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Review

Porcine epidemic diarrhea virus infection: Etiology, epidemiology, pathogenesis and immunoprophylaxis

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ABSTRACT

Porcine epidemic diarrhea virus (PEDV), a member of the genera *Alphacoronavirus* in the family *Coronaviridae*, causes acute diarrhea/vomiting, dehydration and high mortality in seronegative neonatal piglets. For the last three decades, PEDV infection has resulted in significant economic losses in the European and Asian pig industries, but in 2013–2014 the disease was also reported in the US, Canada and Mexico. The PED epidemic in the US, from April 2013 to the present, has led to the loss of more than 10% of the US pig population.

The disappearance and re-emergence of epidemic PED indicates that the virus is able to escape from current vaccination protocols, biosecurity and control systems. Endemic PED is a significant problem, which is exacerbated by the emergence (or potential importation) of multiple PEDV variants. Epidemic PEDV strains spread rapidly and cause a high number of pig deaths. These strains are highly enteropathogenic and acutely infect villous epithelial cells of the entire small and large intestines although the jejunum and ileum are the primary sites. PEDV infections cause acute, severe atrophic enteritis accompanied by viremia that leads to profound diarrhea and vomiting, followed by extensive dehydration, which is the major cause of death in nursing piglets. A comprehensive understanding of the pathogenic characteristics of epidemic or endemic PEDV strains is needed to prevent and control the disease in affected regions and to develop an effective vaccine. This review focuses on the etiology, epidemiology, disease mechanisms and pathogenesis as well as immunoprophylaxis against PEDV infection.

Introduction

Porcine epidemic diarrhea virus (PEDV), a member of the genera *Alphacoronavirus* in the family *Coronaviridae* of the order *Nidovirales*, causes acute diarrhea, vomiting, dehydration and high mortality in neonatal piglets, resulting in significant economic losses. The disease was initially reported in European and Asian pig industries over the last 30 years, with the virus first appearing in England (Wood, 1977) and Belgium (Pensaert and de Bouck, 1978) in the early 1970s. Recently, PEDV has also been reported in the US (Stevenson et al., 2013). Since then, the virus has rapidly spread nationwide throughout the USA (Cima, 2013) and to other countries in North America, including Canada and Mexico. As a result of the significant impact of PEDV, the US pig industry has lost almost 10% of its domestic pig population after only a 1 year-epidemic period, amounting to approximately 7 million piglets.

Similar epidemiological and clinical features between PEDV and another *Alphacoronavirus*, transmissible gastroenteritis virus (TGEV), have led to complications in diagnosis, requiring differential laboratory tests (Saif et al., 2012). Since the emergence of a natural spike gene deletion mutant of TGEV, porcine respiratory coronavirus (PRCV) in 1984, the spread of TGEV has been reduced in PRCV-seropositive herds due to cross-protective immunity with TGEV (Saif et al., 2012). In contrast, PEDV continues to spread and cause economic problems worldwide.

Based on genetic analysis, the family *Coronaviridae* can be divided into the four genera: *Alphacoronavirus*, *Betacoronavirus*, *Gammacoronavirus*, and *Deltacoronavirus*. Bats are the projected host for the gene source of *Alphacoronaviruses* and *Betacoronaviruses*, while birds are the suspect host for *Gammacoronaviruses* and *Deltacoronaviruses* (Woo et al., 2012). In different US regions where PEDV is epidemic, a new coronavirus genetically distinct from PEDV, porcine deltacoronavirus (PDCoV), has been simultaneously (and frequently) detected in diarrheic fecal samples from pigs (Wang et al., 2014a). The clinical impact and disease severity of PDCoV in the field is reportedly less than that of PEDV. A recent study confirmed that PDCoV is enteropathogenic in pigs and acutely infects the small intestine, causing severe diarrhea and/or vomiting and atrophic enteritis, similar to the clinical signs of PEDV and TGEV infections (Jung et al., 2015). At present, differential diagnosis of PEDV, PDCoV, and TGEV is critical to control viral epidemic diarrheas in US pig farms.

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This review focuses on current understanding of the etiology, epidemiology, disease mechanisms and pathogenesis of PEDV and the control measures that may be used to prevent PEDV infection.

Etiology

PEDV structure and genome

PEDV is enveloped and pleomorphic with a range in diameter of 95–190 nm, including the projections, which are approximately 18 nm in length (Pensaert and de Bouck, 1978). Details of the PEDV structure and genome can be found elsewhere (Song and Park, 2012). PEDV has a single-stranded positive-sense RNA genome of approximately 28 kb in size (excluding the poly A-tail) that encodes four structural proteins, namely, spike (S), envelope (E), membrane (M), and nucleocapsid (N) protein, and four nonstructural proteins: 1a, 1b, 3a, and 3b (Kocherhans et al., 2001). Among the viral proteins, the S protein is critical for regulating interactions with specific host cell receptor glycoproteins to mediate viral entry and for inducing neutralizing antibodies (Bosch et al., 2003). The S protein is also associated with growth adaptation in vitro and attenuation of PEDV virulence in vivo (Sato et al., 2011). The M protein is the most abundant component among viral proteins in the envelope and plays an important role in virus assembly by interacting with the S and N proteins (Klumperman et al., 1994; Vennema et al., 1996). The N protein of coronavirus binds RNA and packages viral genomic RNA into the nucleocapsid of virus particles (Spaan et al., 1983).

