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# “Periweaning Failure to Thrive Syndrome (PFTS)” - difficulties of investigating an emerging clinical problem

Bob Friendship; John Harding; Steve Henry

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Members of the Swine Health Management (SHM) section of the American Board of Veterinary Practitioners (ABVP) would like to thank the planning committee of the 2010 Leman Conference for this opportunity to demonstrate the dedication of swine practitioners and our ability to strategically approach difficult production challenges in the swine industry.

In 2008 a presentation for the AD Leman Conference<sup>1</sup> explored a syndrome in newly weaned pigs exhibiting anorexia followed by a catabolic series of events leading to body store depletion. Outcome was either death or euthanasia because of the serious debility of affected pigs. The authors chose the term “catabolic” as descriptive of the condition due to the mobilization of lipid stores, the loss of muscle mass, failure to grow and, eventually, fatty infiltration of liver and debilitation. This discussion described the syndrome, impact in an affected population and provided speculative reasoning that might be mechanistic in development.

We revisit this topic again because of the increased incidence, or at the least, recognition and interest in this ‘failure to thrive’ condition in weaned pig. Although various descriptors such as “cachexia”, “catabolic” and “postweaning wasting” have been used by to identify the syndrome in the past, a number of industry stakeholders recently met at the 2010 IPVS Congress and agreed by consensus to use the name “**Periweaning Failure to Thrive Syndrome (PFTS)**”. These stakeholders included researchers, diagnosticians and practitioners from Ontario, Manitoba,

Saskatchewan, Iowa, Kansas and North Carolina. They encourage the industry adoption of “PFTS” when referring to cases and herds fitting the following case description (Table 1).

## Clinical presentation and progression to outcome

At the time of writing the etiology of the syndrome is not understood, but an infective cause is suspected and various research groups are investigating possible causes. That said, there are a number of key clinical and pathological features that are consistently reported:

- Clinically normal, thrifty and robust pigs are weaned at ~21 days of age and are placed in nurseries or wean-to-finish facilities
- Common industry practices are employed to assist the transition at weaning to solid feed, i.e. initial presentation of small amounts of highly palatable and digestible feed, offered multiple times per day in feeders, on floor mats and in pans. In necessary situations zone heat is provided and flowing, free-access water is provided for the first hours to assure pigs identify and locate it.
- Most pigs weaned in the batch readily start on feed, and rapidly increase intake and gain with no indication of clinical health concern.

**Table 1: “Periweaning Failure to Thrive Syndrome (PFTS)”**

**Clinical case definition:** A pig that is afebrile with normal behavior and body condition at weaning (around 3 weeks) and lacking evidence of respiratory, systemic and enteric diseases, and that within 7 days of weaning is not eating, becomes depressed, may ‘chomp’, becoming progressively debilitated within 2-3 weeks of weaning.

**Context:** There are a multitude of risk factors associated with post-weaning debilitation. This syndrome is usually first recognized in groups/populations of pigs where current mortality exceeds expected mortality. Sufficient examination to confirm absence of common discernible infectious, nutritional, management, and environmental contributors that would elevate the “runt-rate” above basal threshold is expected. PRRSV infected pigs do not qualify for this case definition.

Proposed case definition developed collectively by: Bob Friendship, Henry Gaurvreau, John Harding, Hank Harris, Steve Henry, Dick Hesse, Howard Hill, Yanyun Huang, Randy Jones, Kent Schwartz, Mike Sheridan: Vancouver, July 21, 2010.

