The severity of PRRS virus infection is often related to its interactions with other concurrent diseases.

PRRS virus isolates are known to differ in their ability to cause clinical signs and lesions. The molecular basis for these inherent differences has not been identified and cannot be predicted with our current diagnostic tests.

It has been suggested, but not proven, that PRRS virus has a direct immune suppressive effect in the pig.

Experimentally, pigs have been subjected to co-infections with PRRS virus and a number of different infectious agents including *Streptococcus suis*, *Haemophilus parasuis*, *Mycoplasma hyopneumoniae*, *Pasteurella multocida*, *Actinobacillus pleuropneumoniae*, *Salmonella cholerasuis*, porcine Circovirus type 2, and swine influenza virus. Generally, co-infections result in much more significant disease than either agent acting alone does.

Immunity that develops after infection with a single strain of PRRS virus will frequently not result in protection against other strains of PRRS virus.

Laboratory techniques (including genomic sequencing) have not been developed that can accurately predict cross-protection between different strains of PRRS virus. Additionally, the ability of commercial vaccines to protect against a specific field strain of the virus cannot be predicted through laboratory testing.
“PRRS Plus” – PRRS Virus Infection in Combination with Other Agents
PG Halbur

Introduction

The clinical manifestations of PRRS virus infection vary from subclinical to severe reproductive failure and/or respiratory disease. Severity of PRRS virus-associated disease may result from interactions among factors involving differences in virulence among PRRS virus isolates, differences in concurrent infections (other viruses and bacteria), genetically-based differences in pig susceptibility, environmental differences from farm to farm, varying management factors among farms (i.e., weaning age, pig flow, gilt acclimatization strategies), level of herd immunity to PRRS virus, and other factors or circumstances. This review will primarily focus on differences in virulence among PRRS virus isolates, the effect of co-infections on the severity of PRRS virus-associated disease, and host genetic susceptibility differences. Although equally important, less documentation is available in the literature on the influence of environment and production style on the manifestation of PRRS virus-associated disease.

Differences among PRRS Viruses

It is now widely accepted that PRRS virus isolates differ in virulence. In neonatal and growing pigs, PRRS virus isolates vary markedly in the severity of experimentally induced pneumonia (Halbur et al. 1995, 1996a, 1996b; Thanawongnuwech et al., 1998a). Some isolates produce subclinical disease and minimal lesions while others cause severe disease and severe interstitial pneumonia lesions. Differences in virulence among PRRS virus isolates have also been demonstrated in the pregnant female (Mengeling et al., 1994, 1996, 1998; Park et al., 1996). It is widely accepted that PRRS virus isolates differ in genetic and antigenic make-up (Meng et al., 1994, 1995b, 1996a; Meng, 2000). However, a link between specific molecular sequences and the degree of clinical severity among PRRS virus isolates has not yet been identified. At this time, molecular and antigenic characterization of isolates is used as an epidemiological tool rather than a virulence determinant or vaccine selection tool.

Viral Pathogenesis

The fact that PRRS virus replication occurs in cells of the macrophage lineage is consistent with the idea that PRRS virus leads to immunosuppression (Done and Paton, 1995; Done et al., 1996; Meier et al., 1999; Molitor et al., 1997). However, experimental data has not always supported the perception of a systemic immunosuppressive effect of PRRS virus. It has been proposed that what is perceived as recurrent PRRS infections may be better explained as successive waves of acute infections in susceptible pigs along with infection by opportunistic bacteria (Albina et al., 1998).

PRRS virus primarily infects cells of the macrophage cell lineage. These cells are extremely important in a number of immunological responses, including the destruction of bacteria. Several groups have demonstrated that PRRS virus replicates in and damages pulmonary alveolar macrophages (PAMs) (Molitor et al., 1997; Thanawongnuwech et al., 1997, 1998a, 1998b) and pulmonary intravascular macrophages (PIMs) (Thanawongnuwech et al., 1997, 1998a, 1998b, 2000). One proposed hypothesis is that PRRS virus destroys the PAMs and PIMs, which are then replaced by immature cells that are less effective in containing bacterial infections, thereby resulting in pneumonia and septicemia (Pijoan et al., 1994). The fact that PRRS virus can persist in the bloodstream for several weeks despite the presence of anti-PRRSV antibodies certainly suggests that the immune system is not efficient in clearing PRRS virus infection. Complete clearance of PRRS virus often takes as long as 5 months in immunologically competent pigs (Allende et al., 1999). These remarkable findings emphasize the phenomenal challenges we face in preventing and/or controlling PRRS virus-associated disease outbreaks.

