Enhancing Calf Immunity through Nutrition

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ABSTRACT

Dairy calves are extremely susceptible to gastro-intestinal disease during the preweaned period. The risk for disease decreases as the calf ages; therefore, I think it is important to break the pre-weaned period up into at least 2 distinct phases that likely need to be managed differently, early life (1st and maybe the 2nd week of life) and the remaining time the calf is fed fluid (milk or milk replacer). When a calf is born they have never been exposed to any microorganisms and some aspects of their immune system are not fully developed. Since the calf in utero received its nutrients from the cow through placental transfer, the calf has never had any nutrition orally. After birth, the calf is now in a microbial world and expected to receive all its nutrients orally from its mother's milk. The gastro-intestinal tract of the calf is naïve and develops rapidly during the first few days to weeks. The cells that make up the gastro-intestinal tract are the first line of defense of the immune system; therefore, until the cells are more adult-like the calf is at an increased risk for developing gastro-intestinal diseases. Future research needs to focus on how much, the frequency of feeding, and composition of fluid fed to a calf during this period. Currently, the primary strategies to improve the resistance to gastro-intestinal diseases during this period is focused on decreasing the interaction of potential pathogens with the cells of the calf's gastro-intestinal tract. The uses of prebiotics, probiotics, and hyper-immunized egg protein have all been shown to decrease the incidence of gastro-intestinal diseases and improve the growth of preweaned calves. It is important to note that not all research has shown improvements, but no studies have reported adverse effects with their inclusion in the diet. Calves where the bacteria get into the bloodstream are at an increased risk of becoming septicemic and consequently have a greatly increased risk of death. The high risk of death is associated with an aggressive inflammatory response. Data, in other animal models as well as calves, indicate that supplementing omega-3 fatty acids decreases the inflammatory response and improves survival of septicemic animals. Therefore, supplementing the fluid of calves may improve the survival of septicemic calves. Lastly, the plane of nutrition that calves are fed during the pre-weaned period was reported to improve future lactational performance and emerging data suggests that it may improve the resistance to gastro-intestinal diseases. Further the effect appears to persist past the pre-weaned period. Nutrition can influence disease resistance of calves in many ways, both directly by supplying specific nutrients and indirectly by influencing the exposure to microorganisms.

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INTRODUCTION

It is well documented that dairy calves are extremely susceptible to gastrointestinal diseases and mortality during the first few weeks of life (Roy, 1990). Recent reports from the US Department of Agriculture's National Animal Health and Monitoring System (NAHMS, 1993; 1996; 2007) report that the national mortality rate of heifer calves from 48 hours of life to weaning is approximately 7.8 to 10.8%. Producer perceived records indicate that scours account for 56.5 to 60.5% of all pre-weaned deaths. Approximately ¹/₄ of all pre-weaned calves are therapeutically treated for scours, and the major causes of death from scours are either dehydration or the pathogen gains access to the body and causes septicemia (Fecteau et al., 1997; Lofstedt et al., 1999). Three large surveys were conducted in England during 1936-37 (Lovell and Hill, 1940), 1946-48 (Withers, 1952a,b,c,d) and 1962-63 (Leech et al., 1968) that suggested the mortality of pre-weaned heifer calves was 5 to 6%. It is interesting that mortality rates among pre-weaned calves have not decreased and actually are greater since those early surveys, especially given the fact that the first 2 surveys in England were conducted before the widespread use of broad-spectrum antibiotics. The explanation for this is likely multifactorial, but importantly it also indicates that there is a lot of room for improving gastro-intestinal disease resistance among pre-weaned calves. How much and the composition of fluid (milk or milk replacer) fed to pre-weaned calves and the use of additives such as different fat sources, prebiotics, probiotics, and protein from hyperimmunized eggs all may improve the health of pre-weaned calves.

WHY DO PRE-WEANED CALVES GET SICK?

