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Regarding the article entitled "Iron supplementation does not worsen respiratory health or alter the sputum microbiome in cystic fibrosis"

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Dear Editor,

We read with interest the article by Gifford et al. "Iron supplementation does not worsen respiratory health or alter the sputum microbiome in cystic fibrosis", published in the Journal of Cystic Fibrosis [1]. In this double-blind cross-over randomised placebo-controlled trial, the authors show that 6 weeks of oral iron supplementation does not worsen respiratory health but fail to correct anaemia. This is in contrast to our earlier report that intravenous iron improves haemoglobin but may carry the risk of worsening respiratory infection [2].

One reason for this contrast is the different routes of iron supplementation. Hepcidin is an antimicrobial-like peptide hormone synthesised by the liver that acts as the 'master regulator' of iron metabolism [3]. Hepcidin level increases after acute administration of oral iron supplementation to reduce duodenal iron absorption and sequester iron in the reticuloendothelial system [3,4]. This is a protective mechanism to protect against infection, since most human pathogens are iron dependent [3]. Intravenous iron may overwhelm iron withholding mechanisms, increase lung iron content and increase susceptibility to infection.

Another reason for this contrast is that every patient in our case series received standard treatment for CF exacerbation [2]. Since our report was published, other reports in the Journal of Cystic Fibrosis have highlighted that intravenous antibiotics may improve haemoglobin [5,6]. Gifford et al. demonstrated significant improvement in participants' serum iron level even with low dose oral iron and high serum hepcidin-25 concentrations [1]. Therefore, improving serum iron level alone may not be enough to improve haemoglobin level among people with CF. Interleukin-6 (IL-6) is abundant in the blood of people with CF [7]. IL-6 represses erythropoietin-dependent maturation of erythroid cell lines and limits haemoglobin synthesis [8]. IL-6 levels fall during the treatment of CF exacerbation [7], which may explain the improvement in haemoglobin.

Another report in the Journal of Cystic Fibrosis has highlighted the importance of accurately assessing systemic iron status to avoid injudicious iron supplementation [9]. There may be a risk of respiratory deterioration if oral iron supplementation is continued after the subject has become iron replete, which is not assessed in Gifford et al.'s short (6-week) study [1].

Iron deficiency anaemia remains an important clinical issue for people with CF and further studies on its optimal management are needed. Gifford et al. suggested that a larger randomised controlled trial is needed to demonstrate the safety of oral iron [1]. We suggest that a similar trial of intravenous iron is also needed.

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