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Review

Porcine ear necrosis

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ABSTRACT

Porcine ear necrosis (PEN) is a condition that mainly occurs in intensive pig production systems and mostly affects piglets after weaning. The syndrome manifests itself with lesions on the pinna, which can heal or become more severe resulting in partial loss of the ear. The pathogenesis of the condition is not fully known. Three different hypotheses for the development of PEN are described in this review: (1) damage of the epidermis due to Staphylococcal exfoliative toxins; (2) occlusion of small blood vessels; and (3) ear biting with subsequent β-hemolytic streptococcal infection. Risk factors have not been completely elucidated, but viral and bacterial infections, and husbandry factors such as environment, housing conditions and management, have been suggested. It is also possible that some cases are due to a combination of these factors. The role of parasitic infestations has been not investigated. Due to bacterial involvement, severely affected pigs can be treated with antimicrobials. Control and preventive measures should focus on reducing potential risk factors by implementing herd immunization, as well as improvement of sanitary conditions, feed quality (with respect to mycotoxin contamination), management (appropriate stocking density), and environmental conditions (e.g. number of drinkers and feeders and/or optimal ventilation). Further research is needed to better understand the precise etiology and pathogenesis of PEN, so that risk factors can be identified and more targeted control measures can be implemented.

Introduction

Porcine ear necrosis (PEN), also known as ear tip necrosis, ear necrosis syndrome, ulcerative spirochetosis of the ear, or Streptococcal auricular dermatitis, is characterized by necrotizing ulcerative lesions on the pinna (Richardson et al., 1984). Trauma and bleeding may also be present, which is often associated with trauma and/or ear biting accompanying the necrosis (Park, 2011; Cameron, 2012). Loss of a part of the ear or the entire ear is possible after healing. This is an increasing problem in countries with intensive pig farming (Papatsiros, 2011), but PEN remains a mysterious and unexplored problem in pig production. This review aims to summarize and discuss the current knowledge and to elucidate avenues for future research. The published literature on this topic is limited and must be carefully interpreted, as some papers mention ear lesions and do not specify the cause as ear necrosis or ear biting. In preparing this review, electronic searches were performed in Google Scholar, PubMed, NCBI, ResearchGate, BioMed Central, and Web of Science, using the keywords 'pig', 'swine', 'porcine', 'piglets', 'ear', 'lesions', and 'necrosis'.

Prevalence

One Danish study of 90 herds and over 150,000 finisher pigs reported the prevalence of all clinical signs of illness occurring on pig farms. Ear necrosis was by far the most frequently observed clinical sign at 30%. The prevalence of other conditions such as lameness, other skin diseases (superficial abscesses, wounds on the flank), respiratory signs (coughing, forced respiration) or tail bite lesions did not exceed 15% (Petersen et al., 2008). Another Danish study (Busch et al., 2008) reported that the prevalence of PEN was 46%. Van Staaveren et al. (2018) reported that ear and tail lesions were among the most common problems (prevalence, 9%) in an investigation of animal welfare outcomes on 31 Irish farms, representing 12% of the pig farms in Ireland. Pringle et al. (2009) found the highest prevalence of PEN during the winter (50–70%) in two organic fattening farms that were monitored over a 2-year period. This indicates that prevalence may vary between countries, between farms, and also over time within a farm. Visible lesions of PEN start to appear mostly in weaned piglets between the 6th and 8th week of life (Papatsiros, 2011; Malik et al., 2020) and may

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remain visible until 14–16 weeks of age (Park, 2011). The average age at which lesions occur is 7 weeks, and initial mild lesions may become severe over an average of 4 weeks (Park et al., 2013).