Biological and physicochemical properties of PEDV

A previous study using the cell-adapted German isolate V215/78 documented the biological and physicochemical properties of PEDV (Hofmann and Wyler, 1989). PEDV showed a buoyant density of 1.18. PEDV was easily inactivated by ether or chloroform, and it was relatively stable at 4–50 °C compared to higher temperatures. After incubation in cell culture media at 4 °C with a pH range (3–10) for 6 h, PEDV exhibited low to moderate residual infectivity, whereas at 37 °C for 6 h, it retained its infectivity only between the pH range 5 and 8.5, but the virus was completely inactivated at pH < 4 and > pH 9. These data indicate that PEDV will be inactivated by acidic or alkaline disinfectants if they are applied for a certain period at a higher temperature (>37 °C).

The PEDV strain V215/78 was not neutralized by an antiserum to TGEV (Hofmann and Wyler, 1989). This finding was supported by another report (Pensaert et al., 1981), which showed no cross-reactivity of PEDV CV777 strain with either a Belgian strain of TGEV or feline infectious peritonitis virus (FIPV), as determined by immune-electron microscopy and immunofluorescence (IF). However, a subsequent study found a detectable, two-way cross-reactivity between PEDV and FIPV by more sensitive assays, such as enzyme linked immune-sorbent assay, immunoblotting and immune-precipitation (Zhou et al., 1988). These discrepancies indicate that cross-reactivity between PEDV and other coronaviruses probably varies depending on the sensitivity of the techniques and the viral strains tested. A recent study reported evidence of antigenic cross-activity between the prototype CV777 and recent US PEDV strains and TGEV (Miller strain) by sharing at least one conserved epitope on the N-terminal region of their N proteins (Lin et al., 2015).

Inactivation of PEDV

Pospischil et al. (2002) demonstrated that PEDV is inactivated by disinfectants, namely, oxidizing agents (Virkon S), bleach, phenolic compounds (One-Stroke Environ; Tek-Trol), 2% sodium hydroxide, formaldehyde and glutaraldehyde, sodium carbonate (4% anhydrous or 10% crystalline, with 0.1% detergent), ionic and non-ionic detergents, 1% strong iodophors in phosphoric acid, and lipid solvents such as chloroform.

Cell culture for virus isolation

Vero (African green monkey kidney) cells support the isolation and serial propagation of PEDV in cell cultures supplemented with the exogenous protease trypsin. Another African green monkey kidney cell line, MARC-145, also supported a subsequent cell passage of PEDV (Lawrence et al., 2014). Trypsin plays an important role in cell entry and release of PEDV virions in Vero cells, contributing to efficient replication and spread of the virus to neighboring cells in vitro (Shirato et al., 2011; Wicht et al., 2014). Trypsin resulted in the cleavage of the S protein into S1 and S2 subunits, which most likely accounts for cell-to-cell fusion and the release of virions from infected Vero cells (Shirato et al., 2011). Cytopathic effects consist of vacuolation and formation of syncytia as a result of apoptotic cell death (Hofmann and Wyler, 1988; Kim and Lee, 2014). The hemagglutinating activity of PEDV was demonstrated with rabbit erythrocytes only after trypsin treatment (Park et al., 2010). Only one serotype of PEDV has been reported from different countries (Saif et al., 2012).

Epidemiology

Epidemiology of PEDV worldwide

PEDV first appeared in the United Kingdom (Wood, 1977) and Belgium (Pensaert and de Bouck, 1978) in the early 1970s. The virus was first isolated in 1977 in Belgium and was classified in the family *Coronaviridae* (Pensaert and de Bouck, 1978). Subsequently, in the 1980s and 1990s, PEDV was identified as a cause of severe epidemics in Japan and South Korea (Takahashi et al., 1983; Kweon et al., 1993). Despite extensive application of PEDV vaccines, PED has remained endemic in South Korea (Park et al., 2013).

During the 1980s and 1990s in Europe, outbreaks of PED appeared infrequently, but the virus continued to spread and persisted in an endemic form in the pig population. Subsequent serological surveys showed a low to moderate prevalence of PEDV in European pigs (Van Reeth and Pensaert, 1994; Carvajal et al., 1995). The prevalence of PEDV in European pigs then declined greatly although the reasons are unclear. Outbreaks of PED were observed only sporadically in Europe: in The Netherlands in 1989–1991 (Pijpers et al., 1993); in Hungary in 1995 (Nagy et al., 1996), and in England in 1998 (Pritchard et al., 1999). However, a typical epidemic outbreak of PED was identified in Italy in 2005–2006 (Martelli et al., 2008).

In Thailand in 2007–2008, several outbreaks of severe PED were reported with Thai PEDV isolates in the same clade phylogenetically as the Chinese strain JS-2004-2 (Puranaveja et al., 2009). This new genotype of PEDV continues to cause sporadic outbreaks in Thailand.

In China in 2010–2012, severe PED outbreaks in seropositive pigs were reported in different regions (Li et al., 2012; Sun et al., 2012; Wang et al., 2013). For almost two decades since PEDV first emerged in China, many pig herds have been vaccinated with the prototype strain CV777-inactivated or related vaccines. However, the moderate to high mortality of suckling piglets in vaccinated herds indicates a low effectiveness of the CV777 vaccines (Li et al., 2012). The PED outbreaks in China, in 2010–2012, were caused by both classical and new PEDV variant strains that differ genetically from the prototype CV777 (Wang et al., 2013).