Dairy calves, like all mammalian species, are not exposed to microorganisms prior to birth. Furthermore, they are receiving all their nutrients from placental transfer from their mother and their gastro-intestinal tract has never seen food while they are in utero. Therefore, immediately after birth they are no longer in a sterile environment and are required to get all their nutrition orally. Many components of the immune system, which is important in protecting the calf from potential pathogens, are functional at birth; however, some aspects further develop as the calf ages, which increases the likelihood of developing disease. Colostrum has a lot of antibodies, and during the first few days of life the calf is able to absorb those antibodies into their body from the colostrum, which helps protect them from potential pathogens. This is why it is important that the calf receives adequate amounts of high quality, clean colostrum soon after birth. Calves that do not receive colostrum are at an increased risk of developing scours and 74 times more likely to die in the first 21 days of life (Wells et al., 1996). Unfortunately 20 to 35% of heifer calves did not receive adequate transfer of antibodies from colostrum (Tyler et al., 1998; NAHMS, 2007). There are many potential reasons why many calves do not receive adequate amounts of antibodies from colostrum such as feeding low antibody concentration colostrum or calves do not receive enough colostrum within 12 hours of birth. The ability of calves to absorb antibodies begins to decline within 8 to 12 hours after birth.

Colostrum is only part of the equation; many calves that receive adequate colostrum still develop gastro-intestinal disease. Data indicate that most scours occur during the first 3 weeks of life, and the relative risk of developing gastro-intestinal disease is inversely related to the age of the calf (Roy, 1990). Interestingly, by the time the calf is 3 weeks old, about 1/2 of the antibodies it received from the colostrum are gone and not much has really changed regarding the calves cellular or humoral immune system (Kampen et al., 2006). So why are calves not as likely to develop gastrointestinal disease anymore? Remember, when calves are born they have never had food in their gastro-intestinal tract, so the cells that make up the gastro-intestinal tract need to adapt to extra-uterine life. Guilloteau et al. (2009) reported that many changes occur in the first few days to week regarding the structure of the cells that line the gastro-intestinal tract. Specifically, they reported fetal-type cells are replaced with more adult-like cells within 5 to 7 days after birth. The cells that make up the gastro-intestinal tract are very important and form the first line or the physical barriers of the immune system. Therefore, my lab hypothesizes that the physical barriers of the gastro-intestinal tract are impaired during the first week(s) of life, which increases the risk of developing scours. More research is needed to understand how we can manage the calf during that first week(s) after calving, while she is adapting to the ex utero environment. My lab is currently investigating how nutrition, how much and frequency of feeding of fluid, of the calf during the first week of life influences the gastro-intestinal integrity and resistance to gastro-intestinal diseases. We hypothesize that reduced quantity or increased frequency of fluid feeding, 4 vs. 2 times per day, will reduce the incidence of scours. This research is ongoing, so we do not have recommendations yet regarding quantity and frequency of fluid during the first week of life, but I do want to make the point that there are at least 2 distinct phases that likely need to be managed differently during the pre-weaned period, early life (1st and maybe the 2nd week of life) and the remaining time the calf is fed fluid.

Resistance to disease is a balance between the microorganisms the calf is exposed to and how well the immune system of the calf is functioning (Figure 1). Some microorganisms are more virulent, or nasty, than others and the survival of these virulent microorganisms and transmission of them from one calf to another should be prevented through sanitation of feeding equipment and housing. Gastro-intestinal diseases can be broken broadly into 2 classes, scours-only and septicemia. The major difference between calves with scours-only and septicemia is that during septicemia the microorganisms, commonly bacteria, gain access to blood and reach a critical threshold where they cause whole-body disease. The mortality rate of calves with septicemia is greater than calves with scours-only, 57.4% vs. 15.1% (Fecteau et al., 1997; Lofstedt et al., 1999). The higher mortality is associated with an over-aggressive inflammatory response, which decreases blood pressure and activates the blood-clotting cascade. This decreases the blood flow to many major organs; subsequently causing multiple organ failure. Calves with scours-only, if intervention is early, can be successfully treated with oral electrolytes to prevent dehydration. Therefore, the goal should be to reduce the number of calves that get scours and/(or) septicemia; as well as to improve the survival of calves that either have scours or septicemia. Many of the current strategies to improve the health of pre-weaned calves are focused on preventing the

interaction of potentially pathogenic microorganisms with the gastro-intestinal tract of the calf or by reducing the inflammatory response of calves. In addition, there is emerging evidence that the nutrition and environment of calves during the pre-weaned period influence the health of the animal throughout life (Ballou, 2012; Frei et al., 2012).