Diagnosis and scoring of severity of lesions

Diagnosis is based mostly on the presence of lesions of the affected ears; histologic examination may help to distinguish necrosis from trauma. Identification of the possible cause in an individual herd can be difficult and time-consuming. By minimizing or eliminating potential risk factors, subsequent effects on prevalence and/or severity of PEN can be monitored. Lesion severity can be scored and classified (Pejsak et al., 2011; Malik et al., 2020). Malik et al. (2020) used the following score: score 1, small crust on ear tip; score 2, small wound on ear tip with reddening around; and score 3, bloody, necrotic wound on ear edge; score 4, partial lack of auricle with necrotic edge. Pejsak et al. (2011) scored severity according to the affected surface of the ear as follows: weak changes covering less than 5% of the ear surface; mild lesions covering 5–10% of the ear; and serious lesions covering more than 10% of the ear. However, a universal scoring method has not yet been established. Scoring methods to describe disease severity often use numerical values to facilitate subsequent data analyses. These scores may not always reflect precisely the severity of the disease or lesion, especially when assessment is by visual appraisal and/or performed by an inexperienced person. A binary score (lesion present or not) is the easiest and potentially the least biased method, but the severity of the lesions is not taken into account, failing to capture important information. More complex scoring systems are more difficult to implement in practice. Other conditions that can change the appearance of the pinna should also be considered e.g. frostbite due to exposure to low ambient temperatures, blue discoloration of the ear caused by systemic infections with pathogens such as porcine reproductive and respiratory syndrome virus (PRRSV), *Erysipelothrix rhusiopathiae*, *Salmonella* species (spp), and bovine viral diarrhea virus (BVDV) .

Pathogenesis

The pathogenesis of PEN is not fully elucidated (Richardson et al., 1984) and has not yet been reproduced experimentally. Three hypotheses have been suggested.

According to the first hypothesis, necrosis starts on the outer surface of the injured skin and is caused by exfoliative staphylococcal toxins that damage the epidermis (Park et al., 2013) by damaging desmosomal cadherins (Bukowski et al., 2010). Fudaba et al. (2005) demonstrated that when exfoliative toxins (ExhA, ExhB, ExhC and ExhD), which coding sequences are present in the genome of *Staphylococcus hyicus* (*S. hyicus*) were injected into porcine skin, they caused superficial formation of crusts and blisters, and digested porcine desmoglein 1 (Dsg1). Dsg1 is a desmosome component that binds vertebrate epithelial cells. Similar to *S. hyicus* toxins (Exh), exfoliative toxins A, B and D (ETA, ETB, ETD) produced by *Staphylococcus aureus* (*S. aureus*) belong to serine proteases, but cleave bonds in human Dsg1, causing complex skin infections with blister formation such as staphylococcal scales skin syndrome (SSSS) or bullous impetigo (BI; Nishifuji et al., 2008).

A second hypothesis states that ear necrosis is due to the occlusion of small blood vessels. Pejsak et al. (2011) suggested that *Mycoplasma suis* (*M. suis*) infection can lead to the production of cold agglutinins which act as autoantibodies against antigens present on the erythrocyte surface. Together with erythrocytes, they form immune complexes which occlude circulation (Hoelzle et al., 2006). As the ear tips are supplied by small vessels, they are particularly vulnerable to vascular occlusion and subsequent necrosis (Park, 2011). Septic vasculitis leading to necrosis localized to the pinna has been described in dogs and cats, but not yet in pigs (Lee Gross et al., 2005).

The third hypothesis states that trauma e.g. ear biting or environmental factors, is the primary trigger. The injured ear tip becomes infected with β-hemolytic streptococci present in the mouths of biting pigs and may cause cellulitis and necrosis (Park et al., 2013). It is important to realize that bacteria such as *S. hyicus* or *Streptococcus* spp. are part of the porcine skin microbiota, and therefore their presence on the ear will not necessarily lead to PEN. However, if there is skin trauma or tissue damage, these bacteria could multiply and exacerbate the lesions.

Clinical signs

Porcine ear necrosis lesions vary greatly, ranging from mild to severe (Fig.1). Mild lesions consist of an encrusted sore, localized on the ear tip or ventral margin of the ear. It is unclear why in some cases the ear tip is affected, whereas in others mainly the ventral margin of the ear is affected. Based on the authors' experience, mild cases do not require treatment and can heal. Lesions can also progress to the severe form with epidermal ulceration and necrotic lesions (Richardson et al., 1984). Affected parts of the pinna become dark-red, moist and crusted. The lesions can be present on one or both ears. The effects on pig performance are low, although

