Actinobacillus pleuropneumoniae
Summary

Introduction

1. This note provides a brief summary of the Disease and Product analysis prepared by a DISCONTOOLS group of experts on swine pleuropneumonia caused by *Actinobacillus pleuropneumoniae* (APP). They reviewed the current knowledge on the disease, considered the existing disease control tools, identified current gaps in the availability and quality of the control tools and finally determined the research necessary to develop new or improved tools. Full details are available on the web site at http://www.discontools.eu/

Disease profile

2. Presently there are 19 serotypes of APP with most serotypes belonging to biovar 1 typical APP (NAD-dependent growth) and serotypes 13 and 14 as usually belonging to the "atypical" biovar 2 (NAD-independent growth). Some serotypes may be present as biovar 1 or 2 such as isolates of serotypes 2, 4, 7, 9, 11, 13 and 17. The distinction between biovar 1 and 2 is the full-length or truncated version of the nadV gene. The truncated version of the nadV gene depicts NAD dependency (biovar 1). A correlation between biotype, serotype and virulence is not strictly relevant as there are more and more exceptions of serotype, biovar and apx-profiles (determined by PCR) and different combinations in the US, Canada and Europe. There is considerable variability in the clinical outcome depending on the serotype, strain and the geographical region.

3. All pigs including wild boar and feral pigs can be infected. Usually APP causes respiratory disease, but bacteriemia may occur. Clinical signs are most common in the finishing phase after 10 weeks of age. Maternal immunity may protect pigs from disease outbreaks until that age but exceptions with earlier occurrence do exist. The disease can be hyper-acute, where pigs are found dead with only fever and no further clinical signs. Acute outbreaks usually occur in non-immune animals with a mortality of 15-20%. Sub-acute infections can cause lesser but variable mortality. Chronic disease in endemically infected herds can result in pigs that have survived but with a reduction of growth performance and impaired animal welfare. Pigs can be carriers without stimulating an immune response. They may carry small numbers of organisms in their tonsils until proliferation of the pathogen takes place, which is hypothetically triggered by different stressors. In colonized pigs under the influence of coinfections, climate factors and other stressors there is a high risk for a disease outbreak with pigs suffering from pleuropneumonia or septicaemia. The disease can have a considerable effects on production especially when herd immunity against the involved strain is low. Several trigger factors for disease outbreaks, as coinfections and stress have been empirically reported.

Risk

4. APP is not recorded as causing human disease. All methods of control depend on establishing a correct diagnosis, identification of serotypes causing the problem, and use of commercial or autogenous vaccines or use of antibiotics to which the cultured organisms are sensitive. Apart from economic losses to farmers, the treatment of APP infection increases the use of antibiotics and thereby the risk of the development of antimicrobial resistance transferrable to humans. Eradication has been attempted in some herds, but success depends on the herd and the methodology with failure occurring in most cases, so eradication does not seem feasible at present. Failure might be due to the fact that APP forms biofilms in the tonsils, which might not lead to seroconversion. Healthy animals with APP biofilms on the tonsils have been detected at slaughter. Biofilms of APP together with multiple bacterial species have also been detected in drinking water. The only way to eradicate the disease at present is by replacing all animals with new animals free from APP infection. SPF herds are free from the infection, but the risk of reinfection is high. Unfortunately, any form of eradication is expensive compared to antibiotic treatment or metaphylaxis.
Good management practices including appropriate environmental temperatures, appropriate seasonal ventilation, and appropriate stocking density minimizes APP outbreaks in infected farms. Control of other respiratory pathogens such as swine flu, PRRSV, pseudorabies and *Mycoplasma hyopneumoniae* could be beneficiary in terms of controlling APP infections and reducing pleurisy lesions.

5. There is an economic impact at the abattoir, because pigs affected must be handled separately as they often require pleural stripping or destroying lungs and entry into a separate market. All of this negatively affects packer margins. Pigs recovered from the disease are not advised to be kept for breeding.

Diagnostics

6. A final diagnosis of a case is based on clinical signs, gross post-mortem examination, histopathology with immunohistochemical confirmation, culture, and a range of diagnostic tests. PCR methods have been developed to identify all serotypes. After APP infection irrespective of the serotype antibodies against the ApxIV-toxin can be detected using the ApxIV-ELISA. There are rare reports about APP strains not inducing detectable ApxIV-antibodies. For immunohistochemistry and detection of antibodies against specific serotypes the serotype to be detected should be known, because specific antiserum/antigens must be used for the diagnostic test. The availability of diagnostic kits at national laboratories is variable, and the sensitivity and specificity of the tests used are highly variable between tests and serotypes. The biggest challenge for serological tests not based on the ApxIV toxin is the great diversity of serotypes, and the existence of other bacteria that may cross-react with APP. The immunological basis of a diagnosis is not sufficiently investigated and understood.