- By contrast, PFTS-affected pigs become visually identifiable by 60-72 hours post-weaning. While active, alert and afebrile it is apparent from the flat sides and empty abdomen that these pigs are not eating. It is at this point that affected pigs first become clinically apparent.
- Incidence is quite variable and, in low incidence situations i.e. < 3% of pigs, it may not be fully appreciated or recognized in the critical early stages. The lack of overt disease expression such as diarrhea, respiratory distress, lethargy and depression results in pigs being overlooked. In the more typical presentations with incidence of 5-20% the caretakers identify the problem early on.
- The recommended practice is to move the gaunt, anorectic pigs into a special care pen for additional individual attention. Added heat, electrolyte solution in pans, special high-milk feed supplements, moistened feed and individual pig feeding all are employed to entice consumption. Very few affected pigs respond positively to the additional care and support.
- The terminal phase is surprisingly long with pigs surviving without eating for 17-20 days post-weaning. Affected pigs do consume sufficient water to stay alive, albeit in dehydrated condition. Mortality charts present a pattern of high death loss in the 3<sup>rd</sup> and 4<sup>th</sup> week post weaning, followed by minimal mortality in subsequent weeks. Diarrhea of starvation is a late sign, as is the frequent appearance of various secondary septicemic bacterial diseases. In debilitated pigs the often recognized lesions and signs are of *H. parasuis*, streptococcal arthritis and pneumonia, and varied salmonella serotypes. As these are not diseases noted in the normal pigs in the cohort the clinical interpretation is that they are incidental infections associated with a debilitated and presumably immunosuppressed animal. It is noteworthy as described below that thymic atrophy is a key pathological feature of the late-stage PFTS pig, and is associated with immunosuppression although immunologic function testing has not been performed *in vitro*.

### **Progression of the clinical pathologic process**

A critical point of irreversibility is reached at some point in time if pigs are not voluntarily eating. When this is exactly occurring is difficult to determine clinically but, considering weaning as T<sub>0</sub>, observation (SCH) suggests that recovery after 96hr is infrequent.

- Behavior begins to change post 96hr as activity decreases when the group is stimulated. Affected pigs startle but move only short distances, often do not stay with the group and appear, for lack of a better word, 'confused'. Abnormal oral behavior includes chewing motions and, in some pigs, a 'chomping' behavior with the pig resting its head on the back of a penmate while chewing.
- Growth appears to cease and the weight of normal pigs in the cohort quickly surpasses the PFTS-affected pigs in special care pens. This creates confusion for the casual observer, leading to the false impression that these must have been the smallest pigs at weaning. This is not the case. Field observations indicates the affected pigs are in very good body condition at weaning, and that smaller pigs at weaning are at lower risk of developing PFTS. Progression, then, is to standing, often side by side, with head lowered and essentially immobile 6-8 days after weaning. By this time body condition has severely declined with prominent skeletal features seen, dehydration is obvious as is the impression of pallor. Pigs have entered the terminal phase, which is prolonged without euthanasia intervention.

### **Pathologic changes and assumed metabolic changes**

The most notable postmortem finding is that the affected pigs are in very poor body condition or emaciated, unless they have been euthanized at an earlier stage of illness. There is a general absence of body fat, and the gastrointestinal tract is generally empty. In the few pigs in the recovery stage food is present in the stomach, the intestinal walls thin and the intestinal contents are watery. Severe thymic atrophy is commonly seen, and depending on the health status of the farm, individual pigs may also show evidence of other common nursery diseases such as bronchopneumonia, arthritis or umbilical abscessation. Thymic atrophy appears to be less pronounced in early cases suggesting it is associated with progressive debilitation and thus may not be a primary lesion.

Microscopic lesions are primarily confined to the nasal cavities and gastrointestinal tract and most consistently include gastritis, moderate to severe small intestinal villi atrophy, mild to severe colitis and non-progressive rhinitis. Generalized hepatic lipidosis is noted in many pigs. The presence of hepatic lipidosis along with emaciation and a general absence of body fat are intriguing and suggest the pig is capable of mobilizing but not utilizing fat reserves. This may be explained by the absence or inhibition in the young pig of key liver enzymes required for fatty acid metabolism (M. Tokach, personal correspondence 2010).

