Biofloratech Ltd October 2023

The recent FDA letter on Probiotics in Neonates: Consider all the evidence.

The US FDA recently issued a warning on Sept 29th about the use of probiotics in preterm babies. This was in response to a single case report of a death from sepsis due to a specific strain of B. longum infantis in a baby <1000g in the USA. The product in question was a single-strain product (Evivo™), and the strain was specifically B. infantis EVC001. The FDA are still in the process of investigating this episode however, so a final report is not yet ready. There is no doubt that regulators should always act with caution. However, the FDA warning is not a summary of the evidence – it does not reference any of the published benefits from probiotics for example.

Probiotic sepsis is not a new risk. There are case reports, referenced in the FDA letter, of probiotic sepsis in neonates, most of which show a prompt recovery when treated with antibiotics. There is also a systematic review published last year (https://pubmed.ncbi.nlm.nih.gov/35348825/) which acknowledges this important but very rare complication, similar to that reported in other large meta-analyses and trials. It is important not to ignore any risk associated with treatments that are given to babies, but all professionals should balance benefits against risks – which is normal medical practice.

Coincidentally, this month a systematic review and network meta-analysis was published https://jamanetwork.com/journals/jamapediatrics/article-abstract/2810095 which again confirmed that multistrain probiotics reduced deaths from all causes, reduced NEC, time in hospital and feed intolerance. Probiotics are highly studied, and the evidence for the benefits strongly outweighing the risks is strong. One analysis contained data from over 77,000 babies (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8321836/) and they quote that one study reported three, non-fatal cases of probiotic sepsis only. The presence of ileostomy and NEC are risk factors for sepsis. In babies <1000g, probiotics reduced NEC significantly (OR 0.59).

Multistrain probiotics were, as per other analyses, more effective than single strain ones.

Considering the numbers in the USA:

- 50,000 babies are born <1500g every year.
- 15,000 (about 30%) of these receive probiotics, which has prevented NEC in (at least) 300 of these babies.
- In those 300 babies, 100 of them would have developed surgical NEC and 50 would have died.

It is reasonable, therefore, to conclude that many more lives have been saved using probiotics. We also know that probiotics are widely used by parents in well, mature babies, with no reports of deaths.

The FDA is not a neonatal body and does not practice neonatal medicine. Their job is to alert professionals to risk, whether those risks are already known or not and their job is not to balance benefits against risks – that is a clinician's role. In neonatal medicine, we may often use treatments, like steroids, which are "off-label" and we should evaluate all the evidence, balance benefits against risks, and educate our teams to use treatments as safely as possible.

We anticipate that the final FDA report may be more balanced and should consider the vast amount of positive evidence too. Clinicians should always remain well informed, and parents should also be well informed too. The balance of benefits to risks applies as much to using probiotics as to any of the other treatments and devices used in neonatal care.

Over 2.5 million doses of Labinic drops have been administered worldwide, and there have been no deaths associated with it over the seven years it has been available. We are not however complacent – we know our product is given to vulnerable babies, and we recognise that such a tragic outcome is a remote possibility.

However we also know from independent studies that Labinic Drops™ has saved lives, reduced NEC and sepsis, reduced the carriage of antibiotic-resistant organisms in the gut, has improved feed tolerance, has speeded up time to full feeds, and has reduced hospitalisation. Taken as a whole, we still believe that the positive benefits in the evidence-base strongly outweigh any risks. We continue to support independent research, and we remain committed to helping clinicians achieve the best possible outcomes for your patients and families.