7. PCR diagnostics for isolates of all serotypes have been improved in recent years by the identification of new serotypes and the development of PCR based serotyping methods for all 19 serovars (e.g. by multiplex real-time PCR assays). Due to exceptions of the toxin profile of the serotypes, a toxin profiling PCR can help to determine the most likely pathogenicity of the strain present, keeping in mind, that other factors can contribute to the level of harmful effects. In regards to sampling, most infected animals will carry the bacterium in the tonsil. Easy and poor invasive methods as tonsillar swapping or brushing are appropriate to collect material for PCR diagnostic. Saliva could be appropriate for group sampling, screening and early detection of infection. Nasal swabs can also be used for bacteriological culture and/or even better for PCR. Diagnostic methods in living pigs mainly target at identification of colonizing APP potentially embedded in biofilms. Recently, sequencing techniques (e.g. nanopore sequencing) can also be used, on individual or on pooled samples.

Vaccines

8. Vaccines are available worldwide with commercial bacterins used mostly in North America. Most European countries use also the sub-unit vaccine containing toxoids or commercial bacterins. More efficient commercially available vaccines are needed. Generally, there is variable protection against acute clinical disease by current APP vaccines provided with the strains responsible for the disease and covered by the vaccine. However, in case of chronic disease, the effect of vaccines is more doubtful. Thus, the efficacy of vaccines has so far not been very impressive for preventing infection, colonization and transmission of the agent. Vaccines are only able to reduce signs of acute disease but they are not effective in the eradication, since vaccinated and infected animals can still carry and shed the organism.

9. Live attenuated vaccines have been explored, but no large-scale studies of efficacy against various genotypes that demonstrate efficacy and safety have been published. As it seems that only viable bacteria can stimulate a full and protective immunological response in the recipient pig, an attenuated vaccine is an interesting approach allowing the pathogen to attach to the target tissue and the host to respond properly. Autogenous vaccines are used in practice, but their effects warrant further investigation.

Pharmaceuticals

10. Swine pleuropneumonia is traditionally controlled by antibiotic treatment but whilst this may prevent death it may not prevent the development of lesions. A wide variety of antibiotics can be used following good practice guidelines which are different in the different countries. In most cases, amoxicillins, penicillins, trimethoprim and sulphonamides, tiamulin and others are effective. Quinolones are very effective but belong to critically important antimicrobials. If animals are clinically affected they require injection therapy as they do not eat and are reluctant to drink. As the development of resistance is of major concern using antibiotics, the mechanism of resistance induction should be further investigated in APP. The extent of antimicrobial resistance in APP should be monitored and in-feed or in water medication should always be carefully used and never be administered just by routine. There is a need for studies that result in predictive data on antimicrobial resistance profiles of strains causing disease at a given time and place, so that diseased pigs can be treated and that results of antimicrobial resistance profiling must not be waited upon. In this sense, an epidemiological approach has been recently proposed to apply the most suitable antimicrobial substance considering previous information from the pyramid of production.

Knowledge

11. There are many significant areas of uncertainty in the understanding and knowledge about APP infections, especially in relation to genetics, virulence factors, virulence variants, pathogenesis, immunology, vaccinology, epidemiology and control. There is a lack of knowledge about specific factors of the innate immune defence mechanisms and their stimulation by specific vaccine components and adjuvants. In addition, there are major gaps in understanding the protective immune responses for colonization as well as pneumonia. Another area lacking knowledge is the trigger for the dispersal of biofilms on tonsils and the prevention of such dispersal. Alternatively, methods are needed to treat biofilms to disperse in the presence of effective antimicrobials. Knowledge should be updated in external and internal biosecurity measures with regard to the specific disease. Biosecurity is of paramount importance regarding prevention of APP incursion and spreading in pig herds.

Conclusions

12. This bacterium has received more attention than many other bacteria in animal or pig health. Research has shown the complexity of bacterial pathogenesis and virulence factors without producing effective vaccines needed for control. The disease has a high economic impact for individual pig farms, especially on sow herds producing breeding stock for sale.

13. The widespread use of prophylactic, therapeutic, or in some regions of the world even growth-promoting antibiotics can mask the full extent of the problem. It is not enough to decrease mortality caused by the disease. It is important to take a step further to reduce economic losses due to the decrease in performance and medication costs.

14. Disease caused by APP is a significant animal welfare concern causing suffering and/or death in affected animals and distress in animal caretakers. It negatively affects the efficiency of swine production resulting in economic losses for the producer. The need to use antibiotics to treat the APP infection increases the risk for the development of antimicrobial resistance in APP and commensal organisms in treated swine with the possibility of transfer of this resistance to human pathogens.

15. After successful elimination of APP from a farm it can be expected, that the use of antibiotics will decrease. The development of an effective vaccine would reduce the selection pressure on bacteria to develop and transmit antimicrobial resistance factors while improving animal welfare.