## **Experiences and approaches to investigating an emerging clinical problem**

**Steve** – We have recognized this “occurrence, syndrome, case presentation”, if you will, since the early 1990’s. Samples have been evaluated from numerous cases over the years. For quite some time, the frequent concurrent infections in groups of pigs with influenza, PRRS, PCV2 or a combination led to a ‘default’ diagnosis of systemic illness at weaning as root cause. In more recent years, with groups of pigs consistently free of these infections yet exhibiting the pattern of cachexia, we reevaluated past diagnostic efforts and started over in trying to discover logical and predictable events that could explain the process. PFTS seems to be a group-specific problem within production flows or systems. Weaned pigs from the same sow farm or farms, weaned at the same time, may present morbidity and mortality of 2-3% in one room and 15+% in yet another location. While there is variation from week to week as well, the problem does seem to wax and wane when a farm or system is affected. A general clinical observation is that it is a more severe occurrence in colder times of the year. And, from time to time, PFTS seems to go away entirely for a period of time for reasons unknown. In the longer look, however, this syndrome appears at some level, repeatedly over time, in a majority of farms we serve.

In recent months, in collaboration with the team at K-State,<sup>a</sup> we began to focus on infectious disease as a primary cause of PFTS. With the serendipitous identification of herpes virus through panviral microarray, our efforts began to determine possible significance. Systematic necropsy of affected pigs, conducted in 4 affected systems and multiple locations over several months consistently demonstrated lesions of marked inflammation, inclusion bodies and substantial amounts of thick, purulent material obstructing nasal and, especially, ethmoid turbinates. This pathology was present at early stages in the clinical progression of PFTS. In all cases there is a point approximately 3-4 weeks post-weaning when all affected pigs are euthanized for humane reasons. This provided an opportunity to sample large numbers of pigs, leading to our appreciation of the consistency of lesions, pathology and the presence of herpes inclusions histopathologically.

Virus was cloned, sequenced and identified as porcine cytomegalovirus (PCMV) by two laboratories.<sup>b</sup> While certainly not a unique finding in young pigs, PCMV has not been something we have frequently identified in the past, perhaps because we have not specifically looked for it. We propose a theoretical explanation for a causal relationship between PCMV infection and the development of PFTS in these cases. Acute and severe turbinate inflammation,

especially in the caudal ethmoid-cribriform plate region of the nasal cavity, attenuates the pig’s ability to normally taste and orally explore feed at weaning. Pigs are quite dependent on taste, smell and especially nose and mouth exploration in their feeding behavior. Research has clearly demonstrated that a substantial number of weaned pigs do not explore or consume creep feed even when offered diligently during the suckling period.<sup>2</sup> From this research it is expected that some portion of pigs, at weaning, have no experience with pellets or other solid food. In those pigs the premise we hold is that they may be precluded by the severe, yet anatomically localized lesions induced by PCMV, from normal food discovery and consumption. This premise is based on careful observation of affected pigs and their behavior over time. Early in the post-weaning period affected pigs will be seen to mouth pellets, chew on them but then allow them to fall from the mouth. The activity to find something to eat continues but is ineffective. This attempt to feed/discover seems to diminish over time and ceases at about 120 hours post-weaning. The chewing/chomping mastication behavior, which occurs after 120 hours, may be an effort to dislodge the viscous purulent material in the nasal cavity.

If PCMV is indeed activated at or near the time of weaning the association of identifiable stressors may be most important. This logical step is made based on the general characteristic of herpes viruses to become active under stressful situations. Next logical steps are to investigate PCMV further through animal inoculation experiments, to determine what other associations (i.e. litter influence, dam effect, etc) may be involved.

- a Drs. Dick Hesse, Jerome Nietfeld, Bob Rowland, Ada Cino Ozuna
- b Dr. Hong Li, Washington State University; Drs. Bob Rowland and Dick Hesse, Kansas State University

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**JOHN** – Dr. Henry Gauvreau was instrumental in bringing the initial Saskatchewan case to my attention in 2007, the details of which have been previously published<sup>3</sup>. In this small 100 sow Saskatchewan farrow-to-finish farm nursery mortality was elevated and appeared to follow a cyclical pattern peaking in the spring/summer. The fact that the clinical signs and mortality persisted after PCV2 vaccine was used on the farm was a crucial fact in our decision to initiate this investigation. Soon after the initial visits to this farm my PhD student, Dr. Yanyun Huang, began working on the project and has generated most of the results presented below from 2 ongoing studies.

