearing loss had to be recorded for inclusion. Included in this study was a double-blind, placebo-controlled trial of children with bacterial meningitis in Malawi.

Comparison: IV Dexamethasone vs Placebo

Outcome:
TB Meningitis Study: 545 patients were randomized to receive either dexamethasone (274 patients) or placebo (271 patients). 50 patients (9.2%) were lost to follow-up at five years. In all patients two-year survival, probabilities tended to be higher in the dexamethasone arm (0.63 versus 0.55; p=0.07) but five-year survival rates were similar (0.54 versus 0.51, p=0.51) in both groups. In patients with grade 1 TBM, but not with grade 2 or grade 3 TBM, the benefit of dexamethasone treatment tended to persist over time (five-year survival probabilities 0.69 versus 0.55, p=0.07) but there was no conclusive evidence of treatment effect heterogeneity by TBM grade (p=0.36). The dexamethasone group had a similar proportion of severely disabled patients among survivors at five years as the placebo group (17/128, 13.2% vs. 17/116, 14.7%) and there was no significant association between dexamethasone treatment and disability status at five years (p=0.32).

Review: For children with bacterial meningitis admitted in high-income countries, corticosteroids showed a protective effect of on severe hearing loss (RR 0.61, 95% CI 0.41 to 0.90) and favorable point estimates for severe hearing loss associated with non-Haemophilus influenzae meningitis (RR 0.51, 95% CI 0.23 to 1.13) and short-term neurological sequelae (RR 0.72, 95% CI 0.39 to 1.33). For children in low-income countries, the use of corticosteroids was neither associated with benefit nor with harmful effects. Overall, adverse events were not increased significantly with the use of corticosteroids.

Conclusions:

- These studies suggest a certain benefit in the use of corticosteroids in meningitis due to H flu, strep pneumococcus and with severe TB cases, but the evidence for use in all types of bacterial meningitis in LMIC remains controversial. Additionally, further research is needed to understand the effects in subgroups including patients with HIV and patients with septic shock.

- Adjunctive dexamethasone appears to improve the probability of survival in patients with TBM, until at least two years of follow-up. There does not appear to be a five-year

survival benefit of dexamethasone treatment and the study suggested this may be confined to patients with grade 1 TBM. The failure of dexamethasone to reduce disability despite improving survival in patients with tuberculous meningitis indicates that this drug does not mediate its effects by attenuating inflammation or by suppressing T-cell responses. The study suggests that a stratified approach to steroid use may be most beneficial with patients scoring a GCS <15 receiving a longer course of IV steroids (4 weeks), while those with normal neuro status receive a shorter IV course (2 weeks) followed by a taper.

- Per our neurology talks, it is reasonable to administer steroids empirically in bacterial meningitis prior to 1st dose of abx and continue only if the organism proves to be strep pneumonia.

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Critically Appraised Topic: Quantitative Ultrasound as an alternative for diagnosis of osteoporosis in LMICs by Jeyani Narayan

Clinical Question: Which is better for the diagnosis of osteoporosis in LMICs, quantitative ultrasound (QUS) or dual-energy x-ray absorptiometry (DXA)?

Background and rationale: There is an increased prevalence of malnourishment in children and women of child-bearing age in LMICs and, therefore, an increased risk of osteoporosis in this population in older ages. There is also an increased burden, as women are often the primary caregivers, resulting in an increased risk for poverty and low socioeconomic status. While DEXA is the gold standard for the diagnosis of osteoporosis, quantitative ultrasound presents a simpler, more portable diagnostic method.[1] The validity of QUS has been questioned, however, because of high variability between machines and a dearth of empiric evidence in non-Caucasian populations. The International Society for Clinical Densitometry gave a grade recommendation of Good-A-W-Necessary in 2007. The purpose of this CAT is to analyze more recent evidence presented outside the US to compare the two methods.