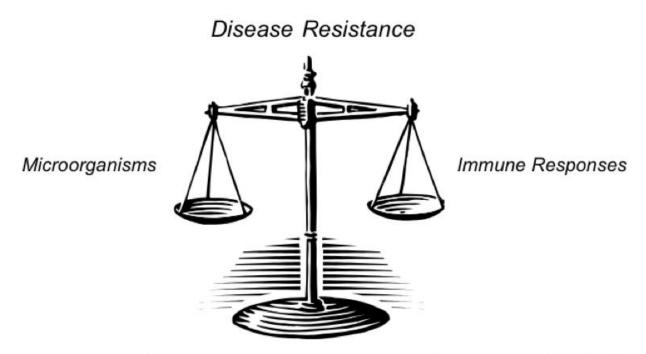


Figure 1: Disease resistance of a calf is great when the balance between microorganisms and immune responses is tipped in favor of the immune responses

FIRST WEEKS OF LIFE

As discussed previously, the risk of developing gastro-intestinal diseases and septicemia are inversely proportional to the age of the calf (Roy, 1990). Therefore, investments in both time and money to reduce the incidence of diseases and improve survival should be focused on this period. There are various nutritional strategies that can influence the resistance and recovery from gastro-intestinal diseases during this developmental period, but the major strategy is to prevent the pathogenic microorganisms from interacting with the gastro-intestinal tract of the calf through the use of prebiotics, probiotics, or hyper-immunized egg protein.

Prebiotics are dietary components that are not digested by the calf, but are used by bacteria in the gastro-intestinal tract to improve their growth. At first glance this may seem bad, why would we want to improve the growth of bacteria in the gastro-intestinal tract? The gastro-intestinal tract of mammals is not sterile. Soon after birth, a wide range of bacterial species colonizes the gastro-intestinal tract of mammals, including calves. Most of these bacterial species do not pose any immediate threat to the survival of the calf and in the past were called "good bacteria" and, of which, many of the common probiotic species are routinely classified as, including: *Lactobaccilus* species, *Bifidobacteria, Enterocooccus faecium*, and *Bacillus* species. There are many plausible mechanisms explaining how both prebiotics and probiotics would reduce the interaction of more pathogenic microorganisms with the gastro-intestinal tract of the calf. Many of the probiotic species had a direct bactericidal activity (Midolo et al., 1995) or compete with the more pathogenic microorganisms for limited resources. As mentioned before, some microorganisms are "more nasty" than others and the presence of the less threatening bacteria limits the accessibility of the nasty microorganisms to interact with the calf's gastro-intestinal tract. In addition, probiotics are themselves bacteria and they may "prime" the immune system of the calf by staying alert, as even the immune system recognizes the "good" bacteria as foreign (Blum et al., 2002; Lomax and Calder, 2009). The common, commercially-available prebiotics available are the fructooligosaccharides (**FOS**), mannanoligosaccharides (**MOS**), lactulose, and inulin.

Data on the influence of prebiotics and probiotics alone on the health of dairy calves is equivocal. There are data that show improvements in reducing scouring and improving growth (Abe et al., 1995; Heinrichs et al., 2003), whereas equally as many studies show no benefits to including either prebiotics or probiotics in milk (Morrill et al., 1995; Hill et al., 2008). The lack of a clear effect in calves is likely due to many environmental factors. Research does however support that prebiotics and probiotics are generally safe and do not have any adverse effects on calf health and performance. In fact, most regulatory agencies around the world classify most prebiotics and probiotics as Generally Regarded As Safe (**GRAS**). I currently look at adding prebiotics and probiotics as an insurance policy; you do not know when you will need them, but when you do, it is good to have them. Lastly, it is important to note that not all probiotic species and further, not all strains of a specific species, ie: not all *Lactobaccilus acidophilus* strains, behave similarly. Therefore, I would recommend only using probiotic species and strains that have been reported, through 3rd party research, to improve health and performance of calves.