Bacterial Co-infection Models

Several groups have attempted to develop models to study PRRS virus co-infections with various bacteria. There is strong experimental evidence to support PRRS virus-induced predisposition to Streptococcus suis in nursery age pigs (Galina et al., 1994; Halbur et al., 2000; Thanawongnuwech et al., 2000) and in neonatal pigs from sows that were experimentally infected with PRRS virus in late gestation (Feng et al., 2001). There is also experimental evidence to support PRRS virus-induced increased susceptibility
to *Salmonella choleraesuis* (Wills et al., 2000), *Bordetella bronchiseptica* (Brockmeier et al., 2000), and *Mycoplasma hyopneumoniae* (Thacker et al., 1999) infection and disease. Experimental efforts have been generally unsuccessful in demonstrating predisposition to disease induced by *Haemophilus parasuis* (Cooper et al., 1995; Segales et al., 1999; Solano et al., 1997), *Actinobacillus pleuropneumoniae* (Pol et al., 1997), or *Pasteurella multocida* (Carvalho et al., 1997). Table 1 summarizes much of the information in the literature on experimental models using PRRS virus and bacterial co-infections.

That PRRS virus predisposes pigs to *S. suis* infection is clear from the numbers of field cases seen in the diagnostic laboratory and from the research. Practitioners commonly report poor success in treating or preventing this problematic co-infection in nursery pigs. The efficacy of several PRRS virus and *S. suis* vaccines and antimicrobial treatment regimens were tested in a well-established PRRS virus/*S. suis* co-infection model (Halbur et al., 2000; Schmitt et al., 2001). Ceftiofur injections and an experimental live autogenous *S. suis* vaccine were the only treatments that significantly reduced mortality associated with PRRS virus/*S. suis* co-infection. This suggests that if PRRS virus/*S. suis* co-infection cannot be prevented, it is most cost effective to focus treatment strategies on controlling *S. suis* infections.

Porcine respiratory disease complex (PRDC) associated with PRRS virus/*M. hyopneumoniae* co-infection is the most common respiratory problem in grow-finish pigs today (Clark, 1998; Dee et al., 1996, 1997; Desrosiers, 1998; Halbur, 1998). Frequently, there are one or more additional opportunistic pathogens, such as *Pasteurella multocida*, complicating the PRRS virus/*M. hyopneumoniae* PRDC cases. A *M. hyopneumoniae*/PRRS virus co-infection model that closely mimicked the field situation was developed and studied in detail (Thacker et al., 1999). Unexpectedly, the model showed that *M. hyopneumoniae* actually made the PRRS virus-induced pneumonia more severe and for a longer duration (Thacker et al., 1999). Vaccination with both MLV PRRS virus vaccine and *M. hyopneumoniae* bacterin eliminated the benefit of the *M. hyopneumoniae* vaccination.