Evidence:

Discordance between quantitative ultrasound and dual-energy X-ray absorptiometry in bone mineral density: The Vietnam Osteoporosis Study[2]

Methods: Bone mineral density was measured at the femoral neck, total hip, and lumbar spine with DXA and broadband ultrasound attenuation was measured at the calcaneus with quantitative ultrasound in 1270 women and 773 men aged 18 years and older. Exclusion criteria included cognitive impairment and inability to consent. The correlation was measured with linear regression.

Outcome: There was a modest correlation between BUA and BMD at the femoral neck (r = 0.35) and the lumbar spine (r = 0.34). The study concluded QUS alone is not a reliable method for diagnosis of osteoporosis.

Pre-screening for osteoporosis with calcaneus quantitative ultrasound and dual-energy X-ray absorptiometry bone density[3]

Methods: Calcaneal QUS was performed in 772 Taiwanese patients (420 women, 352 men). For those over 65 years old and QUS scores < -2.0, follow-up spine and hip DXA was performed. Exclusion criteria included treated osteoporosis and past calcaneal fractures.

Outcome: There was a modest correlation between BUA and BMD at the hip (overall: 0.171, women: r = 0.298) and the spine (overall: 0.135, women: r = 0.237). The positive correlation in a large population indicates QUS could be a useful pre-screening tool prior to DXA.

Diagnostic value of calcaneal quantitative ultrasound in the evaluation of osteoporosis in middle-aged and elderly patients[4]

Methods: Bilateral calcaneal QUS and BMD at the femoral neck, left hip, and lumbar spine were measured in 82 patients over age 50 (70 women, 12 men). Exclusion criteria included recent lower limb fracture, diseases affecting bone metabolism, autoimmune diseases, malignancies, heart, brain, kidney diseases, past or present treatment of osteoporosis, and oral barium meals.

Outcome: For men, the correlation between calcaneal QUS and femoral neck, hip and trochanter were 0.683, 0.645, and 0.612, respectively. Correlation between QUS and lumbar spine was statistically insignificant. For women, the correlation between QUS and BMD at the femoral neck, trochanter, hip, and lumbar spine were 0.746, 0.731, 0.757, and 0.663, respectively. The study concluded that QUS is an effective pre-screening tool.

Analysis and conclusion: The variability of QUS machines was exhibited in the range of the correlations presented despite the relatively large sample sizes in all three studies. While a study published in 2016 (discussed in the background section) noted that QUS has a high negative predictive value, the first study states that most diagnoses were missed with QUS alone. In addition, studies have been conducted primarily in Asia, the US and Europe, and further studies are needed in other LMICs to improve generalizability. The general consensus in these three studies is that QUS presents an effective pre-screening tool but that DXA should follow QUS if there is concern for osteoporosis based on risk factors or a concerning QUS score.

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Critically Appraised Topic: Efficacy of Annual HIV Viral Load Determination in Patients Living with HIV by Kseniya Anishchenko

Case: A 45-year-old male in Malawi was recently diagnosed with HIV and presents to your clinic. He lives in a rural town and has limited access to transportation, as well as limited finances, so he will not be able to come to your clinic after this visit. In the USA you test the viral load for newly diagnosed patients every 3 months, which unfortunately is not possible here due to lack of healthcare resources.

You check a viral load in clinic today, and you start him on first-line ART.

Questions:

1. What is the likelihood of the patient having viral suppression on first-line ART?
2. Is there scientific evidence suggesting that intensified ART monitoring like that done in HICs decreases duration of viremia and improves clinical outcomes?
3. How can viral load testing be improved in Malawi?

Background: According to the WHO, 39 million people are living with HIV (LWH) worldwide, with an estimated 25.6 million people LWH in the African region. Around 20.9 million people in the African region receive antiretroviral therapy (ART). The increasing use of ART in LMICs has prevented millions of HIV-related deaths and decreased the onward transmission of HIV. When an individual is on ART, it is important to monitor HIV viral load at regular intervals to detect viremia and act appropriately to decrease the pool of potentially infectious patients.