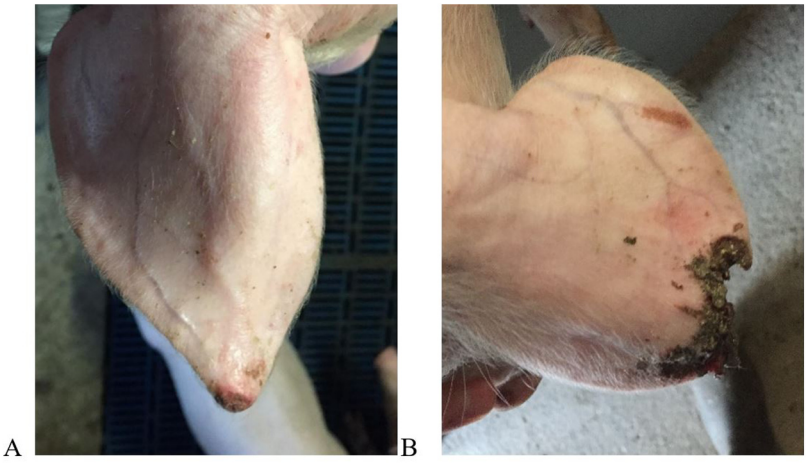

Fig. 1. Graphic presentation of porcine ear necrosis (PEN) lesions: mild lesion (A), severe lesion (B). Photographs taken by Dries Donkers.

Table 1
Overview of different infectious and non-infectious risk factors for porcine ear necrosis (PEN).

	Risk factors	Related to hypothesis [a]	References	Prevention	Possible effect on PEN
Infectious factors	Immunosuppression caused by PCV2 and PRRSV	1, 3	Pejsak et al. (2011)	Vaccination	Indirect
	Staphylococcus hyicus	1	Richardson et al. (1984)	Adequate pen hygiene	Direct
	Staphylococcus aureus	1	Park (2011)		Direct
	Mycoplasma suis	2	Truszczyński and Pejsak (2009)	Quick diagnosis and treatment; no commercial vaccine available	Direct
Non-infectious factors	High humidity/poor air quality in the pen	3	Smulders et al. (2008)	Adequate ventilation	Indirect
	Fully slatted floor without straw	3		Adequate pen design, and additional straw	Indirect
	Low availability of drinkers and feeders	3			Indirect
	High stocking density	3	Park et al. (2013)	Appropriate stocking density	Indirect
	Mycotoxin contamination	1		Non-contaminated feed; mycotoxin binder and/or detoxifiers	Direct
	High environmental temperature	3		Appropriate temperature adjustment/ventilation	Indirect

PCV2, Porcine circovirus type 2; PRRSV, Porcine reproductive and respiratory syndrome virus.
[a] Three hypotheses, as described in the text: (1) skin damage via toxins; (2) occlusion of blood vessels in ear; and (3) ear biting.

severe lesions might decrease performance and impede the sale of piglets (Park et al., 2013). The most frequent histopathological findings in the mild form are hyperkeratosis, acanthosis and intra-epidermal abscesses. The epidermis may be covered by a layer of necrotic cells, degenerated neutrophils, and exudate. Vacuolar degeneration and necrosis of basal cells, with subsequent formation of intra-epidermal vesicles, is less common. Mononuclear cell infiltrates often surround dermal capillaries (Richardson et al., 1984). Histologically, mild PEN is characterized by intra-epidermal abscesses, intracellular edema of keratinocytes, parakeratotic hyperkeratosis of the stratum corneum, and/or infiltration of neutrophils (Mirt, 1999). These findings agree with the definition of skin necrosis.[1] Reiner et al. (2019) also described inflammation and crusts on the ear base of suckling piglets, which did not resemble typical PEN. However, a possible association with PEN, which usually occurs later, in weaned pigs, is worthy of investigation.

Risk factors

Because the precise etiology and pathogenesis of PEN is largely unknown, many potential risk factors have been suggested to explain lesion prevalence and/or severity. It is generally accepted that PEN is a multifactorial condition in which infectious and non-infectious factors may play an important role (Park, 2011). Table 1 presents an overview of reported risk factors.