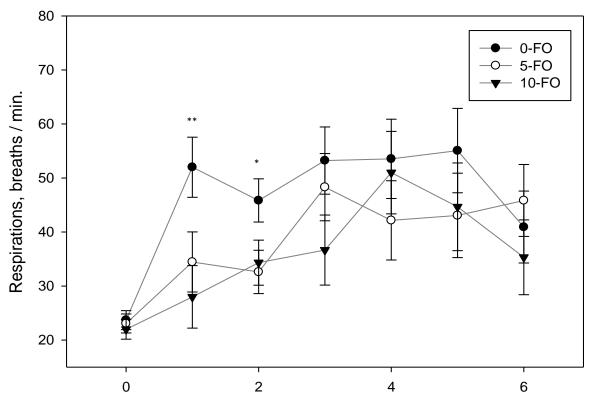
Another strategy to reduce the interaction of pathogenic microorganisms is to feed egg protein from laying hens that were vaccinated against the very microorganisms that cause gastro-intestinal diseases in calves. The laying hens will produce immunoglobulin Y (**IgY**) and concentrate those proteins in their eggs, which can recognize the pathogen, bind to it, and prevent its interaction with a calf's gastro-intestinal tract. Inclusion of whole dried egg from these decreased the morbidity due to various bacteria (Hennig-Pauka et al., 2003) and viruses (Kuroki et al., 1993; Ikemori et al., 1997).

In 2010, my lab evaluated the effects of supplementing a blend of prebiotics, probiotics, and hyper-immunized egg proteins to Holstein calves during the first 3 weeks of life (Ballou, 2011). Calves given the prophylactic treatment (n= 45) were administered directly into the milk 5 x 10^9 colony forming units per day (from a combination of *Lactobacillus acidophilus, Bacillus subtilis, Bifidobacterium thermophilum, Enterococcus faecium,* and *Bifidobacterium longum*), 2 grams per day of a blend of MOS, FOS and charcoal, and 3.2 grams per day of dried egg protein from laying hens vaccinated against K99+ *Escherichia coli* antigen, *Salmonella typhimurium, Salmonella Dublin*, coronavirus, and rotavirus. Control calves (n= 44) were not given any prebiotics,

probiotics, or dried egg protein. All calves were fed 2 quarts of a 20% protein / 20% fat non-medicated milk replacer twice daily. Prior to each feeding fecal scores were determined by 2 independent trained observers according to Larson et al. (1977). Briefly 1 = firm, well-formed; 2 = soft, pudding-like; 3 = runny, pancake batter; and 4 = liquid splatters, pulpy orange juice. The prophylactic calves refused less milk (P < 0.01) during the first 4 days of life (57 vs. 149 grams of milk powder). There were no differences in starter intake or average daily gain due to treatments. However, calves that received the prophylactic treatment had decreased incidence of scours (P < 0.01) during the first 21 days of life (25.0 vs. 51.1%). Scours were classified as a calf having consecutive fecal scores \geq 3. The intensity of disease in this study was low and only 1 out of 90 calves died during the experiment. These data support that a combination of prebiotics, probiotics, and hyper-immunized egg protein improve gastro-intestinal health and could be an alternative to metaphylactic antibiotic use. Future research should determine the efficacy of that prophylactic treatment in calves that are at a higher risk of developing severe gastro-intestinal disease and subsequently death.

In addition to reducing scours, presumably prebiotics, probiotics, and hyperimmunized egg protein could reduce the incidence of septicemia among calves by also decreasing the interaction of the bacteria with the gastro-intestinal cells of the calf, which is the site many of these septicemia causing bacteria enter blood of calves. As discussed previously, the survival of calves with septicemia is low, which is due to an over-aggressive inflammatory response. So presumably lessening the inflammatory response of septicemic calves could improve their survival. Fat sources rich in omega-3 polyunsaturated fatty acids (**PUFA**) attenuated inflammatory responses in many species (Mascioli et al., 1989; Johnson et al., 1993; Korver et al., 1997). The concentrations of omega-3 fatty acids in milk are nearly devoid. Therefore, supplementing milk with omega-3 PUFA may provide a more appropriate inflammatory response in septicemic calves.