Table 1: PRRS virus and bacterial co-infection models

<table>
<thead>
<tr>
<th>Reference</th>
<th>Coinfection</th>
<th>Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brockmeier et al., 2000</td>
<td><em>Bordetella bronchiseptica</em></td>
<td>Clinical disease was more severe in co-infected pigs.</td>
</tr>
<tr>
<td>Carvalho et al., 1997</td>
<td><em>Pasteurella multocida</em></td>
<td>No clear interaction between PRRS virus and <em>Pasteurella multocida</em>.</td>
</tr>
<tr>
<td>Cooper et al., 1995</td>
<td><em>Streptococcus suis</em></td>
<td>No predisposition to <em>S. suis</em>.</td>
</tr>
<tr>
<td>Cooper et al., 1995</td>
<td><em>Salmonella choleraesuis</em></td>
<td>No predisposition to <em>Salmonella choleraesuis</em>.</td>
</tr>
<tr>
<td>Cooper et al., 1995</td>
<td><em>Haemophilus parasuis</em></td>
<td>No predisposition to <em>Haemophilus parasuis</em>.</td>
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<tr>
<td>Cooper et al., 1995</td>
<td><em>Pasteurella multocida</em></td>
<td>No predisposition to <em>Pasteurella multocida</em>.</td>
</tr>
<tr>
<td>Feng et al., 2001</td>
<td><em>Streptococcus suis</em></td>
<td>In <em>utero</em> PRRS virus infection increases the susceptibility of neonates to <em>S. suis</em>.</td>
</tr>
<tr>
<td>Galina et al., 1994</td>
<td><em>Streptococcus suis</em></td>
<td>PRRS virus predisposed pigs to <em>S. suis</em>.</td>
</tr>
<tr>
<td>Pol et al., 1997</td>
<td><em>Actinobacillus pleuropneumoniae</em></td>
<td>Minimal predisposition to <em>Actinobacillus pleuropneumoniae</em>.</td>
</tr>
<tr>
<td>Segales et al., 1999</td>
<td><em>Haemophilus parasuis</em></td>
<td>No predisposition to <em>Haemophilus parasuis</em>.</td>
</tr>
<tr>
<td>Solano et al., 1997</td>
<td><em>Haemophilus parasuis</em></td>
<td>No predisposition to <em>Haemophilus parasuis</em>.</td>
</tr>
<tr>
<td>Thacker et al., 1999</td>
<td><em>Mycoplasma hyopneumoniae</em></td>
<td><em>M. hyopneumoniae</em> infection potentiated the severity and duration of PRRS virus-induced pneumonia.</td>
</tr>
<tr>
<td>Thanawongnuwech et al., 2000</td>
<td><em>Streptococcus suis</em></td>
<td>PRRS virus predisposed pigs to <em>S. suis</em>. PRRS virus strains differed in degree of predisposition to <em>S. suis</em>. PRRS virus MLV vaccines predisposed pigs to <em>S. suis</em>.</td>
</tr>
<tr>
<td>Van Alstine et al., 1996</td>
<td><em>Mycoplasma hyopneumoniae</em></td>
<td>No predisposition to <em>Mycoplasma hyopneumoniae</em>.</td>
</tr>
<tr>
<td>Wills et al., 2000</td>
<td><em>Salmonella choleraesuis</em></td>
<td>Synergism of PRRS virus and <em>Salmonella choleraesuis</em>.</td>
</tr>
</tbody>
</table>
Viral Co-infection Models

PRRS virus and other viral co-infections are also common. At the Iowa State University Veterinary Diagnostic Laboratory, PRRS virus/porcine circovirus type 2 (PCV2) and PRRS virus/swine influenza virus (SIV) co-infections are commonly diagnosed. Researchers in Belgium concluded that dual infection with PRRS virus and SIV, or PRRS virus and porcine respiratory coronavirus (PRCV), resulted in more severe disease and growth retardation than single PRRS virus infection (van Reeth et al., 1996, 1999). Others have also dually infected pigs with PRRS virus and porcine respiratory coronavirus (PRCV) and similarly concluded that this resulted in enhanced disease and lesions (Halbur et al., unpublished data). PRRS virus is found along with PCV2 in the majority of postweaning multisystemic wasting syndrome (PMWS) field cases and many of the PRDC cases submitted to the Iowa State University Veterinary Diagnostic Laboratory (Harms et al., 2001; Sorden, 2000). Perhaps the most convincing experimental evidence of virus-virus interaction to date is that demonstrated by PRRS virus/PCV2 co-infection models. These models clearly established an additive or synergistic effect of PRRS virus and PCV2. Harms et al. (2001) demonstrated more severe clinical signs, lesions, and mortality in pigs dually inoculated with PRRS virus and PCV2, as compared to singular infections. Evidence from diagnostic submissions, together with the above-described models, strongly supports an important role for PCV2 in PMWS and PRDC and enhanced disease with PRRS virus-PCV2 co-infection.

