

Response to Reviewer 1 Comments

Dear Reviewer :

Thank you very much for your comments and suggestions on our manuscript. We have revised our manuscript accordingly. The changes are incorporated into the manuscript with red color. The point-wise responses to the comments is detailed below in red color.

Best wishes!

This study reviewed and developed a perspective about the role of gut bacteria in bilirubin excretion and metabolism. The author has made some appropriate changes, but the “theory”(e.g., Lines 22-30, Line 90, Lines 440-453) still needs to be modified.

Response: Thank you very much for your suggestions and we are making changes to these wordings. As follows:

Line 22-30: In the new **perspective**, the gut is a crucial crossroad of bilirubin excretion, and bacteria colonizing the gut could play different roles in excretion of bilirubin, including *Escherichia coli* as the main traffic jam causers, some *Clostridium* and *Bacteroides* strains as the traffic police, and most probiotic *Bifidobacterium* and *Lactobacillus* strains as bystanders with no effect or only secondary indirect effect on the metabolism of bilirubin. This **insight** could explain why breast milk jaundice causes a longer duration of blood bilirubin, and why most probiotics have limited effects on neonatal jaundice. With the encouragement of breastmilk feeding, our **perspective** could guide the development of new therapy methods to prevent this side effect of breastfeeding.

Line 89-91: These findings inspire us to construct a new comprehensive **perspective** on microbiota and physiological jaundice and try to explain breast milk jaundice from a microbiota view.

Line 440-453: In this new **perspective**, gut is a crucial crossroad of bilirubin route, and bacteria colonized in neonatal gut could play different roles for excretion of bilirubin, including *Escherichia coli* as the main traffic jam causers, some *Clostridium* and *Bacteroides* strains as the traffic police, and most probiotic *Bifidobacterium* and *Lactobacillus* strains as bystanders with no direct effect on the metabolism of bilirubin. This **perspective** could explain why most probiotics have limited effects on neonatal jaundice. In breast milk jaundice, bystanders are predominant and both traffic jam causers and traffic police are inhibited, thus a relatively moderate amplitude, but a longer duration of blood bilirubin increase could be found in breast milk jaundice neonates. In suboptimal intake hyperbilirubinemia and preterm jaundice neonates, the delay of gut microbiota development causes the extended period of traffic jam causers dominant phase, thus more bilirubin is reabsorbed and enters the enterohepatic circulation and the blood bilirubin level increased severely on the 3rd-4th days. With the encouragement of breastmilk feeding, jaundice would be more risk for neonates, and our **perspective** could provide a theoretical basis and guide the development of new therapy methods to prevent this side effect of breastfeeding.