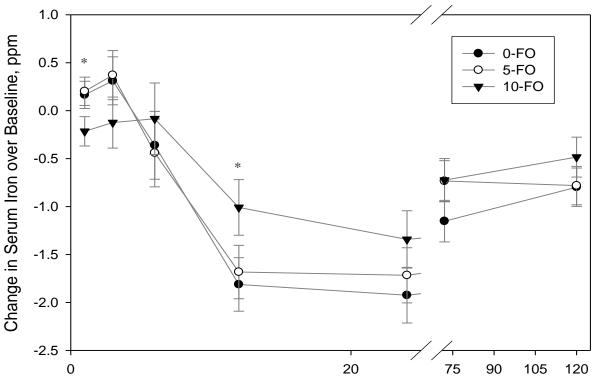
To investigate the ability of supplemental fish oil (source rich in long chain omega-3 PUFA) to decrease the inflammatory response of pre-weaned calves, 38 Jersey bull calves were supplemented with 0 (0-FO), 5 (5-FO), or 10% (10-FO) of the fatty acids from fish oil for 23 days after which they were challenged with Salmonella typhimurium lipopolysaccharide (LPS) to stimulate an inflammatory response (Ballou et al., 2008). We measured heart rates, respiration rates, and various blood metabolites that would indicate how aggressive the inflammatory response was following the challenge. The LPS challenge caused an aggressive inflammatory response as evidenced by average nadir plasma glucose concentrations of approximately 20 mg/dL at 4 h post-challenge and approximately 50% of the calves became transiently laterally recumbent and non-responsive. These are common indicators of septicemia. In addition, 4 calves (2 in each of the 0-FO and 10-FO treatments) died following the LPS challenge. The demeanor of all calves following the LPS challenge was characterized as depressed, lethargic, and anorectic. Supplementing the milk replacer with fish oil attenuated the general changes in sickness scores (P < 0.05; data not shown), but had no effects on the suckle reflex of calves following the LPS challenge. Respiratory rate of 0-FO were rapidly elevated within 1 h of the LPS challenge and were greater (P < 0.02) than either the 5-FO or 10-FO at 1 and 2 h post-challenge (Figure 2).



Time following challenge, hr

Figure 2: Supplementing fish oil in milk replacer lessens the acute increase in respiratory rate following a lipopolysaccharide challenge. Sliced time effects reported as * P <0.10 and ** P <0.05. Data reported as LSMeans ± SEM. Data from Ballou et al. (2008).

The inflammatory response induced by the LPS challenge altered serum iron concentrations. Iron is stored in the liver as ferritin during an inflammatory response to reduce the availability of iron for bacterial growth. Supplementing 10-FO altered (P = 0.06) the concentrations of iron in plasma following the LPS challenge (Figure 3). Therefore the lessened response observed among 10-FO calves was likely a consequence of a reduced inflammatory response. Similarly, the activation of the inflammatory response causes a change in nutrient partitioning and decreases growth (Kinsbergen et al., 1994). During an inflammatory response nutrients are shifted away from growth toward tissues involved in survival of the calf. Supplementing fish oil prior to the LPS challenge decreased the breakdown of body tissues (decreased plasma urea nitrogen and non-esterified fatty acids) and the effect of supplemental fish oil was dose dependent (data not shown). These data indicate that supplementing milk replacer with fish oil lessened many aspects of a severe inflammatory response; therefore, septicemic calves that were previously supplemented with fish oil may have an improved survival. This hypothesis remains to be tested.



Time following challenge, hr

Figure 3: Supplementing 10-FO in milk replacer lessened (P = 0.06) the change in serum iron concentrations following a lipopolysaccharide challenge. Sliced time effects reported as * P < 0.10. Data reported as LSMeans ± SEM. Data from Ballou et at. (2008).

AFTER 2 WEEKS OF LIFE

The risk of gastro-intestinal diseases dramatically declines after the first few weeks of life. However, there is emerging evidence that nutrition and environment of calves during the pre-weaned period has persistent effects on the health of the animal later in life (Ballou, 2012; Frei et al., 2012). How much, the frequency of feeding, and the composition of fluid fed to calves during the pre-weaned period influences the health of calves. The majority of dairy calves in the US are fed restricted quantities of fluid to encourage them to consume calf starter earlier, so they can be weaned at a younger age. This management strategy was widely adopted because it was seen as more economical because a pound of powder was much more expensive than a pound of calf starter. Although it is more expensive to raise a calf during the pre-weaned period, when fed higher planes of fluid nutrition, in most situations, the total cost to raise the calf to a first calf heifer is less expensive than when they are fed restricted quantities of fluid in early life. Further, this restricted fluid feeding strategy was widely adopted without any understanding of the potential long-term impacts on performance and health of the animal. Over the past decade, there was resurgence in the interest of feeding dairy calves higher planes of fluid nutrition (Brown et al., 2005; Raeth-Knight et al., 2009;

Ballou, 2012). These higher planes of nutrition programs are often called "Accelerated", "Intensive", or "Full Potential".