Per WHO guidelines, viral load monitoring in LMIC should be performed once yearly. In HICs it is recommended to do monitoring every 3-4 months, especially in the first years of treatment. The concern remains that using lower frequency viral monitoring in LMIC may delay clinical interventions and result in prolonged episodes of viremia while on ART, allowing for the accumulation of resistance and transmission of HIV. In this study we will discuss the efficacy of annual HIV viral load determination

Performance and Outcomes of Routine Viral Load Testing in People Living with HIV Newly Initiating ART in the Integrated HIV Care Program in Myanmar between January 2016 and December 2017 – Tropical Med Infectious Disease

Patients: Those living in Myanmar and starting ART in the Integrated-HIV Care Program from January 2016 to December 2017. 7153 patients scheduled for VL testing at 12 months and 1976 scheduled for VL testing at 6 months.
Intervention: 6 month VL
Comparison: 12 month VL
Outcome: In the 12-month cohort, 10% of patients had VL > 1000 copies/mL, 79% had repeat VL tests, 42% had repeat VL > 1000 copies/mL (virologic failure) and 85% of patients with confirmed VL>1000 were switched to second-line ART. In the 6-month cohort, 11% had VL > 1000 copies/mL, 83% had repeat VL tests, 26% had repeat VL > 1000 copies/mL (virologic failure) and 39% with confirmed VL >1000 were switched to second-line ART.
A randomized study of intensified antiretroviral treatment monitoring versus standard-of-care for prevention of drug resistance and antiretroviral treatment switch - AIDS
Patients: Those presenting to a rural South African healthcare clinic and who are receiving or newly initiating first line ART. 208 patients randomized to 3 month viral load vs. 208 patients receiving standard of care practice.
Intervention: 3 month VL w/ drug exposure testing and DBS-based drug resistance testing
Comparison: 12 month VL
Outcome: In patients with viral rebound, the median duration of viraemia was 87 days [IQR 70–110] in the intervention group and 101 days [IQR 78–213] in the control group. Therefore, three-monthly viral load testing did not significantly reduce the duration of viremia when compared with standard-of-care annual viral load testing.
Towards the third 90: improving viral load testing with a simple quality improvement program in health facilities in Malawi – International Health
Patients: 34,480 patients at 13 health facilities in Malawi who had routine VL done over a 13-month period, QI was implemented halfway through 13-month period.
Intervention: QI program tools were implemented, which focused on improving patient and provider VL knowledge. This included standard operating procedures for VL testing, VL educational materials and a designated VL focus person.
Comparison: VL tests done prior to intervention
Outcome: There was an 164% increase in the mean number of routine VL tests performed per month ($p<0.001$), showing that QI improvement projects in LMICs can increase VL testing.

Conclusions:
Yearly viral load monitoring is feasible in LMICs. Yearly testing does not seem to increase the duration of viremia when compared to increased viral monitoring and appears similar percentages of patients have VL>1000 whether testing is done at more regular intervals versus at 12 months. Some studies suggest that frequent monitoring may even lead to less frequent changes to second-line ART given clinicians are more comfortable with waiting and monitoring.

Importantly, QI interventions should be implemented in LMICs to ensure yearly viral load testing is done for all patients.

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Critically Appraised Topic: Hypersegmented neutrophils for diagnosis of vitamin B_{12} deficiency by Alex Layden

Background: Vitamin B_{12} deficiency is associated with megaloblastic anemia, neurologic conditions (peripheral neuropathy, ataxia, dementia), neural tube defects, and impaired infant development[1-3]. Classically, vitamin B_{12} deficiency is caused by pernicious anemia, the