The first study aims to identify common swine pathogens associated with, and possibly the cause of PFTS. PFTS-affected and age-matched unaffected pigs from Saskatchewan farms underwent extensive diagnostic examination



**Bob Friendship; John Harding; Steve Henry**

in order to identify all of the common known pathogens and to characterize the pathology associated with PFTS. A total of 43 pigs were examined including 18 PFTS-affected (PFTS-sick) and 7 age-matched healthy cohorts (PFTS-healthy) from the affected farm, and 4 healthy age-matched pigs from each of two non-affected farms (Ctrl). All pigs were humanely euthanized and necropsy examinations performed immediately. Fresh and fixed tissues were collected and processed routinely.

Although the cause of PFTS remains unknown, it is our conclusion based on the current diagnostic investigation that PFTS is not caused by or is not a classical presentation of several common porcine pathogens including PRRS, PCV2, SIV, TGEV, rotavirus, *Clostridium perfringens*, pathogenic *E coli*, *Brachyspira hyodysenteriae* and *pilosicoli.*, *Bordetella spp.*, *Streptococcus spp.*, *Haemophilus parasuis*, *Pasteurella multocida*. These results agree with the consensus of other investigators. The potential roles of enteric calicivirus, coccidiosis, haemagglutinating encephalomyelitis virus (HEV) and porcine cytomegalovirus (PPCMV) as well as uncommon or novel swine pathogens need further investigation.

The uncertain etiology of PFTS makes it difficult to confirm suspected cases, therefore gross and microscopic pathology is the most important tool to characterize the disease and to rule in and rule out suspected cases. The aim of our second study is to compare the microscopic lesions between PFTS-affected and non-affected pigs, and among suspect cases throughout North America. To date, cases from Saskatchewan, Manitoba and Ontario have been assessed. Additional data recently obtained from Kansas will be added to this analysis. Only cases meeting the following criteria were included in the study:

- a. Affected farms had no obvious disease in suckling pigs;
- b. The affected pigs demonstrated anorexia, progressive debilitation and death within 3 weeks of weaning;
- c. No obvious known pathogens were identified at a herd level to explain the mortality;
- d. No other common diseases or conditions were consistently identified in the group of pigs submitted to the diagnostic lab from the farm. More specifically, no more than 50% of pigs pathologically examined from the farm showed evidence of a disease process such as polyserositis or bronchopneumonia indicative of a concurrent bacterial or viral infection.

H & E stained histology slides obtained for all cases meeting the inclusion criteria were examined in a non-blinded manner by Yanyun Huang. The presence and severity of microscopic lesions in multiple tissues were graded subjectively using a predefined scoring system. To assess the

presence or absence of bronchopneumonia and thoracic thymic atrophy the written case reports supplied by the pathologist were reviewed.

A total of 42 sick pigs were included from one farm in Saskatchewan, one farm in Ontario and 8 farms in Manitoba. Healthy pigs from affected farms in Saskatchewan (n = 7) and Ontario (n = 3) were also examined. No healthy pigs from the affected farms in Manitoba were available. Eight control pigs from unaffected farms in Saskatchewan were used for the purpose of comparison.

The most prominent lesions observed in Saskatchewan PFTS-affected pigs included: superficial lymphocytic fundic gastritis, atrophic enteritis, superficial colitis, thymic atrophy, and chronic active rhinitis. Similar lesions, especially the gastrointestinal lesions, were highly prevalent in the PFTS-suspected pigs from Ontario and Manitoba. Importantly, the diagnostic laboratories dealing with potential PFTS cases have been inconsistent with respect to the tissues examined from suspect pigs, thus, diagnosis is difficult and cross-laboratory comparison nearly impossible. For this reason, our key recommendation is that for PFTS investigation, an exhaustive list of tissues be collected by all laboratories for histopathologic examination from suspect cases.