A recent meta-analysis performed by Soberon and Van Amburgh (2013) suggested that higher planes of fluid nutrition positively impacted the long-term productivity of the calf when she was an adult. This analysis indicates that early life experiences, including nutrition, influences long-term performance. Over the past 4 years, my laboratory has conducted research to understand how plane of nutrition during the pre-weaned period influences the immune responses and resistance to infectious disease during the pre- and immediate post-weaned periods (Ballou, 2012; Hanson, 2012; Obeidat et al., 2012). The results indicate that plane of nutrition influences the immune responses of calves and the effects extend into the immediate post-weaned period (Ballou, 2012; Hanson, 2012). Jersey bull calves that were fed a higher plane of fluid nutrition had improved neutrophil and whole blood *E. coli* killing capacities after they were weaned when compared to Jersey calves fed a more conventional, low plane of nutrition (Figure 4; Ballou, 2012).

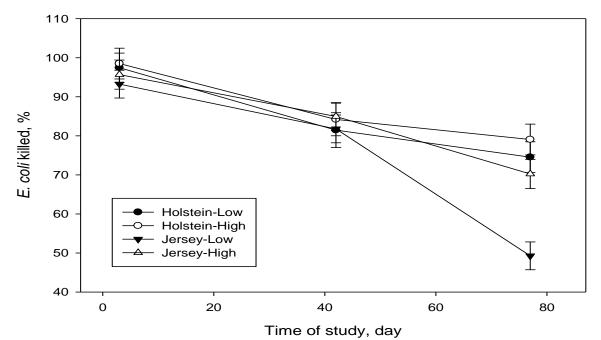


Figure 4: Feeding a higher plane of nutrition during the pre-weaned period improved the ability of whole blood from Jersey calves to kill a live *E. coli* during the immediate post-weaned period. Sliced breed x plane of nutrition contrast at day 77 P < 0.04. Data reported as LSMeans ± SEM Data from Ballou, 2012.

In a follow-up study, Jersey calves that were previously fed a higher plane of milk replacer had a more rapid up-regulation of many immune responses (increased neutrophil oxidative burst and secretion of tumor necrosis factor- α when stimulated with LPS) after they were challenged with an oral bolus of a *Salmonella typhimurium* (data not shown; Hanson, 2012). Furthermore, the higher plane of nutrition calves tended (*P* <

0.10) to have less signs of disease as evidenced by lower concentrations of plasma haptoglobin (data not shown). In addition to data from my laboratory, Ollivett et al. (2012) reported that calves fed a higher plane of nutrition had improved immune responses to an oral *Cryptosporidium parvum* challenge. After the oral challenge, high plane fed calves maintained hydration, had a faster recovery from scours, and continued to convert feed with great efficiency compared to low plane fed calves.

Milk production has increased dramatically over the past few decades, but the incidences of infectious diseases and risk of leaving the herd early due to disease continues to plague the dairy industry. It is well accepted among many species of animals that early life experiences, including nutrition, have long-term impacts on the health of animals. Data from my laboratory and others are suggesting that calves fed higher planes of fluid nutrition may have improved resistance to gastro-intestinal disease that extends beyond the pre-weaned period. More data are needed to understand how plane of fluid nutrition influences the resistance to diseases that are common during the life cycle of dairy cattle, including: gastro-intestinal, respiratory disease, metritis, and mastitis.

IMPLICATIONS

Dairy calves in the first few weeks of life are extremely susceptible to disease, which may be related to the naïve gastro-intestinal tract of calves. Currently, the uses of prebiotics, probiotics, and hyper-immunized egg proteins have all been shown to reduce the incidence of gastro-intestinal disease. If you have a high early mortality I would recommend you look into using a research-backed product with prebiotics, probiotics, and hyper-immunized egg protein. Early data is suggesting that both plane of nutrition and frequency of feeding influence immune responses and disease resistance of calves that extend beyond the pre-weaned period. More data are needed before definitive conclusions can be drawn, but current data do appear promising.

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SESSION NOTES