autoimmune destruction of gastric parietal cells. However, common risk factors for vitamin B_{12} deficiency include poor dietary intake from malnutrition, chronic alcohol use or vegetarian diet; as well as impaired B_{12} absorption (gastric bypass, infection, chronic antiacid use)[3]. Vitamin B_{12} deficiency disproportionately affects low- and middle-income countries. The prevalence of vitamin B_{12} deficiency is more than 50% in populations in Latin America, South Asia, and Sub-Saharan Africa[3-7]. Diagnosis of vitamin B_{12} deficiency is typically measured by serum or plasma vitamin B_{12} concentration with a cut-off of <148pmol/L or <200pg/ml[2, 3]. Other blood biomarkers include methylmalonic acid, homocysteine, and transcobalamin[2, 3]. All four biomarkers are measured by liquid or gas chromatography- mass spectrometry or immunologic assays that are not feasible in resource-limited settings[3]. The presence of hypersegmented neutrophils (a 6-lobe neutrophil or ≥ 5% of neutrophils with 5 lobes) on peripheral blood smear is a marker of poor vitamin B_{12} status perhaps conducive for diagnosis of vitamin B_{12} deficiency in resource limited settings[8].

Clinical Objective: I aimed to review the sensitivity and specificity of hypersegmented neutrophils compared to serum vitamin B_{12} concentrations for the diagnosis of vitamin B_{12} deficiency among adults.

Hypersegmented Neutrophils and Vitamin B12 Deficiency[9]

Population: 515 hospitalized adults with anemia and an available vitamin B_{12} concentrations

Methods: Blood was collected and peripheral blood smears were conducted. Serum vitamin B_{12} concentrations (deficiency <200pg/mL) were measured by radioimmunoassay and peripheral blood smears were analyzed. Neutrophils were considered hypersegmented if 6-lobe neutrophils were present or mean lobe count was ≥3.5.

Results: The presence of hypersegmented neutrophils was 91% sensitive and 78% specific for B_{12} deficiency.

Megaloblastic Anemia and Neutrophil Hypersegmentation[10]

Population: 357 patients with megaloblastic anemia hospitalized between 1969-1977.

Methods: Serum vitamin B_{12} and folate deficiency data were extracted from medical records. Case records of peripheral blood smears were reviewed and neutrophils were considered hypersegmented if at least one 6-lobe neutrophil was present or at least 5% of neutrophils had 5-lobes on peripheral blood smears.

Results: The presence of hypersegmented neutrophils was 98.3% sensitive for megaloblastic anemia.

Vitamin B_{12} Deficiency – Need for a New Guideline[11]

Population: 3,714 patients at a single hospital with measured serum vitamin B_{12} in 1996

Methods: Vitamin B_{12} levels were measured by a radioimmunoassay. Deficiency was defined as vitamin B_{12} <140 pmol/L and a low B_{12} level was defined as <180pmol/L. Pernicious anemia was defined as a low B_{12} level with a positive Schilling test (positive antiparietal cells). Hypersegmented neutrophils on peripheral blood smear was defined as at ≥1 neutrophil with 6 lobes.

Results: The presence of hypersegmented neutrophils was 52% sensitive for pernicious anemia, 39% sensitive for macrocytic anemia and 26% sensitive for low vitamin B_{12}.

Neutrophil nuclear segmentation in mild cobalamin deficiency: relation to metabolic tests of cobalamin status and observations on ethnic differences in neutrophil segmentation[12]

Population: 169 individuals assessed for vitamin B_{12} screening outpatient or in a hospital setting.

Methods: Blood was measured for serum vitamin B_{12}, methylmalonic acid, and homocysteine. Individuals were grouped as: 1) severe vitamin B_{12} deficiency (low vitamin B_{12} <190ng/L and evidence of elevated methylmalonic acid or homocysteine), 2) mild B_{12} deficiency (one abnormal vitamin B_{12} marker), or 3) no deficiency (normal vitamin B_{12} biomarkers). Hypersegmented neutrophils on blood smear were defined as neutrophils with a lobe average >3.05 or ≥4% of 5+ lobes. A subset of individuals (n=65) underwent the deoxyuridine suppression test (dUST) as a bone marrow suppression measure of vitamin B_{12} deficiency.

Results: Hypersegmented neutrophils were detected in 8.9% of patients with severe vitamin B_{12} deficiency and 2.9% of individuals with vitamin B_{12} deficiency determined by dUST.

Detection of vitamin B12 levels with the aid of some hematological and biochemical parameters that are more sensitive[13]

Population: 128 patients with vitamin B_{12} deficiency anemia at a health center between 2005-2007.

