Precision Medicine, Asthma, Vitamin D, Ethical Pediatric Practice, and Qatar

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Subtitle goes here
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I do not have any relevant financial relationship with a commercial interest to disclose.
What is precision (personalized) medicine?

A single treatment strategy cannot suit all patients
Asthma and Vitamin D

- Multiple observational studies show increased asthma and allergy in vitamin D-deficient children.
- But vitamin D-deficient children are usually poorer and have more episodes of illness generally.
- Is low vitamin D the *cause* of worse asthma? In all asthmatic children? Only in vitamin D-deficient children? Only in severe deficiency?
- Is vitamin D an asthma treatment for *all* children?
How to ethically study asthma and vitamin D?

- Placebo vs vitamin D in all asthmatics?
  - Adults? Children?
- Placebo vs vitamin D in vitamin D-deficient asthmatics?
  - Adults? Children?
- Maintenance-dose (NOT PLACEBO) vs high-dose vitamin D in all or deficient asthmatics?
How to ethically study asthma and vitamin D?

- Advantages of placebo
  - The best comparison for a treatment (efficacy, adverse effects)
- Disadvantages of placebo
  - May not reflect true practice, so results not generalizable
  - May conflict with recommendations
    - Adults give informed consent—but why ask a patient to do something medically non-advisable?
    - Children: Can’t give informed consent!—why ask a parent to do something that might harm a child, unless recommendations are wrong?
How to ethically study asthma and vitamin D?

Interpretation of baseline vitamin D levels in North America (AAP)

- > 30 ng/ml  Sufficient
- 20-30 ng/mL  “Insufficient”
- <20 ng/mL  Deficient
- UK: 10 mcg/d (400 IU/d) supplement for nearly all in fall and winter
- <13 ng/mL is deficient; 13-20 ng/mL may benefit from a raised level
- Importance of vitamin D level (bones, muscle, 80% by age 18; steroids, etc)
How to ethically study asthma and vitamin D?

How studies compared vitamin D to placebo:

- **Adults:** Informed consent, baseline vitamin D known, may be deficient but we’ll take good care of you!
- **Children:**
  - We will take a baseline vitamin D level but WON’T look at it until the study is over! So it’s ok to have deficient children receive placebo (3 studies)
  - Require low baseline vitamin D level for eligibility, randomize to placebo or high-dose, follow blood calcium, urine, and for rickets
How to ethically study asthma and vitamin D?

How studies compared vitamin D to placebo: Adults

- 100,000 units; then 4000 units/day vs placebo for 28 weeks

Children: Small sample sizes, no difference

One US ongoing study, ages 6-14

- Baseline vit D levels 10-30 ng/mL
- Placebo vs 4000 U/day
  - US upper tolerable limit <9 years: 3000 U/d
  - First planned as 200 U/d vs high-dose
How to ethically study asthma and vitamin D?

Children placebo studies: Small sample sizes, few outcomes, no difference
What outcome when studying asthma and vitamin D?


- In studies of chronic diseases such as heart failure (or asthma!), conventional composite outcome analyses concentrate on the time to the first event and ignore any repeat events that occur subsequently. This approach can lead to serious loss of statistical power and underestimation of a treatment effect.
How to ethically study asthma and vitamin D?

• Studies comparing maintenance-dose to high-dose vitamin D in adults with asthma: NONE

• Studies comparing maintenance-dose to high-dose vitamin D in children with asthma: ONE
  • 2-14 years old, 400 U/d (oral) vs 300,000 to 600,000 IM q 3 months + 400 U/d (IM+oral) for levels <30 ng/mL, for 12 months
  • Outcome: Asthma exacerbations requiring unscheduled visit
  • Analyze by baseline level every 3 months during the study
Rapid vs Maintenance Vitamin D Supplementation in Deficient Children With Asthma to Prevent Exacerbations

Khalid Alansari, MD; Bruce L. Davidson, MD, MPH, FCCP; Khalid Ibrahim Yousef, MD; Abdel Nasser H. Mohamed, MD; and Imad Alattar, MD
Moderate – severe asthma with Vitamin D level ≤ 25 ng/ml

Group A
IM + oral vitamin D

< 5 years ≥ 5 years
300,000 IU 600,000 IU
+400 IU/d po + 400 IU/d po

Group B
Oral – only daily dose of vitamin D

400 IU/d po

Follow up blood levels of vitamin D at 3, 6, 9, 12 months

Group A
< 30 ng/ml ≥ 30 ng/ml

Group B
< 30 ng/ml ≥ 30 ng/ml

Continue IM Oral maintenance 400 IU/d Stop treatment
Dose + 400 IU/d po Dose 1000 IU/d
Important conclusions

- Maintenance dosing—not placebo—can show a scientifically valid effect
- Measuring blood vitamin D levels proved the intervention happened
- Analyzing for repeat events increased event rate and study power
- Analyzing number of children with an exacerbation, and average number of exacerbations per child, allowed assessment of strength of the findings
- For child asthmatics with the lowest levels, restoring vitamin D rapidly will reduce asthma exacerbations and children with exacerbations by about 60% during the first 3 months
- Moderate to severe asthma: Test, and if necessary, treat
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Studies including *no active treatment* in non-consenting children in situations where safe and effective treatment is recommended are dubious and should probably be

- Short-term
- Carefully reviewed
- Have clear description of risks in the Consent Form

- These studies must be justified each time the situation occurs
K Alansari, R Abraham, J Shadakshraiah, and all others whose research and clinical work builds the foundation for defending and promoting ethical pediatric research and practice not only in Qatar, but around the world