Infectious factors

Infectious factors that may increase the risk for PEN mainly include viral and bacterial infections. Viruses potentially involved include porcine circovirus type 2 (PCV2) and PRRSV. Both viruses are thought to exert immunosuppressive effects, potentially associated with PEN (Pejsak et al., 2011). Tomasini (2015) reported that in immunosuppressed humans, such as patients treated with high-dose corticosteroids, organ transplant recipients or human immunodeficiency virus infected patients, avirulent or low-virulence bacterial infections can cause septic vasculitis, which can theoretically lead to skin necrosis. However, this immunosuppression is likely to be much more pronounced than that caused by PCV2 or PRRSV in pigs. The most common PCV2-associated syndromes are postweaning multisystemic wasting syndrome (PMWS) and porcine dermatitis and nephropathy syndrome (PDNS). Systemic necrotizing vasculitis, as observed in PDNS, can also lead to necrotic skin lesions; however, these vascular lesions can be also observed in the kidneys, spleen or mesenterium (Segalés et al., 2005). The underlying mechanism is thought to be associated with Type III hypersensitivity and deposition of antigen-antibody aggregates (Drolet, 2012). Pejsak et al. (2011) demonstrated that vaccination of sows against PCV2 before farrowing decreased the prevalence of PEN in weaned piglets on a PCV2-positive farm. Lesion prevalence decreased from 13.1% to 5.9% and lesion severity was reduced. When the vaccination protocol ceased, the number of affected piglets rose back to pre-vaccination levels (11.6%) within 3 months. The percentage of mild and severe lesions was 3–4 times higher in pigs from unvaccinated sows than vaccinated sows. This study indirectly showed the importance of PCV2 in the development of PEN on that individual farm. To the authors' knowledge, no similar studies have been published for PRRSV. The possible role of PRRSV in PEN is based on the frequent prevalence of the virus in weaned pigs and the immunosuppressive characteristics of the virus (Drew, 2000). Therefore, viral caused immunosuppression could allow normal skin microbiota to multiply and cause damage. Risk factors should be distinguished from etiologic factors, as their presence increase the risk for disease, but do not necessarily induce the disease in a specific farm (Thrusfield and Christley, 2018). For instance, on PCV2-free farms, PCV2 infections do not contribute to the problem; similarly, PCV2 vaccination regimens also reduce the likelihood that PCV2 is involved in PEN.

S. hyicus is the most frequently isolated bacterium from ear tip necrosis lesions and can produce toxins that damage the skin (Tanabe et al., 1996). *S. hyicus* is present at the early stage of ear tip necrosis, but streptococci can also be found in more advanced lesions. Bacterial colonization of the lesions is considered as a crucial step in the breakdown of the epidermis and lesion deterioration (Richardson et al., 1984). Similar to *S. hyicus*, *S. aureus* is also commonly found on the skin surface of healthy pigs and can produce toxins that could damage the skin. Therefore, the possible involvement of *S. aureus* in PEN has been suggested (Park, 2011). Park et al. (2013) investigated the causative potential of

[1] See: National Toxicology Program, US Department of Health and Human Service, NTP Nonneoplastic Lesion Atlas, Skin - Necrosis. https://ntp.niehs.nih.gov/nnl/integumentary/skin/necrosis/skin-necrosis_508.pdf (Accessed 12 March 2021).

staphylococci. The recovery rate of *S. hyicus* from 96 ear tissue biopsies originating from 11 different farms was 66% and the recovery rate of *S. aureus* was 91%, indicating their high prevalence.

Other bacteria mentioned in the literature in association with PEN are spirochetes of the genus *Treponema*. These are commonly found in skin lesions and mouth microbiota of several species such pigs, cats, dogs and humans. *Treponema* spp. isolated from porcine gingival and ear lesions are closely related but not identical (Pringle et al., 2009), which brings into question connections between *Treponema* spp. and ear biting lesions. Park et al. (2013) demonstrated sparse numbers of spirochetes in PEN lesions on histological examination, but could not culture the bacteria. *Treponema pedis (T. pedis)* is a common species found in porcine ear lesions and shoulder ulcers. Karlsson et al. (2013) reported that spirochetes were found in 73% of shoulder ulcers, in 53% of PEN cases and in 9.7% of gingiva. However, experimental intradermal inoculation of *T. pedis* did not result in PEN (Karlsson et al., 2017). This may suggest that *Treponema* might act as secondary agents, but the paper does not rule out their importance as a primary agent.