Methods: Patients were grouped by serum vitamin B_{12} concentrations: Group 1 (vitamin B_{12} <60pg/ml), Group 2 (61-100pg/ml), Group 3 (101-140pg/ml) and Group 4 (141-178pg/ml). Peripheral blood smears of fasting blood were assessed for hypersegmented neutrophils.

Results: The frequency of hypersegmented neutrophils significantly differed across groups (82% Group 1, 41% Group 2, 24% Group 3, and 3% Group 4, $p<0.001$).

Current hematological findings in cobalamin deficiency. A study of 201 consecutive patients with documented cobalamin deficiency[14]

Population: 144 patients with confirmed vitamin B_{12} deficiency (<200pg/ml) from Internal Medicine and Geriatrics services of a single hospital between 1995-2003.

Methods: Serum vitamin B_{12} levels were measured by radioimmunoassay or ELISA. Data on peripheral blood smears were extracted from medical records.

Results: The presence of hypersegmented neutrophils was 32% sensitive for vitamin B_{12} deficiency.

The Significance of Subnormal Serum Vitamin B12 Concentration in Older People: A Case Control Study[15]

Population: 94 older patients with suspected vitamin B_{12} deficiency

Methods: Case-control design where patients with serum vitamin B_{12} < 150pmol/L were cases (n=43) and patients with vitamin B_{12} concentrations ≥150pmol/L were controls (n=51). Vitamin B_{12} concentrations were measured by radioimmunoassay. Hypersegmented neutrophils were considered present on peripheral blood smears if ≥5% of neutrophils had 5 or more lobes.

Results: Hypersegmented neutrophils were 63% sensitive and 49% specific for vitamin B_{12} deficiency.

A Multicenter Retrospective Analysis of the Clinical Features of Pernicious Anemia in a Korean Population[16]

Population: 97 patients from 5 university hospitals between 1995 to 2010 with diagnosed vitamin B_{12} deficiency and pernicious anemia.

Methods: Data on serum vitamin B_{12} deficiency (<200pg/ml), clinical diagnosis, and peripheral blood smears were extracted from medical records. Hypersegmented neutrophils were defined as presence of ≥5% 5-lobed neutrophils or the presence of 6-lobed neutrophils.

Results: The presence of hypersegmented neutrophils was 55.7% sensitive for pernicious anemia.

Other observational studies found the sensitivity of hypersegmented neutrophils on blood smear for vitamin B_{12} deficiency with neurologic symptoms to be 98.6%[17], 74% for pernicious anemia, and 82.7% for megaloblastic anemia[18]. In another observational study, the presence of hypersegmented neutrophils were 89.5% sensitive and 96.8% specific for megaloblastic hematopoiesis on bone marrow evaluation[19].

Conclusions: **Evidence from 12 observational studies does not support the use of hypersegmented neutrophils on peripheral blood smear as a diagnostic tool for vitamin B_{12} deficiency in adults.** The sensitivity of hypersegmented neutrophils for vitamin B_{12} deficiency was highly variable across studies with sensitivities ranging from 8.9%-98.3%. The sensitivity of hypersegmented neutrophils tended to be higher for studies evaluating severe vitamin B_{12} deficiency (e.g., pernicious anemia or vitamin B_{12} with neurologic symptoms). There is insufficient evidence on the specificity of hypersegmented neutrophils on blood smear for diagnosis of vitamin B_{12} deficiency.

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Critically Appraised Topic: Burden of UTI in children presenting with fever in LMIC

Question: In children presenting with fever, what is the burden of UTI?