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**BOB** – I have dealt with one herd that clearly exhibited the clinical signs and post-mortem findings described above. Dr. Brent Jones was the herd's primary veterinarian and did significant diagnostic work to rule-out many of the diseases such as PRRS and PCVAD that one might consider when dealing with a post-weaning mortality that had reached 10% at the time of my first visit. The details of the case have been previously published<sup>4</sup>. The interesting feature of this case was that the nursery with the signs of PFTS received barrows from a very high health genetic nucleus herd. The female pigs that stayed behind in the nucleus herd remained healthy. The nursery eventually stopped bringing in pigs from the genetic nucleus and without depopulating switched to a different source of weanling pig and had no cases of PFTS in the new arrivals. This to me hints at an infectious cause, most likely a disease that is commonly present on most farms but in this case naïve pigs were encountering the pathogen at a time of vulnerability at arrival to the off-site nursery. My first clinical impression of the pigs in the nursery was that they were infected with HEV. We were unable to find conclusive evidence of this on post-mortem examination and serology from the sow herd indicated that HEV was present. So it was not a case of an HEV-negative sow herd supplying pigs to an off-site nursery where they encountered the virus. Although serology did show that pigs were becoming infected and developing titers to HEV in the

***“Periweaning Failure to Thrive Syndrome (PFTS)” - difficulties of investigating an emerging clinical problem***

nursery. We did not investigate the possibility of PCMV. Gross post mortem examination reports did not indicate that turbinates were examined. Sneezing although present was not remarkable and was not entered on the history form at submission. In retrospect PCMV is also a good candidate to fit this scenario.

However based on other case reports it is apparent that the disease can occur in farrow to finish herds and that the mixing of pigs from different health statuses is not a required feature. Maybe the unique situation described in this case caused “the perfect storm” and so the expression of the disease was greatly enhanced. The fact that the pigs in this case were free of many of the common diseases certainly helped us conclude that this was a new problem, that something very unusual was happening. Very often pig disease presents as a complex of multiple agents and a new and subtle problem can be overlooked. For example, I am quite certain that I failed to identify cases of porcine circovirus infection in herds until it became a major problem because it was just part of a mixture of common diseases.

**Conclusions – the difficulties of investigating an emerging clinical problem**

The genesis and progression of PFTS could well develop as a result of quite a diverse set of production- and infective-disease-related triggering events. Thus, investigating the origins of complex multifactorial problems can be slow, frustrating and expensive (hence the word “difficulties” in the title). Parsed to the simplest step, failure to thrive may well be the outcome of anything that prevents or alters the normal learning behavior of a weaned pig to receive positive feedback and eat.

Although the etiology of PFTS is not presently understood, this is just one of perhaps many “emerging/re-emerging disease syndromes” that will affect pork production systems in the future. The emergence/re-emergence of new diseases may result from changes in production and management systems (such as with PRDC and the “18 week wall”), novel pathogens (such as with PRRS [1990] and PCV2 [1995], or by old pathogens with a new face (such as with SIV H3N2 [1998] and numerous subsequent reassortants). It is likely that many or most emerging/re-emerging disease syndromes will be first recognized in systems and regions with the highest health status herds that have readily accessible and full service swine diagnostic and disease research laboratories. Hence, as health status of North American swine herds improves as expected in the future, the emergence of new diseases is anticipated. **This does**

**not implicate high health herds as the origin of new swine diseases, but rather reflects the reality that the presentation of unique clinical signs, pathology or both are less likely to be masked by common diseases and therefore unrecognized or overlooked.**

In closing, a few words based on our experiences dealing with emerging/re-emerging disease syndromes including PFTS are offered to those with sufficient stamina to persist (both by reading this paper and still looking for unique challenges):

- Collaboration is key – we learn more by working with each other than we do by ourselves,
- Disease investigation involves more than “routine” diagnostics,
- Inconsistent or incomplete sampling is a missed opportunity,
- The story is incomplete until we examine healthy cohorts in addition to the diseased animals
- Formalin is cheap, if in doubt “save it”! One must examine all of the major organ systems to develop a thorough understanding of the pathogenesis at hand. It is therefore essential to fix portions of virtually all organs even if there is no apparent gross pathology.

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