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Correspondence

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,

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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

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significant improvement in participants' serum iron level even 38 with low dose oral iron and high serum hepcidin-25 concentra- 39 tions [1]. Therefore, improving serum iron level alone may not be 40 enough to improve haemoglobin level among people with CF. 41 Interleukin-6 (IL-6) is abundant in the blood of people with CF 42 [7]. IL-6 represses erythropoietin-dependent maturation of 43 erythroid cell lines and limits haemoglobin synthesis [8]. IL-6 44 levels fall during the treatment of CF exacerbation [7], which 45 may explain the improvement in haemoglobin.

Another report in the Journal of Cystic Fibrosis has highlighted 47 the importance of accurately assessing systemic iron status to 48 avoid injudicious iron supplementation [9]. There may be a risk of 49 respiratory deterioration if oral iron supplementation is continued 50 after the subject has become iron replete, which is not assessed in 51 Gifford et al.'s short (6-week) study [1].

Iron deficiency anaemia remains an important clinical 53 issue for people with CF and further studies on its optimal 54 management are needed. Gifford et al. suggested that a larger 55 randomised controlled trial is needed to demonstrate the safety 56 of oral iron [1]. We suggest that a similar trial of intravenous 57 iron is also needed.

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