Contribution of urinary tract infection to the burden of febrile illnesses in young children in rural Kenya

Introduction:
Acute febrile illnesses are common in children worldwide, especially in those under 5-years of age. Infections leading to these febrile episodes are responsible for the majority of under-5 mortality [1]. Febrile illness is typically presumptively treated as malaria in African children in endemic areas, where the majority of these children are given anti-malarial drugs [2–4].
Yet presence of fever alone is not adequate to distinguish malaria from other infectious conditions, especially if the presentation is without focal signs. It is estimated that more than half of children presenting to public health facilities in Africa do not have malaria infection [7]
Urinary tract infections (UTI) in infancy and childhood can present with clinical features that may not localize to the urinary tract and may closely resemble other febrile illnesses without focal signs. Furthermore, UTI may co-exist with these common childhood illness [13]. Where clinical diagnosis alone is employed in management of pediatric fevers, UTI may be missed or its treatment delayed. Such children are at risk of developing bacteremia, meningitis, renal scarring etc.
Long-term complications of renal scarring in adulthood include hypertension and end stage renal disease.
Data from a rural district hospital in western Kenya demonstrate that UTI diagnosis is uncommon. In 2011, 2% of cases had clinically diagnosed UTI but not as a primary diagnosis. Without active investigation for UTI such data may not reflect the real burden of UTI, especially in children under 5 years.
This study was conducted in a malaria endemic region in Western Kenya among febrile children aged between 2 months to 5 years to determine the burden of UTI, causative bacterial pathogens and their antimicrobial sensitivity pattern.
Methods: A cross-sectional study was carried out in a government hospital in western Kenya. 260 inpatients and outpatients patients from 2 months to five years with axillary temperature ≥37.5°C and no antibiotic use in the previous week were enrolled between September 2012 and April 2013. Midstream urine was collected. Urine dipstick tests, microscopy, and cultures were done and susceptibility patterns to commonly prescribed antibiotics established. UTI was defined as presence of pyuria (a positive urine dipstick or microscopy test defined as >5WBC/hpf) plus a positive urine culture.
Results: A total of 260 subjects were recruited; 45.8% were female and the median age was 25months (IQR: 13, 43.5). The overall prevalence of UTI was 11.9%. Inpatients had a higher prevalence compared to outpatients (17.9% v 7.8%, p = 0.027). UTI co-existed with malaria but the association was not significant (OR 0.80, p = 0.570). The most common organisms isolated were Escherichia coli (64.5%) and Staphylococcus aureus (12.9%) and were sensitive to ciproflaxin, cefuroxime, ceftriaxone, gentamycin and nitrofurantoin but largely resistant to more commonly used antibiotics such as ampicillin (0%), amoxicillin (16.7%), cotrimoxazole (16.7%) and amoxicillin-clavulinate (25%).

Malaria was the most common clinical diagnosis assigned to patients in the study (243 of 260 [93.5%]), however only 113 (46.5%) had a positive malaria smear [Table 4]. Other clinical diagnoses included pneumonia (51, 19.6%), acute gastroenteritis (23, 8.8%), and upper respiratory tract infections (21, 8%).

Conclusion: Our study demonstrates UTI contributes significantly to the burden of febrile illness in young children and often co-exists with other infections. Multi-drug resistant organisms are common therefore choice of antimicrobial therapy should be based on local sensitivity pattern.

WHO Recommendation:

The decision to include UTI in IMCI adaptation should be made in countries where:

- health facilities have a functioning water source and materials to collect appropriate urine specimens
for urinalysis;
- morbidity associated with UTI at first-level health facilities has been determined;
- urinalysis by dipstick can be made available at first level health facilities.

In these settings:

- fever is the entry point to assess and classify children with UTI using the IMCI algothrim;
- children at high risk of UTI due to age <two years, classification of “very low weight for age or those with
a previous presumed or confirmed UTI or kidney problem only should have urinalysis by dipstick;
· children classified as “UTI” or “possible UTI” are reviewed after two days if fever persists.
- Antibiotics should be given for seven days and the child reviewed after two days.

The reasons to identify and treat UTI in any environment include:

- identify and treat coexisting bacteraemia and meningitis;
- ensure resolution of the acute symptoms;
- prevent renal damage by eradicating the pathogen;
-identify and consider administering prophylactic treatment to children at risk of recurrent UTI, to prevent renal damage

Citations:

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