Host Susceptibility Differences

Besides differences in virulence among virus isolates, genetic differences among pigs affecting their susceptibility to PRRS virus should also be considered (Halbur et al., 1998). It is common to observe marked differences in the severity of clinical disease and resulting financial losses due to PRRS in herds with similar production and management styles, but with different pig genetics. Producers with multiple sources and types of genetics on the same farm frequently report that certain sources or breeds of pigs are more severely affected by PRRS virus-induced disease (P. Halbur, personal observation). Pigs or sows within a herd also vary in their ability to clear PRRS virus infection over time (Bierk et al., 2001). Christopher-Hennings et al. (2001) also reported differences in the duration of PRRS virus shedding in semen of boars of different breeds. A pig that is resistant to PRRS virus infection has not yet been discovered. The ability to select resistant or less susceptible pigs would be a tremendous benefit to the swine industry. The genetic basis for the apparent differences in pig genetic susceptibility has yet to be defined.

Protective Immunity against Different PRRS Virus Strains

Protective immunity against re-challenge with the same PRRS virus appears to be of long duration. However, protection against challenge with different strains of PRRS virus may be variable and incomplete (Lager et al., 1999), as supported by field observations.

For example, in the late summer of 1996, the number of cases of severe abortion storms in U.S. swine herds reported to diagnostic laboratories increased sharply (Halbur et al., 1997). The syndrome came to be described as "sow abortion and mortality syndrome" (SAMS) or "atypical PRRS" or "acute PRRS" by clinicians and diagnosticians. Clinical outbreaks were characterized by mid- or late-term abortions with 10 to 50 percent of the herd affected in a 1 to 5 week period. Sows typically were anorexic and had fevers of 104°F to 106°F for 2 to 4 days. Sow mortality increased with reports of losses of 5 to 10 percent of the inventory in a 1 to 5 week period. Increased preweaning mortality and decreased nursery pig performance, primarily due to respiratory disease, was common in these “acute PRRS” herds. Although the losses were severe, epidemiological investigations found that clinical losses associated with these outbreaks were not extraordinarily different than those observed in the late 1980’s when PRRS virus was first recognized (Bush et al., 1997). Although most of the herds had used a modified live virus (MLV) PRRS vaccine, in the majority of the cases, diagnosticians observed microscopic lesions typical of PRRS virus (interstitial pneumonia, encephalitis, myometritis) and were able to demonstrate the presence of PRRS virus antigen associated with the lesions. PRRS virus was frequently isolated from the tissue or serum of affected pigs. Most PRRS virus isolates from these outbreaks were determined to be field isolates (wild type), but in some cases, the virus recovered was found to be highly similar to the MLV PRRS virus vaccine utilized in the affected herds.

Isolation of vaccine-like strains of PRRS virus from cases of reproductive failure in breeding herds and/or respiratory disease in growing pigs occurs in the U.S.
Experimental evidence to support vaccine-induced disease has been demonstrated in growing pigs in the U.S. (Thanawongnuwech et al., 1998a; 2000; Halbur et al., 2000). Because of these findings, there continues to be debate and discussion among researchers, diagnosticians, practitioners, and producers over the safe and efficacious use of vaccines (Key et al., 2001; Meng et al., 2000; Nielsen et al., 2001). Ultimately, practitioners and producers must weigh the risks and benefits for themselves.

Summary

It is clear that PRRS virus isolates vary in virulence and this may account for much of the variability in the clinical signs of PRRS in the field. The molecular tools are not yet available to predict virulence, determine the level of cross protection between PRRS virus isolates, or select the most appropriate vaccines for use in specific herds or geographic locations. Concurrent viral and bacterial co-infections can certainly influence the severity and duration of disease and mortality associated with PRRS virus infection and account for a great deal of the differences in losses attributed to PRRS from herd to herd.

References


