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**Diagnosis by ruling out other diseases or conditions: a double edged-sword?**

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Swine production is nowadays highly specialized, mainly with large, intensive and confinement-rearing production systems all around the world. Importantly, farmers of these systems acquired high level of professionalism and education, which demand an outstanding service from their veterinarians and consultants. In parallel, pathological problems have evolved to complex disease scenarios, in which old and new pathogens are mixed and interact with the host, management, environment and the production system. Such scenario forces farmers and veterinarians to be prepared to deal with those multifactorial conditions, and the correct and timely diagnosis is the corner-stone to ensure their control.

The Greek word “diagnosis” literally means “through thinking” (Morley 1991). Although the process of getting a diagnosis may vary among individuals and clinical presentations, it is very important is to be systematic to ensure that decisions are focused and objective (Ramírez and Karriker 2010). The diagnostic process is a rather complex plan that includes two main steps. The first one (inductive or descriptive) implies to answer the questions of “who has what, where, when, since when, how many and how”; in other words, historical, clinical and epidemiological data must be collected in an objective and reliable manner. The second step (deductive) must allow establishing a presumptive diagnosis, including hypotheses on the causality of the condition considered, including a likely differential diagnostic list (compulsory when dealing with challenging cases). The deductive step will also give insights on the presumably correct control or prevention strategies to be implemented.

The diagnosis can be already difficult even when well-established etiological agents and/or risk factors are contributing to the disease problem, especially in the abovementioned complex scenarios. In this context, periweaning failure-to-thrive syndrome (PFTS) is a particularly difficult condition to be recognized and diagnosed as pointed out by Bertolini and others (2018) published on page 95 of this week’s issue of Veterinary Record. Besides relatively unspecific clinical signs consisting of anorexia, progressive debilitation, depression and oral compulsive behavior (in some animals) like chewing, chomping and licking, PFTS-affected pigs do not have hallmark pathological lesions (Huang and Harding 2015). Moreover, PFTS must be diagnosed when such clinical picture occurs in absence of known infectious, nutritional or environmental factors (Huang and others, 2012). In consequence, PFTS diagnosis is mainly established by ruling out other potential causes with similar clinical outcomes. This situation raises a number of key questions for the veterinarian: Did the practitioner rule out all potential infectious agents correctly? Does the country/region have the sufficient etiologic laboratory capabilities to detect them? How does the veterinarian know that nutritional or environmental factors have properly investigated and ruled out? This latter point is even more difficult to assess, since management improvement in affected farms decreases the number of PFTS cases, but does not stop the impact of this syndrome completely.

**PFTS and infectious diseases**

A novel disease is always difficult to establish, since first approach is to rule out existing conditions. Moreover, the veterinarian must be prepared to discard most common conditions by means of clinical-pathological outcomes and laboratory investigations. Taking into account the population-driven nature of most concerning problems in swine, infectious causes are the first to be suspected in potential conditions perceived to be new. A wide infectious agent survey was performed some years ago on PFTS (Huang and others 2012). The authors looked for a total of 20 known pathogens, including 9 bacteria, 10 viruses and one parasite (coccidia), and none of them were significantly related with disease occurrence. Moreover, a limited search for common swine pathogens also yielded no apparent association with PFTS cases in Spain (Segalés and others 2012). In fact, porcine reproductive and respiratory syndrome (PRRS) virus was found in some sporadic pooled sera from PFTS-like pigs by RT-PCR, but those animals did not display interstitial pneumonia and attending farm veterinarians did not consider the clinical picture fall in the usual presentation of PRRS. Therefore, it was concluded that no infectious causal agents were related with the condition. In a subsequent study including cases of Spain and Poland, infectious agents were also discarded (Ramis and others 2015). Further, attempts to reproduce PFTS by means of tissue homogenate inoculation failed (Huang and Harding, 2014). Finally, it would not be surprising that other non-usually investigated infectious agents might be present in PFTS-affected pigs. From this point of view, novel agents are being discovered every year (Fournié and others 2015), and a complete ruling out of infectious participation in the condition is probably not yet possible.

**PFTS and genetics**

Genetic predisposition to diseases is another piece for the puzzle of multifactorial diseases. In most cases such predisposition is unlikely to be linked to one particular gene, but of complex polygenic origin. In consequence, epigenetics (study of genetic control by factors others than an individual's DNA sequences) is probably a key concept to understand those multifactorial conditions (Simmons 2008).

A genetic component has already been proposed for PFTS (Ramis and others 2015). These authors used paternity DNA analyses to demonstrate that certain boars accounted for a significant higher incidence of PFTS in the corresponding affected farms. In consequence, the removal of these boars from the herd reproductive program decreased importantly the incidence of the condition.

Subsequently, a case-control investigation on PFTS was performed in Brazil (Zanella and others 2016) by means of a genome-wide association study to identify potential genetic markers linked to the disease. Specifically, these authors found four chromosomal regions (one located on SSCX, another on SSC8 and two more on SSC14) linked to PFTS predisposition. Interestingly, some of the genes found associated to PFTS are apparently involved in human depression. The work of Bertolini and others (2018) offered further insights on the genetic predisposition of

the condition. Their analyses indicated various regions in chromosomes SSC1, SSC3, SSC6 and SSC11 with haplotype divergences between case and control piglets. Curiously, none of the regions identified in the study of Bertolini and others (2018) coincided with the ones of the work of Zanella and others (2015), which pose some debate on the specific genetic characterization of PFTS. In fact, Bertolini and others (2018) already speculated on a potential differential expression of genes in PFTS depending on the particular genetic background.

**PFTS: a double edged-sword**

Based on existing knowledge, PFTS cased definition is still based on clinical features and ruling out known infectious and non-infectious causes. However, this type of disease represents a double edged-sword at a diagnostic level. On one hand, a case definition for this condition has been proposed and accepted (Huang and Harding 2011), which should help the veterinarian to try to approach properly the diagnostic investigations. On the other hand, there are still many elements that make difficult to be absolutely certain that no other potential factors can be causally associated. In consequence, lack of proper farm investigation and/or laboratory capabilities prompts for a risk of over- or under-diagnosing this condition by field veterinarians. This must be an important matter of awareness for practitioners and diagnosticians, since it forces them to be absolutely accurate, more than usual, in all diagnostic (inductive and deductive) steps to definitively confirm or rule out PFTS. Moreover, current data also forces veterinarians that, once the condition is diagnosed, to thoroughly investigate the potential genetic background predisposing.

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