M. suis is another agent that has been associated with PEN. This bacterium destroys erythrocytes, leading to anemia and bilirubinemia. A subsequent autoimmune response is considered to be important in the pathogenesis in PEN, as cold agglutinins (autoantibodies) can be produced, targeting antigens present on red blood cells surface (Truszczyński and Pejsak, 2009). When body temperature drops, IgM antibodies lead to erythrocyte agglutination (Schmidt et al., 1992). This can take place on the pinna, occluding small vessels and consequently causing ischemia and necrosis of the surrounding tissues. Truszczyński and Pejsak (2009) reported that *M. suis* infection may also cause immunosuppression in the acute phase, rendering pigs more susceptible to other infections. A positive clinical response to appropriate antibiotic therapy confirms the role of bacteria in the development and/or progress of the lesions (Richardson et al., 1984), but this does not prove that bacteria are the primary cause. Alternatively, non-response to antimicrobial therapy cannot exclude an infectious cause, as acquired antimicrobial resistance to commonly used antibiotics can occur (Park, 2011), or inappropriate antimicrobial choices could have been made. The role of parasitic infestations has been not been investigated, however Mirt (1999) mentioned scabies as a possible factor.

Non-infectious factors

Non-infectious factors potentially involved in PEN include environmental factors such as a fully slatted floor with no straw, poor air quality and high pen humidity (Park et al., 2013), as well as management factors such as high stocking density and early weaning, inadequate availability of drinkers and feeders per pig, and mycotoxin contamination of the feed (Park et al., 2013). Park et al. (2013) also suggested fighting and ear biting as possible factors. Smulders et al. (2008) described four factors which increased ear and tail biting: (1) inadequate number of feeding places; (2) high stable temperature; (3) high ratio of slatted areas; and (4) dry feeding. Camerlink et al. (2015) suggested genetics as an important factor influencing the behavior and biting frequency of pigs. All of these factors may greatly influence animal welfare. Diana et al. (2019) showed also that management factors may impact the development of ear, tail, or skin lesions.

Regarding feed quality, special attention has been paid to mycotoxins. Although there is no published evidence of direct involvement of mycotoxins in PEN, some toxins are considered a risk factor because of their potential immunosuppressive and dermonecrotic effects (Osweiler, 2006). Immunosuppressive effects of aflatoxins, ochratoxins, or trichothecenes have been demonstrated in vitro and in vivo, and can result from depressed T/B lymphocyte activity, suppressed production of immunoglobulins and antibodies, or decreased complement activity (Corrier, 1991). Weissenbacher-Lang et al. (2012) demonstrated a correlation between high deoxynivalenol concentrations (0.251 mg/kg) in the feed and microscopic alternations in early PEN i.e. focal epidermal necrosis, histiocyte infiltration, or bacterial growth in the superficial cell debris. Other microscopic lesions, such as collagen lysis, acute vasculitis, granulation tissue, hyperkeratosis, or histiocyte infiltration have been associated with higher concentrations of the ergot alkaloid mycotoxins ergotamine, ergocryptine and ergocristine. Gangrenous ergotism caused by ergot alkaloids is usually a result of vasoconstriction and endothelial damage, which leads to ischemia and finally dry gangrene (Osweiler, 2006).

Other non-infectious factors besides feed contamination with mycotoxins could have an indirect effect on PEN by increasing stress levels and/or aggressive behavior such as ear biting. In this sense, they fit within the third hypothesis of PEN pathogenesis. Further information about possible causes of aggression and biting in pigs can be found in the appropriate in welfare related literature.

