Fetal hemoglobin that binds oxygen more strongly than adult hemoglobin saves children (and sickle-cell patients where it persists longer) from heme-binding (oxygen sequestering) proteins of anaerobic bacteria (Prevotella, et al) - thereby making SARS-Cov2 benign for them

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Letter

Here, I postulate (supported by sequencing data from patients) rationale behind two of the most critical (low SpO₂ [1], need for ventilators) and baffling (doesn't effect children or malaria endemic regions [2]) effects observed in SARS-Cov2 [3–6]. In short, secondary infection with anaerobic bacteria [7–9] which express heme-expressing proteins, and can degrade and utilize hemoglobin as an effective heme source [10, 11] - causing oxygen levels (which binds to heme) to go down. Also, Prevotella is known to lower lymphocyte counts [12], increase IL-6 in plasma [13–15], cause ground glass opacity in lungs [16], and associated with cardiac injury [17] - all symptoms associated with Covid19.

Why are children not effected? They have a different hemoglobin, which binds oxygen more strongly

Fetal hemoglobin (HbF) constitutes approximately 60-80 % of total hemoglobin in a newborn [18], and wanes within a year to less than 1% of total hemoglobin in healthy adults, but persisting in some conditions like sickle-cell adults [19]. HbF binds to oxygen more strongly than adult hemoglobin (HbA), 'enabling the transfer of oxygen from mother to fetus prenatally [20]. The switch from HbF to HbA production is not irreversible, and this variability is often genetically controlled [21]. In fact, this switch is controlled by BCL11A [22], which can be edited to increase fetal hemoglobin [23, 24], a proposed gene-therapy for beta thalassemia and sickle cell disease which has its own significant off-target problems [25].

Figure 1: MSA of heme binding proteins from Prevotella, Capnocytophaga, Bacteroides, Barnesiella: MAFFT (v7.123b) [26] was used for doing the multiple sequence alignment (MSA). MSA figures were generated using the ENDscript server [27].

Heme-binding proteins in *Prevotella*, *Capnocytophaga*, *Bacteroides*, *Barnesiella*

Extracellular heme-binding proteins (hemophores) sequester heme from the environment [28], which may be ‘plundering’ of iron or to sequester oxygen by (oxygen-hating) anaerobic pathogens [29]. For eg, *Prevotella intermedia* produces two proteins homologous to *Porphyromonas gingivalis* HmuY [30] (Fig 1).

Proteins expressed in metagenomic studies of patients

These proteins are expressed in metagenomic studies of patients (3 studies done - sequences in SI.Hemoglobin).

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