Treatment and prevention

Severely affected pigs should be separated from the pen mates and housed in a hospital pen, in order to prevent biting by other animals. Administration of antimicrobials can slow lesion progression, but severely affected necrotic tissue will not heal using antimicrobial treatment alone, and usually dies. Bacteriological culture should be performed from the lesions and antimicrobial susceptibility testing should be requested. Skin samples should be taken from the transition between healthy and affected tissue beneath crusts, or deep swabs of the lesions. Pejsak and Truszczyński (2009) suggested that the entire age group should be medicated for 2 weeks with amoxicillin or amoxicillin with clavulanic acid. However, oral medication for an extended period does not align with current policy for the prudent use of antimicrobials and reducing the spread of antimicrobial resistance in veterinary medicine (Magnusson et al., 2019). Hansen and Busch (2008) isolated *S. hyicus* in one Danish herd affected by PEN. After antimicrobial susceptibility testing was performed, affected pigs were injected with sulfadoxine (200 mg/mL) and trimethoprim (40 mg/mL) for 5 days. The treatment increased the average daily bodyweight gain by 12%, but did not decrease lesion prevalence or severity. The authors speculated that a higher dose or longer course of treatment might have resulted in a positive effect. Diana et al. (2017) also reported that long term antimicrobial use decreased PEN severity; however, pigs were treated for 9 weeks (sulfadiazine-trimethoprim, 14.4 mg/kg/d for 5 days/week). Extended and prophylactic medication regimens are not recommended and are prohibited in some countries because they risk the development of antimicrobial resistance.

One study reported that approximately 95% of *S. aureus* isolates ($n = 87$) in PEN were resistant to penicillin G and ampicillin, and 75% of the isolates were not susceptible to tetracycline (Park et al., 2013). Trimethoprim-sulfamethoxazole (0%), sulfonamide (5%) and tiamulin (15%) had the lowest prevalence of antimicrobial resistance. In the same study, antimicrobial susceptibility of *S. hyicus* isolates was also performed ($n = 63$). More than 80% of isolates demonstrated resistance to penicillin G, ampicillin and ceftiofur, but there was almost no resistance to trimethoprim-sulfamethoxazole (0%) and sulphonamide (5%). In *M. suis* infections, affected pigs could be treated with oxytetracycline.

Vaccination of piglets against PCV2 or PRRSV may reduce the prevalence of ear necrosis. Sow vaccination may also enhance piglet immunity through antigen specific immunoglobulins or lymphocytes in the colostrum (Joisel et al., 2008).

Reducing potential risk factors such as adequate pen design, avoiding overcrowding, limiting mixing of pigs, optimal ventilation and air quality, and good feed quality[2] e.g. by aiming to eliminate exposure to mycotoxins in the feed. Post-harvest mycotoxin mitigation strategies such as mycotoxin detoxifiers, including binders (Jouany, 2007), and modifiers containing yeasts (Molnar et al., 2004), or specific enzymes (Duvick et al., 1998), which can be mixed in the feed to reduce exposure, could be considered. Ear biting and aggression between pen mates can be reduced by improving sanitation, and potentially by dietary supplementation with methionine, threonine and tryptophan (Meer et al., 2017).

Conclusions

Despite a scarcity of data and wide potential for future studies, the published literature and research on PENS is limited. PENS is a common disorder in pigs worldwide, especially in nursery pigs. The exact etiology and pathogenesis are not yet known; this hampers optimal treatment. It is unclear whether reductions in antimicrobial use due to strict regulations will influence the prevalence and severity of PEN. As the current state of knowledge does not allow causative factors to be ruled in or out, control and prevention measures should focus on reducing potential risk factors reported in the published literature, and increasing the immune status of animals. Under field conditions, practitioners should check for potential risk factors and to assess their role in the problem. Histopathological investigations can help to identify whether associated pathology originated on the skin surface or systemically. It is possible that multiple pathogenic mechanisms could be involved, depending on farm conditions; necrosis on the pinna can be a clinical sign of several specific underlying pathways. To identify and quantify the importance of potential risk factors, large multi-farm observational studies are required. As the existing PEN literature is limited, further research is required, in particular studies investigating prevalence, etiology and pathogenesis, to elucidate factors that may decrease risk.

Conflict of interest statement

None of the authors of this paper has a financial or personal relationship with other people or organisations that could inappropriately influence or bias the content of the paper.

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[2] See: https://www.merckvetmanual.com/ear-disorders/diseases-of-the-pinna/necrotic-ear-syndrome-in-swine (Accessed 12 March 2021).

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